Hydrogenation or Dehydrogenation of *N*-Containing Heterocycles Catalyzed by a Single Manganese Complex

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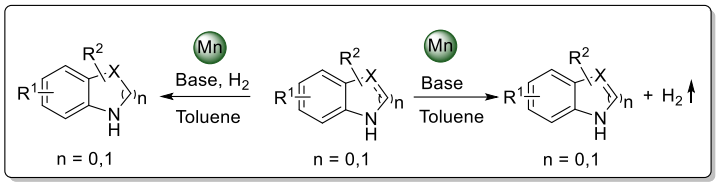
Supporting Information Placeholder

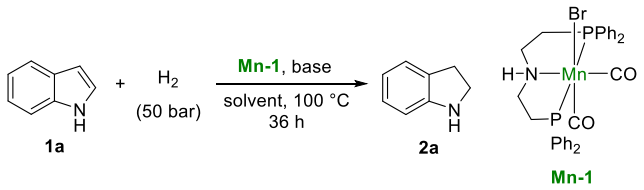


ABSTRACT: A highly chemoselective base-metal catalyzed hydrogenation and acceptorless dehydrogenation of N-heterocycles is presented. A well-defined Mn-complex operates at low catalyst loading (as low as 2 mol %) and under mild reaction conditions. The described catalytic system tolerates various functional groups and the corresponding reduced heterocycles can be obtained in high yields. Experimental studies indicate a metal ligand cooperative catalysis mechanism.

Transition metal catalyzed hydrogenation of polar bonds is a well-accepted and widely used method for the synthesis of a diverse set of value-added products such as alcohols, amines, saturated heterocycles etc.[1] However, most of the reports focus on using rare and expensive transition metals or heterogeneous catalysts, which may require harsh reaction conditions resulting in a low functional group tolerance. The replacement of noble-metals by sustainable base-metals is currently getting increased attention due to their lower toxicity and ubiquitous abundance.[2] On the other hand, saturated and unsaturated heterocycles are considered as liquid organic hydrogen carriers (LOHC) due to their reversible dehydrogenating properties. Using *N*-containing heterocycles as LOHC allows avoiding problems associated with commonly studied LOHC reagents including ammonia borane, sodium borohydride, metal hydrides. First of all, they are abundant and economically advantageous. Second, the dehydrogenation process for these molecules is endothermic, which prevents uncontrolled thermal reactions. Thus, *N*-containing heterocycles are considered to be a good alternative if compared to hydrocarbons due to the lower energy barrier for de/hydrogenation processes.[3-5] Examples of a single catalyst which are able to catalyze both, the hydrogenation and dehydrogenation process are very rare in the literature. Zhou, Li and co-workers[6] as well as Fujita and co-workers[7] studied iridium complexes for this transformation. Later, Crabtree and co-workers[8] and Albrecht and co-workers[9] reported the use of iridium complexes for the catalytic hydrogenation and dehydrogenation of *N*-heterocycles in water. In addition, Fischmeister and co-workers reported a mild reversible hydrogenation of quinoline derivatives using an iridium-based catalyst.[10] Although, the field is predominant by the application of iridium catalysts, Jones and co-workers focused on using base-metals such as Fe[11] and Co[12] for this transformation.[13] However, Mn-based systems still remain unknown. Therefore, the development of single catalysts for the reversible dehydrogenation process is interesting and desired. Recently an increasing number of reports featuring the high reactivity of Mn-complexes for the hydrogenation of aldehydes, ketones, nitriles, esters and amides have been published.[14-23] More challenging substrates such as organic carbonates, carbamates and urea derivatives could also be hydrogenated using manganese complexes.[24-27] To the best of our knowledge, only few reports addressing the reduction of heteroaromatic systems were published.[28-31] Based on our interest in manganese catalysis as well as hydrogenations and dehydrogenations we decided to explore the hydrogenation of indoles as representatives of N-heterocyclic compounds. The indole scaffold is considered to be one of the most important organic frameworks for the discovery of new drugs as many of the indole derived compounds play a significant role in nature. Among them are tryptophan, an α-amino acid which is essential to humans, the neurotransmitter serotonin, and melatonin, a hormone which regulates the sleep-awake cycles. The indoline skeleton is equally important and it is found in numerous bioactive compounds, pharmaceuticals, herbicides, and insecticides.[32,33] Hydrogenation of indoles is a difficult task due to the high stability of the aromatic heterocyclic ring. Among the conventional methods to achieve saturated heterocycles we may highlight the use of $NaBH_3CN$. It is one of the most used methods, however due to the use of super-stoichiometric amounts of the hydride source and the generation of high amounts of waste, such as cyanides, other improved systems are still desired.

The catalytic hydrogenation using hydrogen gas as the reducing agent is an attractive process due to the low cost of hydrogen, atom economy and minimal waste generation. Encouraged by our previous results we were interested to find out whether a bench stable Mn-PNP catalyst would be active enough for the hydrogenation of *N*-containing heterocyclic compounds. Simple unsubstituted indole **1a** was chosen as a model substrate to test the above-mentioned reaction. We were pleased to see that indoline **2a** was formed in high yield (85%) upon running the reaction for 24 h at 100 °C, 50 bar of H_2, with 2 mol % of the catalyst and 5 mol % of base (Table 1, entry 1). The yield did not increase when the reaction was performed in polar protic tert-amyl alcohol and polar aprotic dioxane as solvent (Table 1, entries 2-3). Increasing the reaction time to 36 h led to indoline **2a** in 92% yield (Table 1, entry 4). Using $CsOH^*H_2O$ instead of KO^{t}Bu provided the product with the same efficiency (Table 1, entry 5). The application of other bases did not improve the reaction outcome (Table 1, entries 6-8). Decreasing the catalyst loading to 1 mol % resulted in 47% yield of indoline only (Table 1, entry 9). The application of $Mn(CO)_5Br$ precursor in the reaction resulted in the full recovery of the indole (Table 1, entry 10), which highlights the crucial role of the ligand.

Table 1. Optimization of the reaction conditions[a]

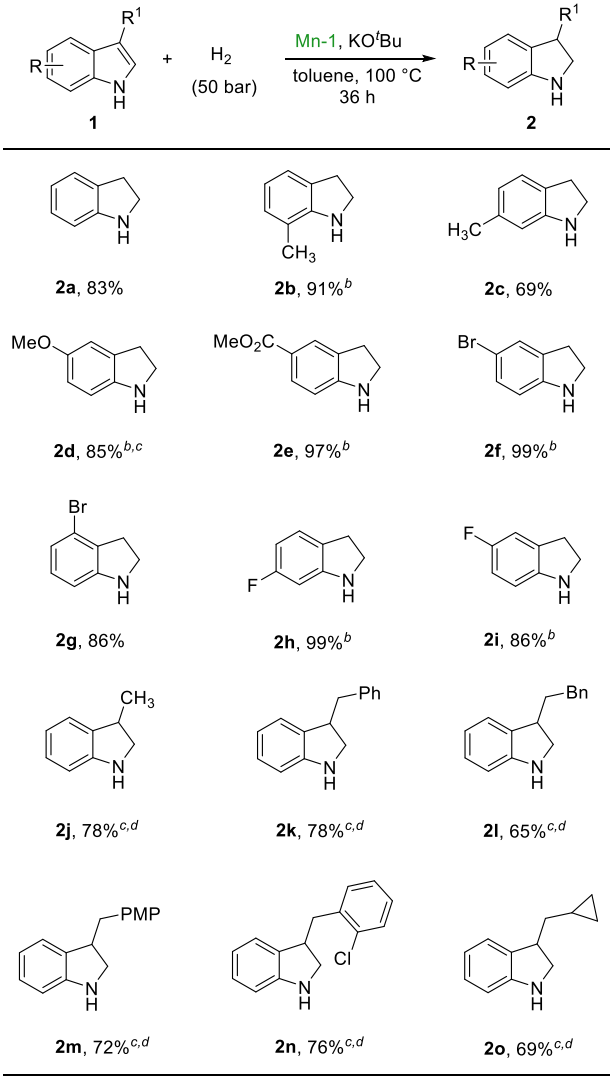


entry	[Mn-1] (mol %)	base (mol %)	solvent	yield (%)[b]
1[c]	**Mn-1**(2)	KO^{t}Bu (5)	toluene	85
2[c]	**Mn-1** (2)	KO^{t}Bu (5)	TAA	57
3[c]	**Mn-1** (2)	KO^{t}Bu (5)	dioxane	18
4	**Mn-1** (2)	KO^{t}Bu (5)	toluene	92
5	**Mn-1** (2)	$CsOH^*H_2O$ (5)	toluene	92
6	**Mn-1** (2)	Cs_2CO_3 (5)	toluene	88
7	**Mn-1** (2)	K_3PO_4 (5)	toluene	36
8	**Mn-1** (2)	NaO^{t}Bu (5)	toluene	71
9	**Mn-1** (1)	KO^{t}Bu (2.5)	toluene	47
10	$Mn(CO)_5Br$	KO^{t}Bu (5)	toluene	nd

[a]Reaction conditions: indole **1a** (0.25 mmol), [Mn], base in 1 mL of solvent at 100 °C under 50 bar of H_2 for 36 h. [b]Determined by GC analysis using dodecane as internal standard. [c]Reaction time is 24 h. TAA = *tert*-amyl alcohol.

In order to demonstrate the potential and applicability of the newly developed catalytic hydrogenation system, a range of substituted indoles **1a-1o** were tested under the optimized reaction conditions (Scheme 1). Different substituted indoles were efficiently and selectively hydrogenated to the corresponding indolines with good to very good yields. Simple substituted indoles with methyl groups in the C-6 and C-7 positions were also well tolerated and led to the desired products **2b** and **2c** in very good yields. An elevated temperature was needed when 5-methoxyindole was applied in the reaction, resulting in 85% of the corresponding indoline **2d**. Remarkably, methyl indole-5-carboxylate was selectively hydrogenated, yielding the desired indoline in 97% yield, with the ester group remaining intact.

Scheme 1. Manganese-catalyzed hydrogenation of indoles[a]

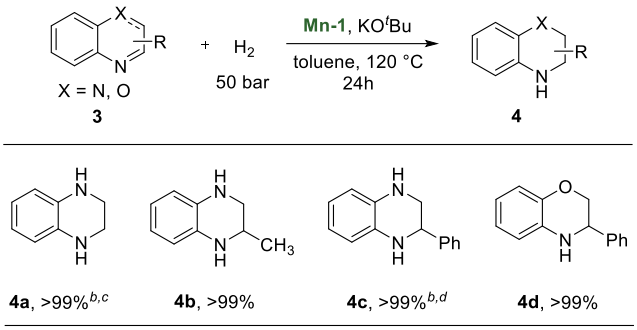


[a]Reaction conditions: **1** (0.25 mmol), **Mn-1** (2 mol %) and KO^{t}Bu (5 mol %) in toluene (1 mL) at 100 °C under 50 bar of H_2 for 36 h. Isolated yields provided. [b]Yields for scale-up experiment (2.5 mmol of starting material used). [c]130 °C. [d]**Mn-1** (5 mol %) and KO^{t}Bu (12.5 mol %).

Halogen containing substrates were also tolerated, resulting in high yields for the products **2f-2i**. It is worth mentioning that no hydrodehalogenation occurred under the optimized reaction conditions. Scale up experiments were performed resulting in high yields of the corresponding indolines. Quantitative yields were observed for the substrates **1e**, **1f** and **1h** which indicates the high potential of this transformation. In addition, the hydrogenation of C3-substituted indoles could be performed. The application of an elevated reaction temperature (130 °C) and a higher catalyst loading (5 mol %) were required for the reaction to proceed successfully. To the best of our knowledge, manganese catalyzed reduction of C3-substituted indoles using molecular hydrogen was not yet reported.

In addition to indoles other different N-containing heterocycles could be applied in the transformation (Scheme 2). Unsubstituted and substituted quinoxalines **3a-c** as well as benzoxazine **3d** were successfully applied in the reaction resulting in quantitative yields of the corresponding products.

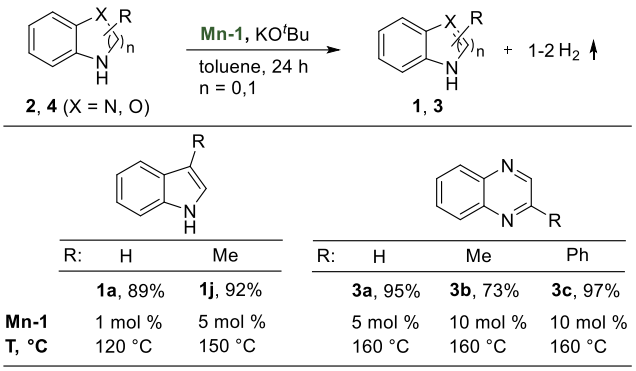
Scheme 2. Manganese-catalyzed hydrogenation of N-containing heterocycles[a]



[a]Reaction conditions: **3** (0.25 mmol), **Mn-1** (1 mol %) and KO^{t}Bu (2.5 mol %) in toluene (1 mL) at 120 °C under 50 bar of H_2 for 24 h. Isolated yields provided [b]140 °C [c]**Mn-1** (2 mol %) and KO^{t}Bu (5 mol %). [d]**Mn-1** (3 mol %) and KO^{t}Bu (7.5 mol %).

Considering the above results we decided investigate whether a manganese catalyzed dehydrogenation would also be accessible demonstrating for the first time the applicability of manganese complexes in both, hydrogenation and dehydrogenation reactions. Thus we started to investigate the applicability of **Mn-1** to catalyze the dehydrogenation of other *N*-containing heterocycles under oxidant-free conditions (Scheme 3). To our delight indoline was successfully dehydrogenated using only 1 mol % of the catalyst at 120 °C for 24 h leading to 89% of indole. The liberated hydrogen gas was detected using GC. Although, the hydrogen storage capacity for indoline is relatively low, 1,7 wt% compared to the current favorite, the N-ethylcarbazole/dodecahydro-N-ethylcarbazole system with a capacity of storing 5.8 wt % of hydrogen, its conversion to indole requires low catalyst loading and comparable low temperatures which makes our developed catalyst system potentially interesting for the LOHC (liquid organic hydrogen carrier) concept. A higher catalyst loading (5 mol %) and temperature (150 °C) were required for the successful dehydrogenation of 3-methylindoline leading to product **1j** in 92% isolated yield. Harsher conditions had to be applied for the dehydrogenation of 1,2,3,4-tetrahydroquinoxaline as well as substituted 1,2,3,4-tetrahydroquinoxalines. Thus, by using 5 mol % of the catalyst and conducting the reaction at 160 °C for 24 h we could achieve 95% of quinoxaline. Substituted 1,2,3,4-tetrahydroquinoxalines underwent dehydrogenation by using 10 mol % of the catalyst at 160 °C for 24 h.

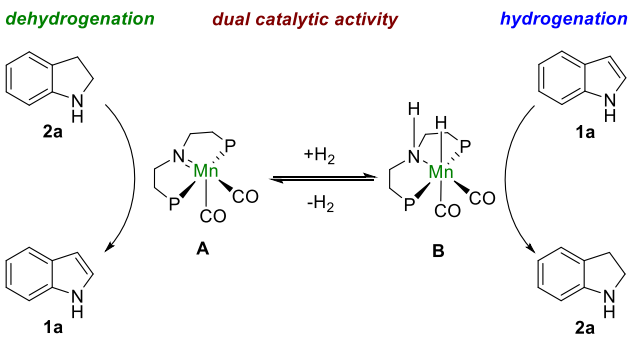
Scheme 3. Manganese-catalyzed dehydrogenation of N-heterocycles[a]



[a]Reaction conditions: **2** or **4** (0.25 mmol), **Mn-1** (1-10 mol %) and KO^{t}Bu (2.5-25 mol %) in toluene (1 mL) at 120-160 °C for 24 h. Isolated yields provided.

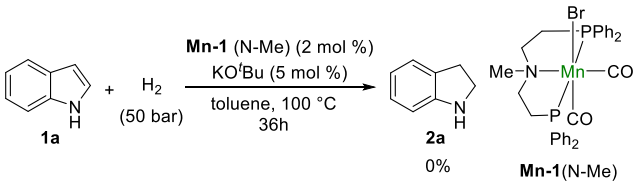
The proposed catalytic cycle for the hydrogenation of indole and dehydrogenation of indoline is depicted in Scheme 4. The first step for the hydrogenation process is the activation of **Mn-1** using the base (KO^{t}Bu) and formation of an active species **A**. Next, species **A** reacts with hydrogen forming H-N-Mn-H species **B**, which successfully hydrogenates indole to indoline. The dehydrogenation reaction begins also with the formation of an active species **A** which dehydrogenates indoline to indole and becomes species **B** which releases a hydrogen molecule afterwards.

Scheme 4. Proposed reaction mechanism of reversible indole hydrogenation and dehydrogenation using Mn-1 complex



In order to support the described proposed mechanism and to understand whether this reaction proceeds via a metal-ligand cooperative mechanism,[34] we performed the hydrogenation of indole **1a** using N-Me substituted **Mn-1** catalyst. As expected, no formation of indoline was observed under the applied reaction conditions, indicating the crucial role of species **B** for the catalytic cycle.

Scheme 5. Mechanistic studies



In conclusion, we describe for the first time that a single manganese catalyst can catalyze both, the hydrogenation and acceptorless dehydrogenation of N-containing

heterocycles. The products of both hydrogenation and dehydrogenation reactions can be isolated in good to excellent yields and high chemoselectivity. The applied catalyst **Mn-1** is air and moisture stable and can be synthesized using a readily available manganese precursor and ^{Ph}PNP-pincer ligand, highlighting the practicability of the developed protocol. Mechanistic studies indicate a metal-ligand cooperative catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website

Experimental data (PDF)

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Notes

The authors declare no competing financial interest

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