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. 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. 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. 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 as well as Fujita and co-workers studied iridium complexes for this transformation. Later, Crabtree and co-workers and Albrecht and co-workers 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. Although, the field is predominant by the application of iridium catalysts, Jones and co-workers focused on using base-metals such as Fe and Co for this transformation. 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. More challenging substrates such as organic carbonates, carbamates and urea derivatives could also be hydrogenated using manganese complexes. To the best of our knowledge, only few reports addressing the reduction of heteroaromatic systems were published. 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-wake cycles. The indoline skeleton is equally important and it is found in numerous bioactive compounds, pharmaceuticals, herbicides, and insecticides. 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 NaBH₄CN. It is one of the most used methods, however due to the use of superstoichiometric 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 H₂, 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·H₂O instead of KOtBu 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**

<table>
<thead>
<tr>
<th>entry</th>
<th>[Mn-1] (mol %)</th>
<th>base (mol %)</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mn-1(2)</td>
<td>KOtBu (5)</td>
<td>toluene</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Mn-1 (2)</td>
<td>KOtBu (5)</td>
<td>TAA</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>Mn-1 (2)</td>
<td>KOtBu (5)</td>
<td>dioxane</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>Mn-1 (2)</td>
<td>KOtBu (5)</td>
<td>toluene</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>Mn-1 (2)</td>
<td>CsOH·H₂O (5)</td>
<td>toluene</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>Mn-1 (2)</td>
<td>Cs₂CO₃ (5)</td>
<td>toluene</td>
<td>88</td>
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<tr>
<td>7</td>
<td>Mn-1 (2)</td>
<td>K₂PO₄ (5)</td>
<td>toluene</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>Mn-1 (2)</td>
<td>NaO⁻Bu (5)</td>
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<td>71</td>
</tr>
<tr>
<td>9</td>
<td>Mn-1 (1)</td>
<td>KOtBu (2.5)</td>
<td>toluene</td>
<td>47</td>
</tr>
<tr>
<td>10</td>
<td>Mn(CO)₅Br</td>
<td>KOtBu (5)</td>
<td>toluene</td>
<td>nd</td>
</tr>
</tbody>
</table>

*Reaction conditions: indole 1a (0.25 mmol), [Mn], base in 1 mL of solvent at 100 °C under 50 bar of H₂ for 36 h. | Reaction 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-10 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**

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 benzoazine 3d were successfully applied in the reaction resulting in quantitative yields of the corresponding products.

**Scheme 2. Manganese-catalyzed hydrogenation of N-containing heterocycles**

\[
\text{X} = \text{N, O}
\]

![Scheme 2](image)  
4a, >99%c 4b, >99% 4c, >99%d 4d, >99%

4cReaction conditions: 3 (0.25 mmol), Mn-1 (1 mol %) and KOt-Bu (2.5 mol %) in toluene (1 mL) at 120 °C under 50 bar of H₂ for 24 h. Isolated yields provided 140 °C Mn-1 (2 mol %) and KOt-Bu (5 mol %). 4Mn-1 (3 mol %) and KOt-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 indole 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 indole 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**

![Scheme 3](image)  

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.
heterocycles. The products of both hydrogenation and dehydrogenation reactions can be isolated in good to excellent yields and high chemoselectivity. The applied catalyst MNP-1 is air and moisture stable and can be synthesized using a readily available manganese precursor and 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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