Transfer hydrogenation of carbonyl groups, imines and *N*-heterocycles catalyzed by simple, bipyridine-based Mn^{I} complexes

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Abstract: Utilization of hydroxy-substituted bipyridine ligands in transition metal catalysis mimicking [Fe]-hydrogenase has been shown to be a promising approach in developing new catalysts for hydrogenation. For example, Mn^{I} complexes with 6,6'-dihydroxy-2,2'-bipyridine ligand have been previously shown to be active catalysts for CO_2 hydrogenation. In this work, simple bipyridine-based Mn catalysts were developed that act as active catalysts for transfer hydrogenation of ketones, aldehydes and imines. For the first time, Mn-catalyzed transfer hydrogenation of *N*-heterocycles was reported. The highest catalytic activity among complexes with variously substituted ligands was observed for the complex bearing two OH groups in bipyridine. Deuterium labeling experiments suggest a monohydride pathway.

Introduction

Transition metal-catalyzed transfer hydrogenation (TH) of polar bonds has a great number of important applications in organic synthesis and it is a practical and convenient method for production of value-added products, such as alcohols, amines, and saturated *N*-heterocycles.[1] Compared to other methods such as direct hydrogenation and the use of metal hydrides, transfer hydrogenation offers a number of important advantages. First, it avoids the use of pressurized flammable gas and specialized equipment, or handling moisture-sensitive and reactive reagents. In addition, common hydrogen donors such as alcohols or formic acid are readily available, inexpensive and can be safely handled. For many decades, precious metal-based catalysts were prevalent in hydrogen activation and hydrogen transfer reactivity.[1a-c, 1g, 2] However, for practical implementation of transfer hydrogenation in large scale synthesis, the use of inexpensive, non-toxic and earth-abundant first row transition metals in combination with robust and synthetically accessible ligands is essential. While there were many reports on development of efficient Fe- and Co-based catalysts for transfer hydrogenation,[3] the use of manganese, the third most abundant metal in the Earth's crust, for hydrogenation,[4] dehydrogenation[5] and transfer hydrogenation[6] catalysis has started to emerge just recently. Notably, although transfer hydrogenation of ketones, aldehydes and imines has been reported for Mn complexes,[6] transfer hydrogenation of aromatic *N*-heterocycles leading to the formation of saturated cyclic amines still remains a challenge for first row transition metals, both in heterogeneous[7] or homogeneous systems.[8] The majority of the examples of TH of aromatic *N*-heterocycles involve precious metal catalysts[9] such as Ru,[10] Rh[11] and Ir[12] complexes, and to the best of our knowledge, no examples of Mn-catalyzed TH of aromatic *N*-heterocycles have been reported up to date. Overall, the design of earth-abundant, non-toxic metal catalysts based on simple and robust non-phosphine ligands remains an important problem to develop practical and economically viable synthetic methods.

We focused our attention on simple bipyridine-based Mn complexes decorated by additional functional groups to modulate their reactivity in catalysis. In particular, bipyridine Mn complexes are well-studied in electroreduction catalysis,[13] but they are much less explored in homogeneous hydrogenation and have not yet been studied in transfer hydrogenation. Recently, in search for a non-phosphine ligand for hydrogen activation by manganese, we found that the Mn^{I} complexes with a commercially available ligand, 6,6'-dihydroxy-2,2'-bipyridine, act as active catalysts for CO_2 hydrogenation to formate and in the presence of secondary amines, to formamide.[14] This ligand resembles the structure of active site of [Fe]-hydrogenase, in which the presence of the OH group in the *ortho*-position of the pyridine ring is proposed to play an important role in H_2 activation.[15] Bioinspired Ir complexes with dihydroxy-substituted bipyridine and bipyrimidine were also devepoled that act as efficient catalysts for reversible hydrogenation of CO_2 and dehydrogenation of formic acid.[16] Recently, Li and co-workers showed that Ir complex with 6,6'-dihydroxy-2,2'-bipyridine is an active catalyst of TH of aldehydes and ketones, while unsubstituted and mono-hydroxy-substituted bipyridine analogs show no activity or much lower product yields.[17]

In this study, we expand the reactivity of the Mn complexes with simple substituted bipyridine ligands to transfer hydrogenation of ketones, aldehydes and imines. We found that while the most active and stable catalysts were dihydroxy-substituted complexes, complexes with other electron-rich bipyridines not containing OH groups also showed some catalytic activity, indicating that the effect of the proton shuttle groups in the ligand second coordination sphere is less pronounced for transfer hydrogenation compared to CO_2 hydrogenation by the same complexes. For the first time, we report transfer hydrogenation of aromatic *N*-heterocycles by a Mn complex, although the substrate scope is currently limited.

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Supporting information for this article is given via a link at the end of the document. CCDC 1897115 (**5**) and 1897116 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

Results and Discussion

Transfer hydrogenation of ketones, aldehydes and imines. A series of Mn complexes with substituted bipyridine ligands have been synthesized (Figure 1) to evaluate their reactivity in TH. Complexes **1**-**4** have been reported previously,[13b, 14, 18] while complexes **5** and **6** were obtained by heating a mixture of $Mn(CO)_5Br$ and the corresponding ligand in toluene, isolated, and fully characterized by NMR, IR, UV-vis spectroscopy and elemental analysis. The X-ray structures of complexes **5** and **6** are shown in Figure 2 and reveal a similar geometry to other reported complexes **1**-**4**.

First, we examined the catalytic activity of complex **1** in a model reaction of transfer hydrogenation of acetophenone using 2-propanol as the hydrogen source. Using 1 mol% of **1** and 5 mol% of KO^{t}Bu in 2-propanol, at 80 °C for 24 h, we observed a full reduction of acetophenone to 1-phenylethanol (Table 1, entry 1). After optimization of the reaction conditions (Tables S1 and S2), the catalyst loading could be lowered to 0.3 mol% of complex **1** and 1 mol% of KO^{t}Bu to give quantitative conversion and high isolated yield of the alcohol product.

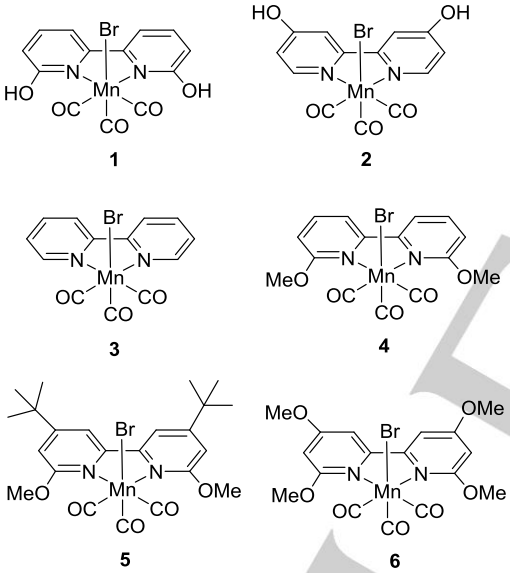


Figure 1. Mn complexes used in this study.

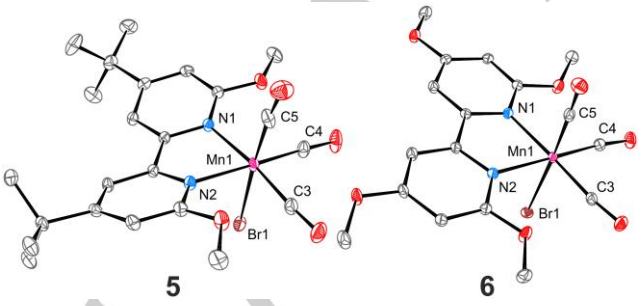
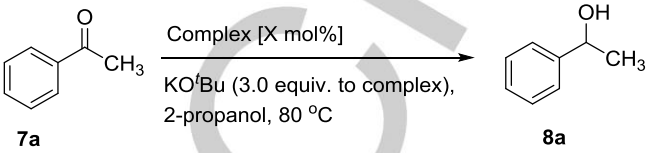


Figure 2. ORTEP of complexes **5** and **6** at 50 % probability level. Hydrogen atoms are omitted for clarity. Selected interatomic distances for **5** [Å]: Br1–Mn1 2.5448(2), Mn1–N1 2.0704(10), Mn1–N2 2.0713(11), Mn1–C3 1.8083(14), Mn1–C4 1.8112(14), Mn1–C5 1.8327(16). Selected interatomic distances for **6** [Å]: Br1–Mn1 2.5440(3), Mn1–N1 2.0849(16), Mn1–N2 2.0699(16), Mn1–C3 1.803(2), Mn1–C4 1.8047(19), Mn1–C5 1.800(2).

Table 1. Optimization of conditions for the TH of acetophenone.[a]



7a **8a**

Entry	Complex [mol%]	T, °C	Conversion of **7a** [%][b]	Yield of **8a** [%][c]
1	**1** (1.0 mol%)	80	>99	95
2	**1** (0.5 mol%)	80	>99	96
3	**1** (0.3 mol%)	80	>99	94
4	**1** (0.2 mol%)	80	60	52
5	**2** (0.3 mol%)	80	>99	94
6	**3** (0.3 mol%)	80	<1	n.d. [d]
7	**4** (0.3 mol%)	80	70	65
8	**5** (0.3 mol%)	80	40	28
9	**6** (0.3 mol%)	80	60	52
10	**1** (1.0 mol%)	50	70	60
11	**4** (1.0 mol%)	50	7	n.d.

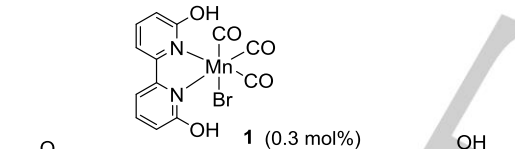
[a] **7a** (1.0 mmol), 2-propanol (2 mL), 24 h. [b] Determined by recovered acetophenone. [c] Isolated yield. [d] n.d. – not determined.

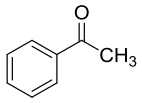
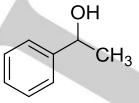
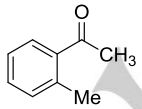
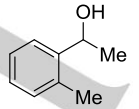
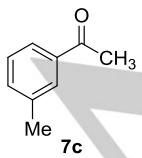
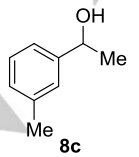
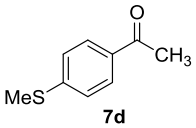
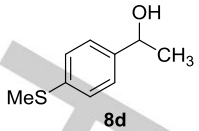
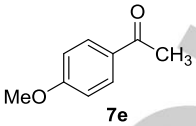
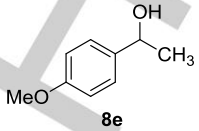
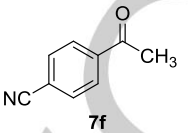
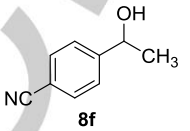
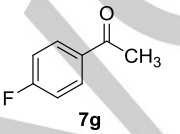
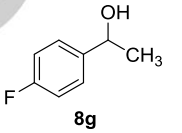
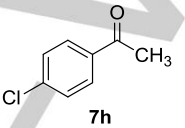
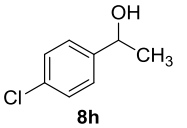
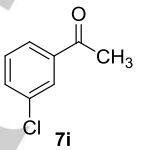
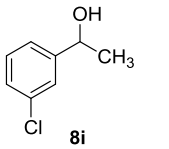
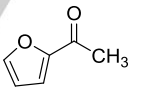
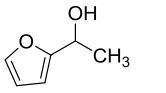
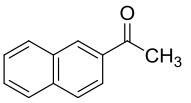
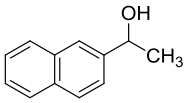
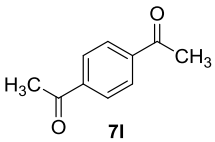
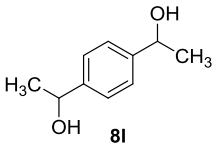
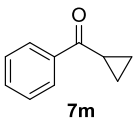
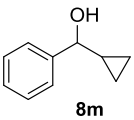
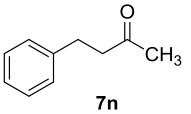
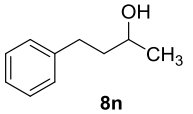
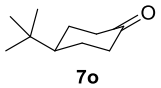
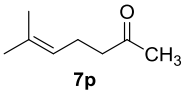
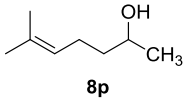
Interestingly, complex **2**, in which the OH groups are present in the *para*-positions, showed similar catalytic activity as compared to *ortho*-substituted analog **1**. These finding indicates that position of the OH group is not crucial for high catalytic activity, unlike in previously reported direct CO_2 hydrogenation. Notably, when 2,2'-bipyridine complex **3** was used as a catalyst, no product formation was observed. Complexes **4**, **5** and **6**, bearing electron-donating methoxy-substituents, were significantly less active. These results suggest that the presence of the OH group that can be deprotonated under basic conditions is an important feature required for high catalytic activity. The effect of the presence of OH substituents in the bipyridine ligand was especially evident when TH was performed at lower temperature: at 50 °C complex **1** showed 70% conversion, while complex **4** did not show considerable activity (Table 1, entries 10 and 11). At room temperature, complex **1** also shows catalytic activity giving low conversion (30% after

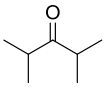
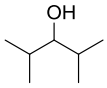
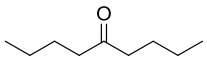
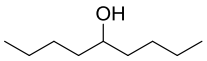
24h), while complex **4** was completely inactive and only unreacted starting material could be detected (see Supp. Info, Table S2). The comparison of kinetic data at 50 °C also shows greater activity for OH-substituted complexes **1** and **2** compared to MeO-substituted **4** and **6** (Figure S64 and Table S6, Supp. Info). First order kinetic behaviour on complex **1** was confirmed by a kinetic study (Figure S65-66), which led us to focus our attention on the utilization of complex **1** for TH catalysis. At the same time, complex **2** with *para*-OH substituents showed non-first order kinetic behaviour, which could be due to more complicated reaction pathways.

Using the optimized reaction conditions, the general applicability of the protocol was studied with a large range of aromatic and aliphatic substrates (Table 2). The transfer hydrogenation of aromatic ketones bearing electron donating or electron withdrawing substituents (Table 2, entries 1-13) proceeded in high conversions with high isolated yields of the corresponding products. The substrates with cyano, fluoro, chloro and sulfide functional groups were well-tolerated under these conditions. The alkene C=C double bond remained unreacted under these conditions (entry 16), and in the case of diketone **7l**, the corresponding dialcohol **8l** was obtained as a major product (entry 12). Aliphatic ketones (Table 2, entries 14-18) were also effectively hydrogenated to give the corresponding alcohol products in good yields.

Table 2. Transfer hydrogenation of ketones.[a]



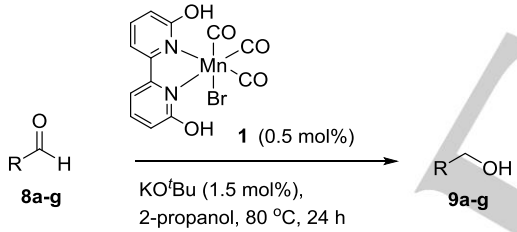
Entry	Ketone	Product	Yield [%][b]
1	 **7a**	 **8a**	94
2	 **7b**	 **8b**	86
3	 **7c**	 **8c**	88
4	 **7d**	 **8d**	99
5	 **7e**	 **8e**	92
6	 **7f**	 **8f**	68
7	 **7g**	 **8g**	92
8	 **7h**	 **8h**	88
9	 **7i**	 **8i**	91
10	 **7j**	 **8j**	75[c]
11	 **7k**	 **8k**	92
12	 **7l**	 **8l**	68[d]
13	 **7m**	 **8m**	70
14	 **7n**	 **8n**	84
15	 **7o**	 **8o**	79[e]
16	 **7p**	 **8p**	67

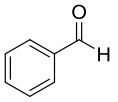
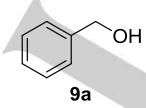
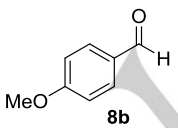
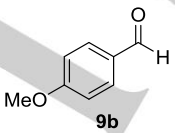
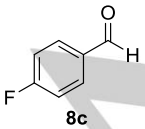
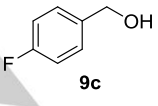
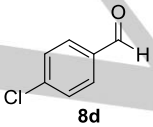
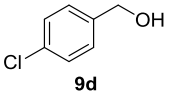
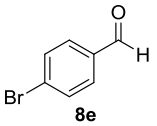
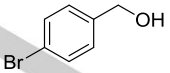
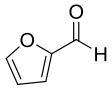
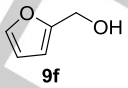
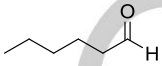
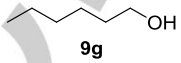
17	 **7q**	 **8q**	87	
18	 **7r**	 **8r**	84	

[a] **7a-r** (1.0 mmol), complex **1** (0.3 mol%), KO^{t}Bu (1.0 mol%), 2-propanol (2 mL), 80 °C, 24 h. [b] Isolated yield. [c] 0.5 mol% **1** was used. [d] Mono-alcohol was present as a minor product in 15% yield. [e] Yield for both *cis*- and *trans*-isomers.

We have also successfully employed catalyst **1** in the transfer hydrogenation of aldehydes under similar conditions using 0.5 mol% of catalyst **1** and 1.5 mol% of KO^{t}Bu. Aromatic aldehydes with electron-donating or electron-withdrawing groups were reduced to the corresponding alcohols smoothly in good to excellent yields (Table 3, entries 1-6). Aromatic aldehydes with chloro- and bromo-substituents were also tolerated and produced the alcohol products in good yields. For aliphatic aldehyde, 1-hexanal (Table 3, entry 7), the product, 1-hexanol, was obtained in 60% yield, due to base-catalyzed side-reactions.

Table 3. Transfer hydrogenation of aldehydes.[a]



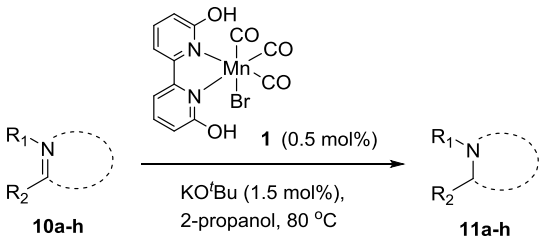
Entry	Aldehyde	Product	Yield [%][b]
1	 **8a**	 **9a**	94
2	 **8b**	 **9b**	80
3	 **8c**	 **9c**	70
4	 **8d**	 **9d**	78
5	 **8e**	 **9e**	72
6	 **8f**	 **9f**	65
7	 **8g**	 **9g**	60[c]

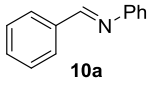
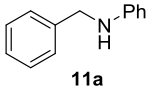
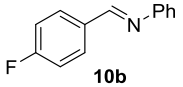
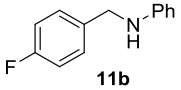
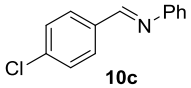
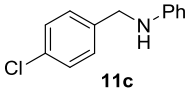
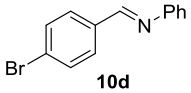
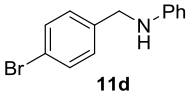
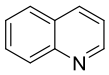
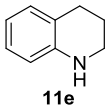
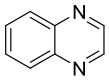
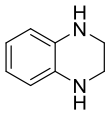
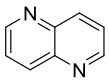
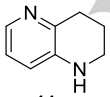
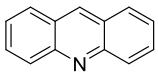
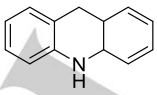
[a] **8a-g** (1.0 mmol), complex **1** (0.5 mol%), KO^{t}Bu (1.5 mol%), 2-propanol (2 mL), 80 °C, 24 h. [b] Isolated yield. [c] NMR yield.

In order to extend the applicability of this catalytic system, we subsequently tested TH of imines. Under optimized conditions (0.5 mol% catalyst, 1.5 mol% KO^{t}Bu), several substituted N-benzylidineanilines underwent transfer hydrogenation from 2-propanol, affording the corresponding amines in high yields (86–99%, Table 4, entries 1-4).

Given the activity of complex **1** in the TH of imines, we set out to expand the application of this catalytic system for the TH of aromatic *N*-heterocycles. Saturated nitrogen heterocycles are among the most important scaffolds in pharmaceuticals and biologically active molecules, and developing an accessible synthetic method based on the Earth-abundant homogeneous metal catalysts remains a challenge.[8] Gratifyingly, when exploring TH of quinoline, we found that catalyst **1** could hydrogenate quinoline to 1,2,3,4-tetrahydroquinoline. However, the catalyst loading has to be increased to 2 mol% in order to obtain acceptable yields (entry 5). Several other *N*-heterocycles, such as acridine, quinoxaline and 1,5-napthhydrine, were also reduced with excellent yields (entries 6-8). Unfortunately, no reactivity was observed with pyridine, pyrrole, indole and 3-methyl-1*H*-indole. The ICP-MS analysis of the catalyst **1** and catalyst precursors (6,6'-dihydroxy-2,2'-bipyridine ligand and $Mn(CO)_5Br$) showed that no precious metal impurities were present at the detectable level. Notably, the MeO-substituted analog **4** did not show considerable catalytic activity in TH of quinoline or 1,5-naphthyridine (<3% conversion), suggesting that the presence of OH groups at the bipyridine ligand plays an important role in enabling the TH of aromatic *N*-heterocycles. Overall, although at the current stage, the substrate scope remains limited, the system reported here is the first example of Mn-catalyzed transfer hydrogenation of *N*-heterocycles. Further studies are currently underway to investigate the performance of various Mn catalysts in TH of aromatic *N*-heterocycles in order to improve the efficiency and scope of the reaction.

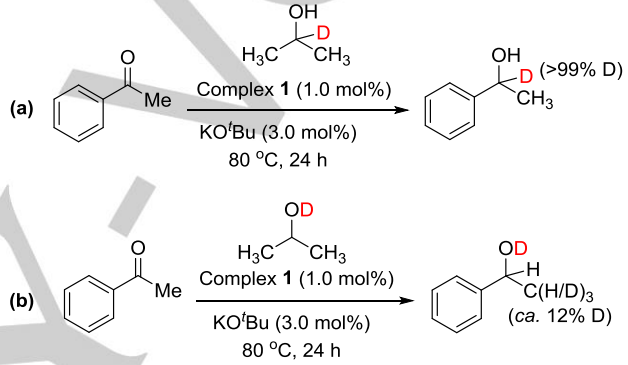
Table 4. Transfer hydrogenation of imines and *N*-heterocycles.[a]



entry[a]	Aldehyde	Product	Yield [%][b]
1	 **10a**	 **11a**	96
2	 **10b**	 **11b**	90
3	 **10c**	 **11c**	85
4	 **10d**	 **11d**	80
5	 **10e**	 **11e**	45[d]
6	 **10f**	 **11f**	84
7	 **10g**	 **11g**	94
8	 **10h**	 **11h**	92

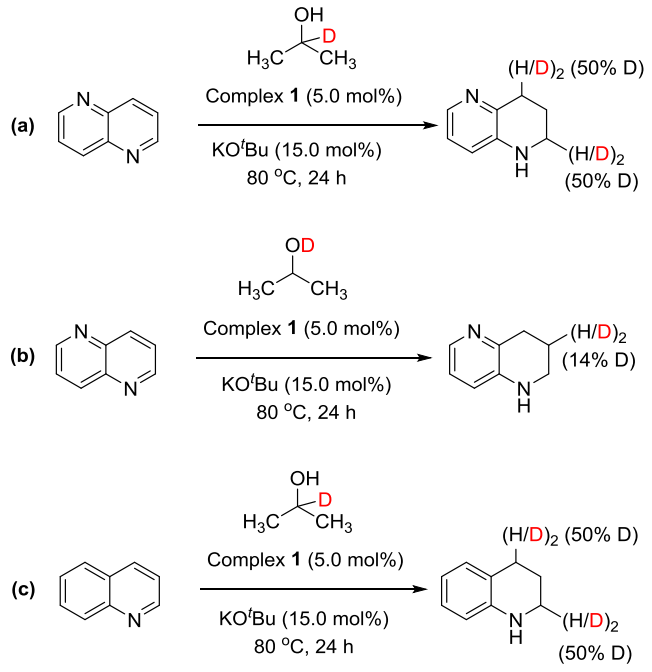
[a] **10a-d** (1.0 mmol), complex **1** (0.5 mol%), KO^{t}Bu (1.5 mol%), 2-propanol (3 mL), 80 °C, 12 h. [b] **10e-h** (1.0 mmol), complex **1** (2 mol%), KO^{t}Bu (6 mol%), 2-propanol (2.5 mL), 80 °C, 48 h. [c] Isolated yield; [d] 72 h.

Mechanistic studies. After expanding the substrate scope, we performed deuterium labeling experiments to gain insight into the mechanism of transfer hydrogenation. Bäckvall and coworkers suggested two possible mechanisms for transition metal-catalyzed TH, "monohydride" and "dihydride" pathways. In a "monohydride" pathway, hydrogen transferred from isopropyl alcohol keep their "identity", *i.e.* the proton from OH group is transferred to the O-atom, and C-H of ^{i}PrOH to a carbonyl carbon of the ketone, while in the "dihydride pathway" the two hydrogens are scrambled.[19] To distinguish between these two possibilities, 2-propanol-2-d_1 (Scheme 1, equation [a]) and 2-propanol-OD (Scheme 1, equation [b]) were used as a hydrogen source for transfer hydrogenation of acetophenone. When isopropyl alcohol deuterated only in the α-CD position was used as a solvent, nearly complete deuteration (>99%) was observed at the α-CH position of the resulting alcohol. However, when OD-deuterated isopropyl alcohol was used, no deuteration was observed at the detectable level in the α−CH position in the product; H/D exchange was observed only in the hydroxyl group of the product and methyl groups (*ca.* 12%), the latter likely due to base-catalyzed enolization. This finding indicates that the transfer hydrogenation of a ketone occurs via a "monohydride" pathway, as scrambling of the deuterium into both the C–H and O–H positions would be expected for the "dihydride" pathway.



Scheme 1. Deuterium labeling experiments: transfer hydrogenation of acetophenone using (a) 2-propanol-2-d_1 and (b) 2-propanol-OD.

Furthermore, we performed deuterium labeling experiments using *N*-heterocyclic substrates, 1,5-napthyridine and quinoline. Interestingly, when 2-propanol-2-d_1 was used as the solvent and hydrogen source, selective incorporation of deuterium was observed at the 2- and 4-positions, corresponding to incorporation of one D-atom to each of the CH_2 groups (*i.e.* 50% deuteration at each of the methylene positions), while the 3-position did not contain D atom at detectable levels (Scheme 2). On the contrary, when 2-propanol-OD was used, no deuterium was detected in 2- and 4-positions, and some deuterium was detected only in the 3-position (*ca.* 14% D incorporation in the CH_2 group).

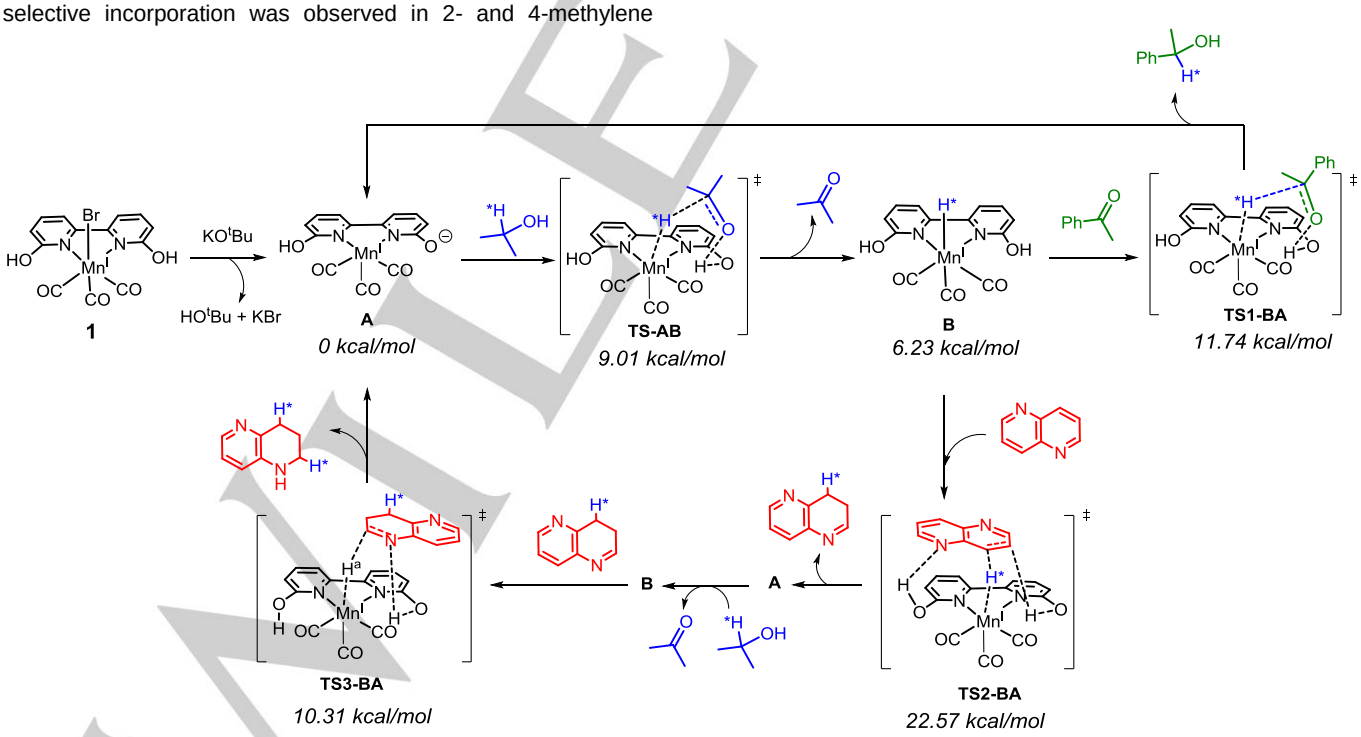


Scheme 2. Deuterium labeling experiments: (a) TH of 1,5-naphthyridine with 2-propanol-2-d_1, (b) TH of 1,5-naphthyridine with 2-propanol-OD and (c) TH of quinoline with 2-propanol-2-d_1.

Similarly, when quinoline was used as a substrate in combination with 2-propanol-2-d_1 as a hydrogen source, selective incorporation was observed in 2- and 4-methylene positions (*ca.* 50% each), corresponding to incorporation of one D-atom in each of the CH_2 groups. In order to explain the possible mechanism of such selectivity in deuterium labeling experiments, we carried out DFT study to elucidate in detail the mechanism of TH of ketones and *N*-heterocycles.

Considering that complex **1** also showed superior reactivity as compared to the MeO-substituted analog **4** in TH of ketones and *N*-heterocycles, especially when catalytic reaction was performed at lower temperatures, we focused our attention on the computational study of the mechanism of TH reactions catalyzed by complex **1**. Previous computational studies of the hydrogenation of CO_2 by complex **1** showed that OH group likely plays an important role in the mechanism. For example, deprotonation of one of the OH groups may enable bifunctional activation of H_2, via participation of the O-atom of deprotonated ligand in heterolytic cleavage of H_2.[20] In addition, deprotonation of the OH group leads to a negatively charged ligand, which may increase hydricity and therefore reactivity of intermediate Mn-H species.[21] The comparison of catalytic performance of **1** and **4** also shows that the presence of OH substituents is crucial for providing low barrier pathways for TH.

Since no catalysis was observed in the absence of the base, we propose that at the initial step the precatalyst **1** reacts with a base leading to Br abstraction and deprotonation of the OH group at the bipyridine ligand to afford a five-coordinate intermediate **A**. A similar step was also proposed in theoretical studies of CO_2 hydrogenation by **1** reported by Yang and co-workers.[20]



Scheme 3. Proposed mechanisms for TH of acetophenone and 1,5-naphthyridine catalyzed by **1** supported by DFT calculations. The relative solvent corrected energies are shown in italics (in kcal mol^{-1}).

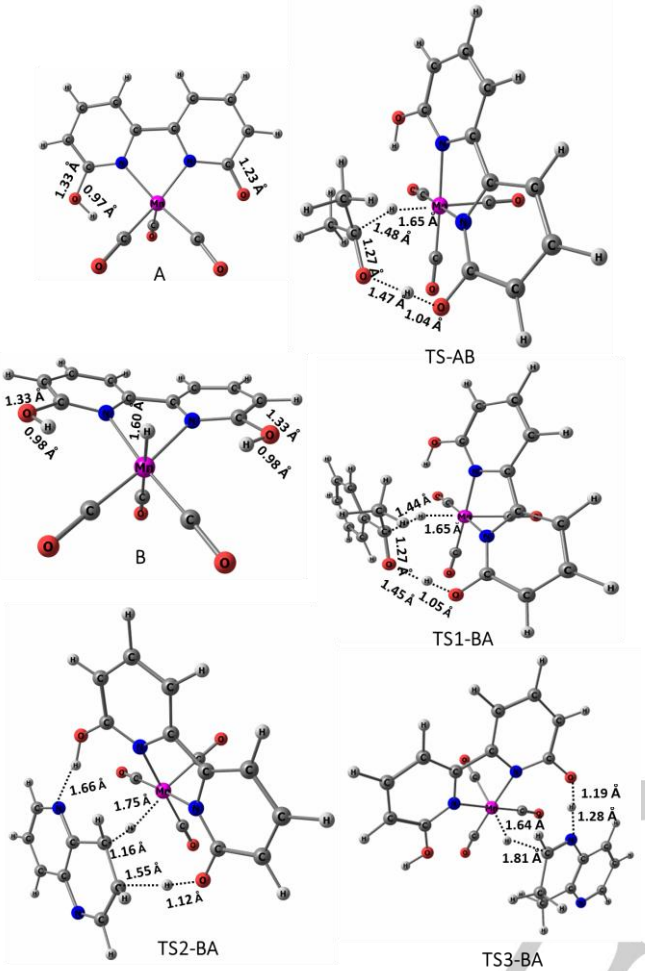


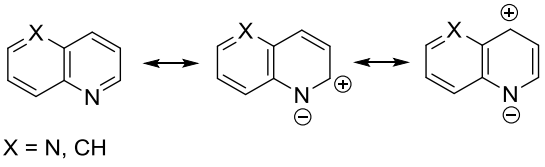
Figure 3. Geometry-optimized structures of key intermediates and transition states for calculated pathways. The bond lengths are given in angstrom.

Interestingly, we found a low energy pathway for the concerted dehydrogenation of 2-propanol leading to elimination of acetone and formation of a Mn hydride intermediate **B**. The transition state **TS-AB** for this process has an activation energy barrier of 9.01 kcal mol^{-1}. The imaginary mode in **TS-AB** clearly indicates the transfer of alcohol proton to the deprotonated ligand, whereas the metal hydride is being simultaneously formed. The transition state involves the migration of hydride from CH of 2-propanol to the Mn and proton from OH to a pendant O-atom of the deprotonated ligand, resulting in the shortening of the Mn···H (1.651 Å), O···H (1.036 Å) of ligand and lengthening of the C···H (1.484 Å) and O···H (1.469 Å) of 2-propanol distances (Figure 3, **TS-AB**). The transition state has a single imaginary frequency of –291.26 cm^{-1}. The hydride intermediate **B** has a higher energy than **A** by about 6.23 kcal mol^{-1}, with Mn–H and OH bond lengths of 1.602 Å and 0.976 Å, respectively (Figure 3, **B**).

Finally, acetophenone accepts a proton from the pendant OH of the ligand and hydride from the metal via a similar transition state **TS1-BA**, which has one imaginary frequency of –328.7 cm^{-1}. In the transition state **TS1-BA**, lengthening of the Mn···H (from 1.602 to 1.653 Å), O···H of ligand (from 0.976 to 1.047 Å) and shortening of C···H (1.443 Å) and O···H (1.448 Å) of acetophenone are observed. (Figure 3, **TS1-BA**). Overall, such concerted pathway for TH of acetophenone having a highest overall barrier of 11.74 kcal mol^{-1} is consistent with the reactivity of complex **1** being observed at relatively mild conditions (Table 1).

This mechanism is also consistent with the results of the deuterium-labeling experiments (Scheme 1), which show selective transfer of the hydrogen from the CH group of 2-propanol to the carbon atom of the carbonyl of acetophenone (marked as H* in Scheme 3), while no D-labeling is observed when 2-propanol-OD is used.

We then set out to find a plausible pathway to explain selective D-incorporation in TH of *N*-heterocycles. While the search of the transition state for initial hydrogenation of C=N bond of 1,5-naphthyridine or quinoline was not successful, we found an accessible pathway which involves first transfer hydrogenation of the C=C bond (in C3-C4 positions) of the heterocycle followed by TH of the C=N bond (Scheme 3 and Supp. Info, Scheme S1). In the case of 1,5-naphthyridine, after initial formation of **A** via dehydrogenation of 2-propanol, 1,5-napthtyridine undergoes concerted transfer of the proton and the hydride at the C-3 and C-4 positions, respectively, via transition state **TS2-BA**, which provides a highest barrier along the reaction pathway of 22.77 kcal mol^{-1}. This process eventually leads to elimination of 3,4-dihydro-1,5-naphthydirine intermediate and complex **A**. The transition state involves increase of the Mn···H (from 1.602 to 1.745 Å), O···H (from 0.976 to 1.124 Å) and shortening the C···H distances (1.156 and 1.545 Å) of 3,4-dihydro-1,5-naphthyridine (Figure 3, TS2-BA); this transition state is characterized by one imaginary frequency of –844.8 cm^{-1}. The **TS2-BA** is additionally stabilized by H-bonding interaction of the ligand OH group with the second nitrogen of 1,5-naphthyridine, N-5, which is absent in quinolone, which might also lead to higher barriers (see Supp. Info, Scheme S1 and Figures S67, S70). The selectivity of orientation of the C=C bond of 1,5-naphthyridine or quinoline in such a way that only C-4-position reacts with Mn–H and not C-3 is consistent with known propensity of C-2 and C-4 positions in pyridine-like fragments to undergo nucleophilic attack, consistent with the resonance structures of these heterocycles (Scheme 4).[22]



Scheme 4. Resonance structures of 1,5-naphthyridine and quinoline.

Complex **A** can then be converted again to **B** via TH from 2-propanol as described above. The subsequent hydride and proton transfer to an imine C=N group of 3,4-dihydro-1,5-naphthyridine occurs at a lower barrier via transition state **TS3-**

BA to afford the final product, 1,2,3,4-tetrahydro-1,5-naphthyridine. The transition state **TS3-BA** is associated with migration of the proton and hydride to 1 and 2 positions of 3,4-dihydro-1,5-naphthyridine. The **TS3-BA** has one imaginary frequency of –556.5 cm^{-1}, corresponding to the movement of hydride from metal and proton from ligand to the 3,4-dihydro-1,5-naphthyridine with increase the Mn···H (from 1.602 to 1.637 Å) and O···H (from 0.976 to 1.188 Å) and shortening C···H distances (1.806 Å) and N···H (1.283 Å) of 3,4-dihydro-1,5-naphthyridine. The analogous mechanism was also calculated for quinoline as a substrate, leading to overall higher barriers, which is consistent with lower reactivity observed with this substrate (Table 4).

The results of the deuterium labeling experiments leading to selective incorporation of D-atom in C-2 and C-4 positions when 2-propanol-2-d_1 is used are thus fully consistent with the mechanism elucidated via DFT (see Scheme 3; the proton from CH group of 2-propanol is labeled as H*). On the other hand, partial deuteration in at the C-3 position is likely due to imine-enamine tautomerization in 3,4-dihydro-1,5-naphthyridine intermediate and base-catalyzed H/D exchange with OD-labeled 2-propanol.[12d]

Conclusions

In summary, we established that simple, N-donor bipyridine-ligated Mn^{I} complexes act as efficient catalysts for transfer hydrogenation of ketones and imines. For the first time, Mn-catalyzed TH of aromatic *N*-heterocycles has been reported to give saturated cyclic amines, and further studies will be directed at expanding the substrate scope of this reaction. Among several substituted bipyridines, the complex supported by dihydroxy-substituted bipyridine was superior in catalytic activity to the analogous complexes with methoxy-substituents. Deuterium labeling studies revealed a “monohydride” pathway for TH of acetophenone and showed selective D-incorporation during the TH of *N*-heterocycles. Based on DFT studies, we propose the possible pathway for the complex with 6,6’-dihydroxy-2,2’-bipyridine, in which the presence of the OH group in bipyridine ligand plays a role in the hydrogen transfer steps. In addition, we suggest a possible mechanism for stepwise TH of *N*-heterocycles consistent with the observed deuterium-labeling studies. Overall, this study sheds light on the important role of bipyridine ligand substitution in hydrogen transfer catalysis, which can be useful for the design of highly active and selective catalysts.

Experimental Section

General Procedure for ketone transfer hydrogenation. The stock solutions of complex **1** (4.9 mg, 0.012 mmol in 2.0 mL of 2-propanol) and KO^{t}Bu (4.5 mg, 0.040 mmol in 2.0 mL of 2-propanol) were freshly prepared prior to the experiment. Under a nitrogen atmosphere, 0.5 mL of a stock solution of complex **1** (containing 0.3 mol% of **1**) and 0.5 mL of a stock solution of KO^{t}Bu (containing 1.0 mol% of KO^{t}Bu) were mixed together in an 11 mL screw-cap vial and stirred for 5 min, after which the ketone (1 mmol) and 2-propanol were added (total volume of 2.0 mL). The screw top vial was closed tightly and the cap was wrapped with electrical tape to prevent atmosphere exchange. The vial was taken out of the glove box and heated in an oil bath for 24 hours at 80 °C while the contents were continuously stirred. The reaction was cooled to room temperature, filtered through Celite and washed by diethyl ether, then solvents were removed under vacuum, and the residue was purified by silica gel chromatography using *n*-hexane/ethyl acetate as an eluent. Isolated products were characterized by ^{1}H NMR and GC-MS, with spectra matching those reported in the literature.

General procedure for aldehyde transfer hydrogenation. The stock solutions of complex **1** (8.1 mg, 0.020 mmol in 2.0 mL of 2-propanol) and KO^{t}Bu (6.7 mg, 0.060 mmol in 2.0 mL of 2-propanol) were prepared prior to the experiment. Under a nitrogen atmosphere, 0.5 mL of a stock solution of complex **1** (containing 0.5 mol% of 1) and 0.5 mL of a stock solution of KO^{t}Bu (containing 1.5 mol% of KO^{t}Bu) were mixed together in an 11 mL screw-cap vial and stirred for 5 min, after which the aldehyde (1 mmol) and 2-propanol were added (total volume of 2.0 mL). The screw top vial was tightly closed and the cap was wrapped with electrical tape to prevent atmosphere exchange. The vial was taken out of the glove box and heated in an oil bath for 24 hours at 80 °C while the contents were continuously stirred. The reaction was cooled to room temperature, filtered through Celite and washed by diethyl ether, the solvents were removed under vacuum, and the residue was purified by silica gel chromatography using *n*-hexane/ethyl acetate as an eluent. Isolated products were characterized by ^{1}H NMR and GC-MS, with spectra matching those reported previously or authentic samples.

General procedure for imine transfer hydrogenation. A fresh stock solution of complex **1** (8.1 mg, 0.020 mmol in 2.0 mL of 2-propanol) and KO^{t}Bu (6.7 mg, 0.060 mmol in 2.0 mL 2-propanol) were prepared prior to the experiment. Under a nitrogen atmosphere, 0.5 mL of a stock solution of complex **1** (containing 0.5 mol% of **1**), 0.5 mL of a stock solution of KO^{t}Bu (containing 1.5 mol% of KO^{t}Bu) were mixed together in an 11 mL screw-cap vial and stirred for 5 min, after which the imine (1 mmol) and 2-propanol were added (total volume of 3.0 mL). The screw top vial was tightly closed and the cap was wrapped with electrical tape to prevent atmosphere exchange. The vial was taken out of the glove box and heated in an oil bath for 24 hours at 80 °C while the contents were being stirred. The reaction was cooled to room temperature, filtered through Celite and washed by diethyl ether, the solvents were removed under vacuum, and the residue was passed through a short plug of silica gel using ethyl acetate as an eluent. Isolated products were characterized by ^{1}H NMR and GC-MS.

General procedure for *N*-heterocycle transfer hydrogenation. Complex **1** (8.2 mg, 2 mol%), KO^{t}Bu (6.8 mg, 6 mol%) and 2-propanol (1.5 mL) were mixed together in an 11 mL screw-cap vial and stirred for 5 min, after which the heterocyclic compound (1.0 mmol) and 2-propanol were added (total volume of 2.5 mL). The screw top vial was tightly closed and the cap was wrapped with electrical tape to prevent atmosphere exchange. The vial was taken out of the glove box and heated in an oil bath for 24 hours at 80 °C while the contents were continuously stirred. The reaction was cooled to room temperature, filtered through Celite and washed by diethyl ether, then solvent was removed under vacuum, and the residue was passed through a short plug of silica gel using ethyl acetate as an eluent. Isolated products were characterized by ^{1}H NMR and GC-MS.

Computational details. The DFT calculations were performed at m06 level of theory[23] using Gaussian 09.[24] The LANL2DZ ECP's[25] and valence-basis sets were used at Mn. For rest of the atoms, 6–31+G (d, p) were employed.[26] The structures reported are either minima (NIMAG =

0) or transition states (NIMAG = 1) on the potential energy surface. The IRC calculations were performed to confirm the nature of each transition state. The solvation energies were calculated in 2-propanol (ε = 19.26) using CPCM model.[27] Important bond parameters for the intermediates and the transition states (TS) are provided in Figure 3. The computed reaction profile along with calculated solvent-corrected energies (Scheme 3 and Supp. Info, Scheme S1 and Figures S67-S70) and atomic coordinates are provided in the Supp. Info.

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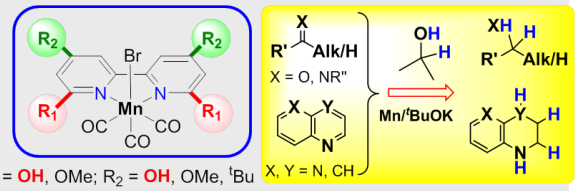
✓ ***OH** groups enable high reactivity*



R_1 = **OH**, OMe; R_2 = **OH**, OMe, ^{t}Bu

Simple but versatile substituted bipyridine Mn complexes catalyze transfer hydrogenation of ketones, aldehydes, imines and even such challenging substrates as aromatic *N*-heterocycles. The presence of OH groups in bipyridine is crucial for high catalytic reactivity.

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Transfer hydrogenation of carbonyl groups, imines and *N*-heterocycles catalyzed by simple, bipyridine-based Mn^I complexes