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Efficient and practical transfer hydrogenation of ketones catalyzed by a simple bidentate Mn-NHC complex

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Abstract: Catalytic reductions of carbonyl-containing compounds are highly important for the safe, sustainable, and economical production of alcohols. Herein, we report on the efficient transfer hydrogenation of ketones catalyzed by a highly potent Mn(I)-NHC complex. Mn-NHC 1 is practical at metal concentrations as low as 75 ppm, thus approaching loadings more conventionally reserved for noble metal based systems. With these low Mn concentrations, catalyst deactivation is found to be highly temperature dependent and becomes especially prominent at increased reaction temperature. Ultimately, understanding of deactivation pathways could help close the activity/stability-gap with Ru and Ir catalysts towards the practical implementation of sustainable earth-abundant Mn-complexes.

The reduction of ketones to their corresponding alcohols is an important transformation for the production of pharmaceuticals, flavors, fragrances, and agrochemicals. Catalytic transfer hydrogenation (TH) protocols offer an attractive and sustainable alternative to well-known stoichiometric approaches.[3] Recently, the development of non-noble metal catalytic systems has been achieved, based on abundant 3d transition metals such as Fe, Co, and Mn, which have received significant attention.[2] This has led to an impressive expansion of the field and the discovery of novel reactivity patterns of 3d metals versus their noble metal analogues. Remarkably, of the Mn-catalysts currently discussed in the open literature,[3a] several of the most active systems do not rely on phosphine ligands, but instead are based on simple bidentate N-donors (Scheme 1, A-C).[3b, 3h, 3i, 4] Sortais and co-workers reported on the use of 2-picolylamine as a ligand for Mn, while also disclosing a series of in-situ systems bearing bidentate diamines as ligands.[3b, 3c] Additionally, the group of Khusnutdinova very recently disclosed a Mn-bipyridine-derived complex which showed good activity for the TH of ketones, aldehydes, and imines at 0.3 mol% Mn (3000 ppm Mn; 330 TON).[5]

However, several challenges remain to be addressed before earth-abundant catalytic systems can be practically utilized in (industrial) organic synthesis. For example, compared to noble metals, reported metal loadings for 3d transition metals (TM) remain up to four orders of magnitude higher at several thousands of ppm (i.e., 0.1 – 1.0 mol%).[1, 5] Although catalyst consumption typically is not a large concern for academic researchers, it likely presents a critical hurdle for any commercial application. Moreover, in order to reduce operational cost it is desirable to replace highly complex, synthetically challenging, and expensive phosphines for simpler and more scalable alternatives.

N-Heterocyclic carbenes (NHCs) in principle meet the main requirements to replace phospine donors. The steric and electronic properties of NHCs are highly tunable, their synthesis is well established, scalable, and can conveniently be performed in air.[6] Introduction of NHC to noble metals has been very successful, resulting in highly active and (enantio-)selective hydrogenation catalysts for a variety of chemistries.[7] Following these works, several groups have reported the synthesis of Mn(I)-NHCs[8] and their applications in reduction catalysis (Scheme 1, D & E).[3c, 9] Taking notice of the recent developments in the field of Mn(I)-NHC catalysis, we hypothesized that the combination of a bidentate ligand bearing a strongly donating NHC group and an amine donor function could lead to a highly active and stable catalytic system. At the same time such a complex would maintain attractive ligand simplicity. Based on prior work with NHCs in our group[7d, 7e], we sought to synthesize and test two simple bidentate Mn-NHC complexes 1 and 2 (Scheme 1).

![Scheme 1. Mn-complexes for sustainable reduction catalysis.](image_url)

Herein, we report on the catalytic transfer hydrogenation of a broad scope of aromatic and aliphatic ketones with novel Mn(I)-NHC complex 1 (Scheme 1). The catalyst shows unprecedented activity and turnover numbers (TONs) and enables quantitative alcohol yields at Mn concentrations as low as 75 ppm (0.0075 mol%), thereby reducing the activity-gap with noble metal based systems[1, 10] by two orders of magnitude.
Ligands L1 and L2 were prepared by reaction of 1-mesityl-1H-imidazole with the corresponding 2-bromoethylamine hydrobromide salt (Scheme 2). We found that the removal of HBr and subsequent ion metathesis to the hexafluorophosphate analogues of L1/L2 was required to obtain the target complexes in their pure form. Compounds 1 and 2 were further obtained by reaction of the in-situ generated free carbene with Mn(CO)5Br in THF. Recrystallization from DCM/Et₂O produced analytically pure materials that were fully characterized with 1H/13C NMR, FTIR, single-crystal X-ray structure determination, and elemental analysis (see Supporting Information).

Scheme 2. Synthetic procedure for Mn(I)-NHCs 1 and 2.

The FTIR spectra of 1 and 2 each feature three sharp peaks around 2004, 1919, and 1892 cm⁻¹, indicative of an octahedral complex in which the three CO ligands are bound in cis-fashion. Single-crystal X-ray analysis confirmed the octahedral geometry and revealed the formation of Mn(I)-NHC bonds with lengths of 2.053 Å in 1, and 2.055 Å in 2, respectively (Figure 1). Coordination of the ligand to Mn effectively locks the configuration of the ethylene linker in place. As a consequence, equivalency of the geminal protons within the ethylene linker fragment is lost and they appear as four independent resonances in 1H NMR (see SI).

Figure 1. ORTEP diagram of 1 (left) and 2 (right). Thermal ellipsoids are drawn at 30% probability. Hydrogen atoms (except bound to N and NMe) and co-crystallized solvent are omitted for clarity.

Complex 1 is a highly active pre-catalyst for TH of ketones with PrOH. Fully methylated analogue 2 is inactive under the selected conditions (Table 1, entries 1-2). Initial experiments were performed using acetonophene as a model substrate at 50 °C and 0.5 mol% Mn. Increased reaction temperature allowed a tenfold reduction of catalyst loading down to 0.05 mol% (500 ppm) and resulted in quantitative yields of 1-phenylethanol within 1 h (Table 1, entries 3-5). Further reduction of catalyst concentration led to incomplete reaction progress, while achieving a high turnover number of 4700 at 100 ppm loading (Table 1, entries 6-7). This indicates 1 is catalytically active and remarkably stable over a large number of turnovers and potentially allows for additional optimization. Next, we investigated critical reaction parameters such as base loading, solvent, and the nature of the hydrogen donor to optimize catalysis with 1 (see SI). Presence of 2 eq. KOtBu to Mn was insufficient to quantitatively activate 1 at this low catalyst concentration of 0.05 mol% Mn (Table S2). We believe this effect is caused by traces impurities in the solvent that react with the base. Generally, highest conversions were observed when hydrogen donors were used as the co-solvent (Table S3). Strongly coordinating solvents such as MeOH and EIOH led to (almost) fully diminished performance, while aliphatic media gave intermediate results. When used neat, secondary alcohol donors 2-propanol, 2-butanol, and 3-methyl-2-butanol all resulted in virtually identical alcohol yields (Table S4). Reaction with the formic acid/NEt₃ mixture or potassium formate as the alternative hydrogen donor unfortunately did not lead to any activity. Thus, all subsequent reactions were performed in neat PrOH with 1 mol% KOtBu as the base relative to the reaction substrate.

**Table 1.** TH of acetonophene with 1 and 2.[⁴]

| Entry | Catalyst | Temp. [°C] | Yield [%] | TON |
|-------|----------|------------|-----------|-----|
| 1     | 1 (0.5 / 5000) | 50         | 92        | 184 |
| 2     | 2 (0.5 / 5000) | 50         | 1         | 2   |
| 3     | 1 (0.5 / 5000) | 80         | 93        | 186 |
| 4     | 1 (0.1 / 1000) | 80         | 94        | 940 |
| 5     | 1 (0.05 / 500) | 80         | 94        | 1880|
| 6     | 1 (0.02 / 200) | 80         | 85        | 4250|
| 7     | 1 (0.01 / 100) | 80         | 47        | 4700|

⁴ Conditions: 1.0 mmol acetonophene, 0.01 – 0.5 mol% Mn, 2 eq. KOtBu to Mn, 2.5 ml PrOH, T = 50 – 80 °C, 1 h. Yield determined by GC-FID using n-C₆ as IS.

Following the discrete optimization, we sought to study the influence of reaction temperature and catalyst concentration. Increased temperature induced pronounced catalyst deactivation, which became particularly noticeable at low metal loadings below ~100 ppm 1 (Figure 2 and SI). At 70 °C and 50 ppm Mn (0.005 mol%), 1 reacts with a high initial TOF of 11.800 h⁻¹ and completes 11.100 turnovers in 6 h (56 % yield). Reaction at 60 °C is slower (TOF 6100 h⁻¹), but surpasses the integral TON of reaction at 70 °C after approximately 2.5 h (TON = 9600). After 6 h the reaction is 76 % complete, after having undergone 15,100 turnovers. Further reduction of catalyst concentration to 25 ppm expedites the deactivation process and TON-crossover takes place after only 20 min (1800 TON). Under these conditions the reaction progress halts at 8 %. In contrast, at 60 °C 1 achieves a very high TON of 17,300 in 6 h and, importantly, at that time does not show signs of imminent reaction termination. These observations indicate that catalyst deactivation is independent of total catalytic turnover and must be caused by another, as of yet unknown, phenomenon. Ultimately, very good alcohol yield could be obtained in 6 h at 75 ppm 1 and 60 °C (Table S6).
Having established critical performance parameters, we performed a substrate scope to investigate the effect of several functional groups and varied electronic and steric configurations on catalysis with 1 (Scheme 3). Reactions were performed at 40 °C and 500 ppm Mn (0.05 mol%) to minimize potential detrimental effects caused by irreversible catalyst deactivation. These conditions were estimated to provide a reasonable trade-off between reaction rate, catalyst consumption, and the temperature-influenced rate of deactivation. Aromatic ketones A1 to A9 were all reduced in good to quantitative yield, except for sterically demanding 2,4,6-trimethylacetophenone A4. Aliphatic ketones were significantly less reactive towards reduction. The corresponding alcohols from ketones B1 – B4 were all obtained in fair yield of 56 %. Bulky 1-adamantyl methyl ketone B5 was only partially reduced under the selected conditions. Evidently, steric accessibility is an important factor for catalysis with 1. Long-chain aliphatic alcohols from B7 – B9 were obtained in good to excellent yield, depending on the exact location of the functional group. Dicyclohexyl methyl ketone B10 was not reduced, while reaction with B11 was not selective and resulted in extensive (cyclic) side product formation. Evidently, steric accessibility is an important factor for catalysis with 1. Long-chain aliphatic alcohols from B7 – B9 were obtained in good to excellent yield, depending on the exact location of the functional group. Dicyclohexyl methyl ketone B10 was not reduced, while reaction with B11 was not selective and resulted in extensive (cyclic) side product formation.

Chemoselectivity for carbonyl versus alkene reduction was probed with aliphatic and aromatic examples C1 and C2. 6-Methyl-5-hepten-2-one C1 was selectively reduced to the corresponding unsaturated alcohol in 67 % yield. Aromatic benzylideneacetone C2 showed good chemoselectivity and enabled production of the unsaturated alcohol in 82 % yield (90 % selectivity C=O vs. C=C, 9 % fully reduced product was observed). GC-MS suggests TH of heterocyclic compounds D1 and D2 was quantitatively followed by dehydration to 2-vinylfuran (92 % yield) and 2-vinylthiophene (68 % yield). Unfortunately, introduction of nitrogen to the heterocyclic ring led to complete loss of catalytic activity (D3 – D5). Conclusively, functional group tolerance was studied using para-substituted acetophenones E1 to E9. Incorporation of halides or a phenyl moiety had no effect on performance (E1 – E3), nor did presence of an ester (E4). Similar to the products of D1 and D2, 4-acetylaniline E5 and 4-acetanisole E6 were reduced to the corresponding vinylic products. Catalytic performance was severely decreased for substrates containing a hydroxyl (E7), cyano (E8), or nitro-group (E9). Thus, our results show that 1 is a potent catalyst for a broad scope of substrates. Strongly coordinating substrates are a limitation in the scope and lead to complete loss of catalytic activity.

To gain mechanistic insight into catalysis with 1, we investigated the pre-catalyst activation in a series of 1H NMR stoichiometric reactivity experiments (Scheme 4). Addition of 2 eq. iPrOH in presence of 2 eq. KOtBu in benzene-\(d_6\) led to the formation of two new resonances at \(\delta = -4.09\) ppm and \(\delta = -3.59\) ppm. We attribute these peaks to the two expected cis and trans Mn(I)-H species (relative to N-H), which are formed in an approximate 5:1 ratio. Under these conditions Mn-NHC is quantitatively converted into the corresponding Mn-Hs upon dehydrogenation of iPrOH. No hydrides were be observed in absence of base and iPrOH. In contrast, only ~2 % hydride signal was observed with 2, suggesting that loss of the reactive N-H functionality in 2 prevents metal-ligand cooperativity and formation of the active hydride species from iPrOH. These
findings, combined with the practical inactivity of 2, indicate catalysis with 1 likely operates via the well-established bifunctional protonation/deprotonation mechanism.\[^{[6b, 11]}\]

![Scheme 4. Stoichiometric \(^1\)H NMR studies into pre-catalyst activation.](image)

In conclusion, we have prepared the novel Mn(I)-NHC complex 1 and reported on its remarkable catalytic activity for transfer hydrogenation of ketones with PrOH. Catalysis with 1 proceeds with very high maximum TON of at least 17,000. The complex is useful at unprecedented catalyst loadings and enables quantitative alcohol yields at only 75 ppm Mn. Such loadings approach those more conventionally utilized for Ru and Ir catalysts, thus highlighting the high potential of 1 and other 3d TM-catalyzed processes for sustainable catalysis. Significant catalyst deactivation was observed at elevated temperatures, which inhibited further reduction of metal content. Therefore, we believe thorough understanding of the deactivation processes will ultimately enable a leap forward in rational catalyst design towards improved catalytic systems.

**Experimental Section**

Supporting information contains all available data for synthesis, characterization, and catalysis for this work.

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**Keywords:** Manganese • N-Heterocyclic Carbene • Transfer Hydrogenation • Ketones • Alcohols

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