Mechanistic Complexity of Asymmetric Transfer Hydrogenation with Simple Mn–Diamine Catalysts

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ABSTRACT: The catalytic asymmetric transfer hydrogenation (ATH) of ketones is a powerful methodology for the practical and efficient installation of chiral centers. Herein, we describe the synthesis, characterization, and catalytic application of a series of manganese complexes bearing simple chiral diamine ligands. We performed an extensive experimental and computational mechanistic study and present the first detailed experimental kinetic study of Mn-catalyzed ATH. We demonstrate that conventional mechanistic approaches toward catalyst optimization fail and how apparently different precatalysts lead to identical intermediates and thus catalytic performance. Ultimately, the Mn–N,N complexes under study enable quantitative ATH of acetophenones to the corresponding chiral alcohols with 75–87% ee.

INTRODUCTION

Homogeneous hydrogenation catalysis with earth-abundant 3d transition metals (TMs) such as Fe, Co, and Mn has received remarkable attention from the catalytic community in recent years as a benign and sustainable alternative to processes involving noble metals.1,2 This increased focus has led to the rapid development of highly potent first-row transition metal catalysts for a vast number of transformations involving hydrogen-transfer steps, such as hydrogenations, dehydrogenations, and coupling reactions.3–7 While Ru and Ir remain the conventional metals for these reactions,8 several examples have emerged of early TMs matching or even surpassing the catalytic activity of noble metals, highlighting the vast chemical potential of this class of homogeneous catalysts.9–12

In addition, first-row TM catalysts exhibit striking reactivity patterns unprecedented in hydrogenation catalysis.13,14 A chemically distinct feature of some manganese hydrogenation catalysts is that they do not rely on commonly employed strong donor ligands such as phosphines.15,16 Indeed, for Mn, the introduction of simple bi- or tridentate nitrogen-donor ligands was sufficient to promote hydrogenation of carbon dioxide to formate and formamide17 and transfer hydrogenation of C=X bonds (X = O, N), e.g., ketones, imines, and aldmines.18–25

In order to understand the origin of catalytic activity and causes for the current limitations of Mn systems, we carried out a detailed mechanistic and kinetic study of Mn catalysts in the asymmetric transfer hydrogenation of ketones. The groups of Kirchner,26 Clarke,27 Beller,28,29 and Morris30 reported the use of Mn catalysts bearing multidentate phosphine ligands for the asymmetric hydrogenation of ketones. However, we decided to focus on simpler diamine-based Mn catalysts, as were reported by Sortais and co-workers.31 From a practical and cost point of view, we deemed these catalysts attractive candidates for industrial applications32,33 as the active system could be generated in situ and was shown to achieve the ATH of a large scope of aryl ketones. After an extensive screening of (chiral) diamines, the combination of 1 mol % Mn(CO)5Br and ligand (1R,2R)-N,N′-Me2-DPEN was identified as the most potent, ultimately enabling good to quantitative yields of corresponding alcohols with 30–90% enantiomeric excess (ee) (Scheme 1).

Scheme 1. Chiral Mn–N,N Catalysts for Asymmetric Transfer Hydrogenation of Ketones
Thus far, the open literature does not provide substantial mechanistic analysis of Mn-catalyzed ATH due to the lack of isolated or well-defined bidentate Mn complexes for the asymmetric transfer hydrogenation of ketones. Herein, we describe the identification, isolation, and characterization of a series of simple chiral Mn−N,N catalysts. The combination of stoichiometric reactivity studies, DFT calculations, and analysis of reaction kinetics allowed the complex reactivity patterns of apparently simple Mn−N,N catalysts to be identified in the asymmetric transfer hydrogenation of ketones.

**In-Situ Screening and Precatalyst Isolation.** We began our studies by evaluating a series of readily available chiral diamines and aminophosphines as ligands for the Mn-catalyzed ATH of acetophenone (Scheme 2). The Mn complexes were prepared by stirring Mn(CO)5Br with 1 equiv of the chiral ligand in toluene at room temperature for 15 min. The toluene solution with the Mn/L-combination was transferred into iPrOH containing the substrate and KOtBu as a base. In these initial experiments, a catalyst loading of 1 mol % with respect to acetophenone was used, while base was present at 10 mol %. The highest catalytic activities were observed for bidentate aminophosphine ligands L6, L9, and L10, unfortunately with low ee’s not exceeding 20%. In contrast, a high enantiomeric excess of 76% was achieved with tosyl protected DPEN ligand L8 but at a much lower conversion compared to the unprotected DPEN ligand L7. Interestingly, dialkylated diaminocyclohexanes (L2 and L4) led to modest catalytic activity combined with good enantioselectivity, whereas nonalkylated analogue L1 was less active and selective, and tetra-alkylated ligand L5 showed no activity at all.

Having identified N,N′-dimethyl 1,2-diaminocyclohexane L4 as the best ligand in our initial evaluation in terms of the trade-off between activity and enantioselectivity, we sought to isolate the precatalyst formed upon complexation of L4 to Mn−(CO)5Br (Scheme 3). The corresponding complex 1 was readily formed upon refluxing in n-hexane for several hours and was obtained in 34% yield after recrystallization from DCM/n-hexane/diethyl ether at −20 °C. The compound was fully characterized using 1H/13C NMR, FT-IR, elemental analysis, and single-crystal X-ray analysis (see the Supporting Information).

Upon complexation, the methyl groups in L4 lose equivalency and appear in 1H NMR of 1-Cis as two sharp doublets at δ = 2.9 ppm and δ = 2.7 ppm in CD2Cl2.
hypothesize that the observed dissimilarity of the methyl groups originates from the locked chair conformation of the cyclohexane ring due to chelation to Mn. The different steric environments of the axially and equatorially bound nitrogen atoms (i.e., varied proximity to ring-bound C−H) lead to the observation of the two distinct signals. The NH resonances of 1-Cis are present as two broad singlets at \( \delta = 3.3 \) ppm and \( \delta = 2.6 \) ppm, further indicating the chemical inequivalence of the amino groups (see the Supporting Information for full characterization).

Under the selected reaction conditions, we could observe the formation of a secondary product that has a distinct \(^1\)H NMR spectrum from 1-Cis. This complex features a \(^1\)H NMR spectrum in which resonances from the NH and N−Me groups overlap and produce a band of signals between \( \delta = 3.0−2.8 \) ppm. This compound could be separated from 1-Cis by slow vapor diffusion crystallization from the original mother liquor by further addition of n-hexane (see the Supporting Information, 1-Trans, procedure A).

Single-crystal X-ray diffraction data of both products revealed their identities as cis and trans isomers. The solid-state structure of 1-Cis features the methyl groups bound in cis fashion, both oriented in opposite direction to the bromide ligand bound in the axial position of octahedral complex 1-Cis.

Figure 1. ORTEP diagrams of 1-Cis (left) and 1-Trans (right). Thermal ellipsoids are drawn at 30% probability. Co-crystallized solvent and hydrogen atoms (except bound to nitrogen and N−Me) have been omitted for clarity.

Figure 2. Proposed catalytic cycle for asymmetric transfer hydrogenation with 1-Cis. \( \Delta G \) and \( \Delta G^\dagger \) represent reaction and activation Gibbs free energy changes in kJ mol\(^{-1}\) at 333 K, respectively. Cycle for formation of (R)-product shown.
The second product was identified as 1-Trans, a minor isomer (<20%) of 1 in which the NH protons are oriented trans (Figure 1). The ratio of 1-Cis/1-Trans was found to be strongly dependent on the complexation conditions; a nearly inverse ratio of 1-Cis/1-Trans was obtained when the reaction was performed in dichloromethane at 25 °C (Scheme 3).

Isomers 1-Cis and 1-Trans did not interconvert upon prolonged heating at 70 °C in THF-δ₆ or C₆D₆, indicating that their formation and relative abundance is a kinetic ratio governed by synthetic conditions rather than chemical exchange phenomena. Additionally, no ligand substitution occurred when 1-Cis or 1-Trans was refluxed in benzene in the presence of 2 equiv of triphenylphosphine, further confirming their thermal and chemical stability. The presence of a 2-fold L₄ excess during complexation did not result in the formation of cationic [Mn(L)₂(CO)₄]⁺ species, which are frequently observed when stronger phosphine-donor ligands are utilized.27,28,34

With the isolated complexes 1-Cis and 1-Trans in hand, we tested whether they would have different catalytic performances. Both complexes, however, produced a virtually identical yield of (R)-1-phenylethanol of ∼40% in 1 h at 60 °C with 74% ee, which is a slight improvement in performance over the situation when the catalyst was generated in situ (Table S2). Preactivation of precatalysts 1-Cis and 1-Trans with NaHBEt₃ allowed the catalytic reaction to be operated base free. Catalytic performance was not improved and was identical for both complexes, again indicating that the catalytically active species formed from precatalysts 1-Cis and 1-Trans are identical.

Mechanistic Investigations and Origin of Stereoselectivity. We next employed density functional theory (DFT) to rationalize the observed trends in catalysis with complexes 1-Cis and 1-Trans. The reaction mechanism was

“Dotted yellow lines highlight steric interactions of unfavorable high-energy TS.”

(Figure 1).
Stereoselectivity, as it may lead to preferential precoordination of four combinations for Re. Therefore studied the enantiodeterminative step in more detail and complete the catalytic cycle. A low barrier of only 12 kJ mol⁻¹ readily reacts with free iPrOH in an exergonic reaction with a high barrier of 60 kJ mol⁻¹ and results in the formation of reactive Mn–alkoxide resting state VI. Liberation of the 1-phenylethanol product is an activated process with a high barrier of 60 kJ mol⁻¹ and results in the formation of reactive Mn–amido intermediate VII–I. Deprotonated complex VII–II readily reacts with free PrOH in an exergonic reaction with a low barrier of only 12 kJ mol⁻¹ to regenerate MnOPr species II and complete the catalytic cycle.

Cis-complex 1-Cis possesses two accessible and reactive N–H moieties (H¹ and H² in Figure 2), whereas trans-ligated systems only bear one (H³). The steric environment of both N–H’s, however, is different because of the close proximity of up-and-down oriented carbon/hydrogen atoms in the cyclohexyl ring (Scheme 4). This difference potentially impacts stereoselectivity, as it may lead to preferential precoordination of the Re or Si face of acetoephone to 1-Cis and 1-Trans. We therefore studied the enantiodeterminative step in more detail using DFT and calculated the energies for coordination of the N–H’s to both forms of 1-Cis and two for 1-Trans (Scheme 4). These studies revealed preferential formation of (R)-1-phenylethanol for both conformers which originates from coordination of the Si face to proton H¹. Enantioselective induction is predominantly achieved through steric repulsion between the substrate CH₃ and nearby ligand-bound CH and NH (transition states for 1-Cis shown in Scheme 4).

The catalytic cycle starts by activation of precatalyst 1-Cis with KOtBu and PrOH (or KOiPr, created in situ) to form Mn–isoproxy complex II, which is a resting state in the catalytic cycle. β-Hydride elimination of the anionic isoproxy ligand with concomitant formation of Mn–hydride complex III proceeds with the highest activation Gibbs free energy in the catalytic cycle of 70 kJ mol⁻¹. Acetone is removed from III to produce catalytically active Mn–hydride IV. The ketone substrate subsequently coordinates to IV via NH-assisted hydrogen bonding, forming Mn-adduct V, and reacts endergonically (ΔG°(Ⅲ)= 30 kJ mol⁻¹, ΔG°(Ⅳ)= 39 kJ mol⁻¹) through enantiodetermining hydride transfer, leading to the formation of Mn–alkoxide resting state VI. Liberation of the 1-phenylethanol product is an activated process with a high barrier of 60 kJ mol⁻¹ and results in the formation of reactive Mn–amido intermediate VII–I. Deprotonated complex VII–II readily reacts with free PrOH in an exergonic reaction with a low barrier of only 12 kJ mol⁻¹ to regenerate MnOPr species II and complete the catalytic cycle.

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to be remarkably stable at temperatures tested up to 75 °C and does not produce any dehydrogenation products (e.g., acetone). This observation is in stark contrast to the behavior of aminopincer Mn−PNP or Mn−NHC complexes, which are known to promote secondary alcohol dehydrogenation and typically form readily observable manganese−hydride complexes. Complex II, however, reduces acetophenone to the corresponding alcohol, despite the notable absence of detectable hydride resonances in 1H NMR (Figure S25). Furthermore, II−OtBu is resilient toward heterolytic hydrogen activation under basic conditions and did not form detectable amounts of Mn−hydride species upon pressurization with 3 bar of hydrogen gas.

We hypothesized that the introduction of more sterically demanding N-alkyl groups on the chiral ligand could improve the stereoselectivity. To test this hypothesis, complex 1-Trans−iPr was prepared (Scheme 6). ATH of acetophenone with 1-Trans−Pr led to the formation of (R)-1-phenylethanol with an identical ee of 71% as with 1-Cis and 1-Trans, while catalytic activity was dramatically reduced to only one turnover (Table S2). Fully methylated complex 2 did not show any catalytic activity, therewith stressing the importance of accessible NH protons and confirming the proposed bifunctional mechanism involving protonation/deprotonation of the amino group of 1-Cis and 1-Trans.

Compounds 1-Cis and 1-Trans are moderately enantioselective ketone transfer hydrogenation catalysts, which may be beneficial for future benchmarking of computational models and methods. We carried out a detailed kinetic analysis of the ATH using acetophenone as a model substrate with 1-Cis. At 60 °C, complex 1-Cis (0.5 mol %) reacts with an initial turnover frequency of 79 h⁻¹ and (R)-1-phenylethanol is produced quantitatively in 4 h with 73% ee. The initial reaction rates increase with increased catalyst loading (0.1−1.0 mol %).
and are in agreement with a catalyst reaction order of 1.0 (Figure 3a,b and the Supporting Information). The influence of base concentration on precatalyst activation and the catalytic reaction rate was evaluated at various base loadings (see the Supporting Information). No effect is observed when 2−20 equiv of base relative to 1-Cis was used, while lower base concentration resulted in reduced catalytic performance. Additionally, the catalyst reaction order in the presence of a large excess (5 mol %) of KOtBu similarly was equal to 1.0 (see the Supporting Information). Thus, all observations suggest that base solely acts as the precatalyst activator and does not play a significant role in the catalytic cycle for ATH.

The interpretation of kinetic data for acetophenone and iPrOH is less straightforward and revealed orders of 0 and 0.6, respectively (Figure 3c−f). Previously, Heeres and co-workers have derived a kinetic rate equation for the Ru-catalyzed ATH of ketones, taking into account effects caused by the reverse reaction (terms in the nominator), and effects due to catalyst inhibition by acetophenone (A), iPrOH (B), 1-phenylethanol (C), and acetone (D) (terms in the denominator), with parameters $k_1$, $m$, $n$, and $p$, as the reaction orders for inhibition caused by the respective reaction component (eq 1).

$$\frac{-dA}{dt} = -r_A = \frac{k_1^AC_AC_B - k_1^CC_C}{1 + k_2^AC_A + k_3^C_D}$$  

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The predicted facile formation of Mn−alkoxide II also provides a rationalization for the positive fractional reaction order of the hydrogen donor and solvent, iPrOH. If inhibition by iPrOH is much faster than substrate inhibition (i.e., $k_3^C_A > 1 + k_2^C_A$) and $C_A$ effectively is constant, eq 2 can be further reduced to eq 3. The extent of inhibition by iPrOH, as expressed in parameter $m$, directly impacts the observed reaction order in iPrOH, leading to the positive fractional reaction order value of 0.6 for ATH with 1-Cis.

$$\frac{-dA}{dt} = -r_A = \frac{k_1^AC_A}{k_3^C_D}$$  

The relative stability of Mn−alkoxide complexes in hydrogenations has been observed before by our group for closely related Mn−P,N complexes. This led us to investigate the extent of product inhibition in ATH with 1-Cis by means of additional stoichiometric reactivity studies. The Mn−1-Cis and the kinetic rate equation simplifies to eq 2. Both DFT and stoichiometric reactivity studies suggest a rapid reaction of the activated complex with iPrOH (B) to MnOiPr complex II. The $\beta$-H elimination step to convert II to Mn−hydride III and acetone is the rate-determining step (RDS) in the catalytic cycle. Subsequent elementary reactions lead to transfer of the hydride to acetophenone through a sequence of low-barrier transformations (Figure 2). This process is similar to conventional saturation kinetics and is consistent with a zeroth order reaction rate in acetophenone, since the substrate is not involved in the RDS.
phenylethoxide complex $\text{II} - \text{OPhEt}$ was detected with $^1\text{H}$ NMR after reaction of 1-Cis or $\text{II} - \text{OtBu}$ with 1-phenylethanol and base (Scheme 7). Addition of $\sim$ 3 equiv of iPrOH led to the formation of a mixture of Mn−alkoxide complexes $\text{II}$ and $\text{II} - \text{OPhEt}$, suggesting both may be present and that product inhibition cannot be ruled out in catalysis with 1-Cis.

In summary, catalyst inhibition by iPrOH is a significant process for the 1-Cis-catalyzed ATH of ketones and results in observed zeroth order kinetics for the substrate and a positive fractional reaction order for the hydrogen donor.

Activation Energies and KIE Measurements. We concluded our mechanistic studies with the determination of apparent activation energies and kinetic isotope effect (KIE) measurements to get a better experimental insight into the RDS. Acetophenone ATH with 1-Cis proceeds with an apparent, nonasymmetric activation energy of 87 kJ mol$^{-1}$ (Figure 4a). Detailed analysis of reaction rates allowed determination of the apparent $E_A$ for the formation of individual (R) and (S) enantiomers, which is particularly useful for benchmarking computational models. The reaction to (R)-1-phenylethanol exhibits a barrier of 85 kJ mol$^{-1}$, while the pathway to (S)-1-phenylethanol proceeds with a marginally higher barrier of 93 kJ mol$^{-1}$. This observed $\Delta E_A^{app}$ of 8 kJ mol$^{-1}$ for formation of both enantiomers corresponds well with the computed value of $\Delta \Delta G^\ddagger$ for ATH of acetophenone with 1-Cis (Scheme 4), with the overall observed and predicted barriers for the RDS showing some difference ($\Delta \Delta E$ of 15 kJ mol$^{-1}$; 70 kJ mol$^{-1}$ from DFT versus experimental 85 kJ mol$^{-1}$). At this moment, however, it remains unclear what is the cause of this observed divergence between theory and experiments.

Studies in $^3\text{PrOD}-d_4$ reveal a strong primary kinetic isotope effect (KIE) of 2.72 ± 0.07, consistent with hydride transfer from $^3\text{PrOH}$ being involved in the RDS of the catalytic cycle. This finding correlates well with the proposed mechanism (Figure 2), where $\beta$-hydride elimination from the coordinated isoproxyxig ligand to form Mn−hydride III was identified as the most energetically demanding transformation. When $^3\text{PrOD}$ was used, we observed a secondary KIE of 1.22 ± 0.07 (Figure 4b). Proton transfer is clearly of less importance than hydride transfer, yet this process too has a clear impact on the rate-determining processes in the catalytic reaction mechanism.

ee Erosion and Preservation. The reversible nature of the transfer hydrogenation reaction of ketones with secondary alcohols as hydrogen donors is known to induce an erosion of product enantiomeric excess. A strategy to prevent such ee erosion is to use an azetroph mixture of formic acid and triethylamine as the hydrogen donor. However, to the best of our knowledge, the reduction of ketones with 3d base metals and formic acid has not yet been reported. As with Ru-based systems, we performed the reaction under dilute conditions in order to prevent the decrease of ee over time (Figure 5a). Indeed, in the presence of a large excess of iPrOH, erosion of ee was less pronounced. Increased reaction temperature resulted in significantly reduced product ee (Figure 5b).

We hypothesized that use of a more sterically demanding ketone substrate would lead to improved ee’s compared to acetophenone (Figure 5c and d). Indeed, the ATH of isobutyrophenone under identical conditions results in quantitative production of (R)-2-methyl-1-phenylpropanol with 87% ee, albeit at a reduced reaction rate, i.e., $\sim$ 85%
TOF\(^0\) obtained with acetophenone reduction at 60 °C with 1 mol % 1-Cis.

## CONCLUSION

In conclusion, we have synthesized and characterized a series of simple chiral manganese–diamine complexes which were evaluated for their catalytic performance in asymmetric transfer hydrogenation of acetophenones. Complexes 1-Cis and 1-Trans are stereoselective ATH catalysts for the synthesis of enantio-enriched secondary alcohols in good to quantitative yields. We conducted a detailed theoretical and experimental mechanistic investigation including the first detailed kinetic study for the Mn-catalyzed ATH of ketones. Our ligand screening revealed that introduction of simple diamine ligands does not induce sufficient steric strain to facilitate high enantioselectivity. We however found that such strain cannot practically be applied on the described Mn complexes bearing N-donors while concomitantly maintaining high catalytic activity. We demonstrated that different stereoisomeric precatalysts upon activation converge to shared intermediates and thus exhibit identical catalytic performance. This renders conventional approaches toward catalyst optimization unsuccessful and thus demands more thorough studies. Mechanistic insight and the recent applications of bidentate ligands containing a NHC group\(^1,4,25\) suggest that introduction of a strongly donating but small bidentate ligand could lead to highly active and selective second-generation Mn catalysts for ATH of ketones.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscrn.9b00457.

Experimental procedures and raw kinetic data (PDF)

Coordinates of optimized structures (XYZ)

#### Accession Codes

CCDC 1903883–1903885 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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