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Manganese(I)-Catalyzed Enantioselective Hydrogenation of Ketones Using a Defined Chiral PNP Pincer Ligand

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Abstract: *A new chiral manganese PNP pincer complex is described. The asymmetric hydrogenation of several prochiral ketones with molecular hydrogen in the presence of this complex proceeds under mild conditions (30–40 °C, 4 h, 30 bar H_2). Besides high catalytic activity for aromatic substrates, aliphatic ketones are hydrogenated with remarkable selectivity (e.r. up to 92:8). DFT calculations support an outer sphere hydrogenation mechanism as well as the experimentally determined stereochemistry.*

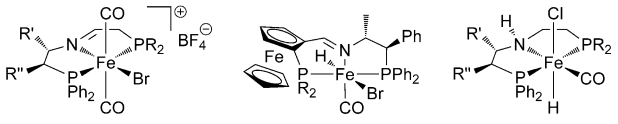
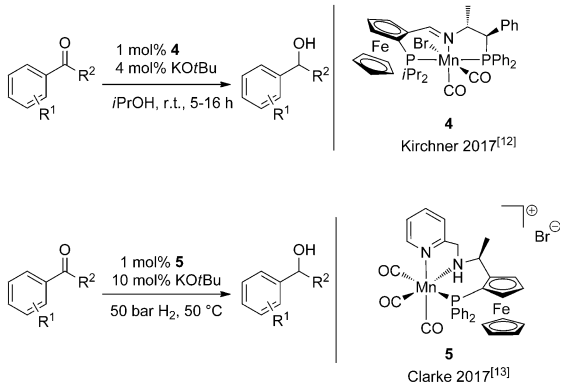


Figure 1. Different iron complexes as enantioselective catalysts for the reduction of prochiral ketones.

Chiral organometallic complexes continue to attract significant attention from academic and industrial chemists for the production of enantiomerically pure products such as pharmaceuticals, flavors, and fragrances.[1] In fact, today homogeneous asymmetric hydrogenations constitute a state-of-the-art technology, which was awarded with the Nobel Prize to Noyori and Knowles in 2001.[2] The first examples of enantioselective hydrogenations were independently developed by the groups of Knowles[3] and Horner.[4] Since then, numerous chiral phosphine ligands have been developed for a wide range of applications.[5] However, the vast majority of the resulting catalysts are based on noble metals of the platinum group like ruthenium, rhodium, and iridium as catalytically active centers. In the last decade, the replacement of these platinum-group metals by earth-abundant, inexpensive, and non-toxic transition metals like Cu[6] and Fe[7] has been intensively studied, especially to transform prochiral ketones into the corresponding secondary alcohols. Nevertheless, asymmetric catalytic applications using non-noble metals are still very limited.

An important breakthrough in this area was reported by Morris and co-workers in 2008 using a dicationic iron complex with a tetradentate P_2N_2 ligand.[7b,d,8] Subsequently, catalyst systems with pincer ligands were developed by Morris and Kirchner (Figure 1).[9] Notably, all these iron complexes predominantly hydrogenate aromatic substrates with high selectivity, while aliphatic ketones gave much lower enantiomeric ratios. In addition, related chiral complexes with tetradentate ligands were successfully introduced in the field of asymmetric transfer hydrogenation.[10]

In 2016, several seminal works described the use of manganese-based catalysts for (de)hydrogenation reactions.[11] In this respect, the first chiral Mn pincer complex (**4**) was introduced by the group of Kirchner for asymmetric transfer hydrogenation of ketones.[12] Most recently, Clarke and co-workers published the first asymmetric hydrogenation reaction by using the cationic complex **5** with a facially coordinating chiral PNN ligand (Scheme 1).[13] Remarkably, various aromatic ketones were reduced with excellent enantioselectivity; however, no asymmetric reduction was demonstrated for aliphatic substrates. This is not surprising since aliphatic ketones are much less explored and enantioselectivity values comparable to those obtained with aromatic substrates are rare, even when using noble metal-based catalysts.[14] Thus, the development of non-noble metal catalysts for the asymmetric hydrogenation of aliphatic ketones with high selectivity remains a highly challenging goal.



Scheme 1. Chiral Mn pincer complexes for asymmetric (transfer)hydrogenation.

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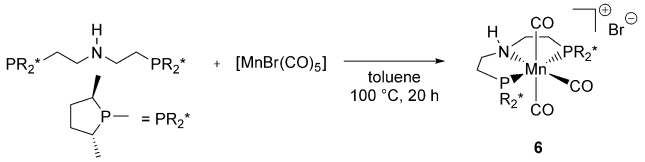
Inspired by the recent developments using homogeneous Mn catalysts,[11,15] we became also interested in Mn-catalyzed asymmetric hydrogenations of (hetero)aromatic and aliphatic ketones. To the best of our knowledge, no manganese catalysts have been described for enantioselective hydrogenations of the latter compounds.

At the start of our investigation, the new chiral pincer complex **6** with bis(2-((2*R*,5*R*)-2,5-dimethyl-phospholanoethyl))amine was obtained in 72% yield through the reaction of $[MnBr(CO)_5]$ with the corresponding ligand (Scheme 2).



Scheme 2. Synthesis of **6** by using $[MnBr(CO)_5]$ as the metal precursor.

This ligand was prepared from the TMS-protected (2*R*,5*R*)-2,5-dimethylphospholane by a modified reported procedure.[16] Elemental analysis as well as three carbonyl bands in the IR spectrum (2009, 1908, 1821 cm^{-1}) indicated that the ionic complex **6** is formed, which was also confirmed by X-ray crystallography. As shown in Figure 2 the manganese is coordinated by the pincer and three carbonyl ligands in a distorted octahedral geometry.

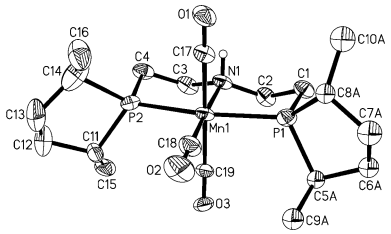
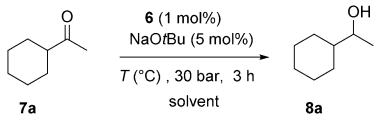


Figure 2. Molecular structure of the cationic fragment of complex **6** (for more details, see the Supporting Information). Displacement ellipsoids corresponds to 30% probability. Lower occupancy sites and hydrogen atoms except that attached to nitrogen are omitted for clarity. Selected bond lengths [Å] and angles [°]: Mn1–P1 2.2629(17), Mn1–P2 2.2741(17), Mn1–N1 2.109(3); P1-Mn1-P2 166.43(5), P1-Mn1-N1 83.06(12), P2-Mn1-N1 83.38(13).

With the well-defined chiral manganese pre-catalyst **6** in hand, we tested the hydrogenation of cyclohexyl methyl ketone (**7a**) as a model substrate for the reduction of aliphatic ketones. Initial tests applying 1 mol% **6** revealed moderate conversion at 30 bar of hydrogen and 50 °C. Interestingly, in most cases the choice of solvent had only a small influence on the enantioselectivity, while the effect on the catalyst activity is more pronounced (Table 1).

To our delight, high enantiomeric ratios (90:10 and 89:11, respectively) and complete conversion were obtained in heptane and *tert*-amyl alcohol after only 3 h favoring the *R* enantiomer (Table 1, entries 2 and 5).[17] Slightly higher selectivity (92:8 e.r.) is observed in *i*PrOH (Table 1, entry 7). From a practical point of view it is noteworthy that

Table 1: Mn-catalyzed hydrogenation of cyclohexyl methyl ketone **7a**: Optimization of the reaction conditions.[a]



Entry	Solvent	*T*	Yield[b] [%]	e.r. [%]
1	CH_2Cl_2	50	29	88:12
2	heptane	50	>99	90:10
3	Et_2O	50	63	89:11
4	toluene	50	80	90:10
5[c]	*t*AmylOH	50	>99	89:11
6	EtOH	50	24	79:21
7	*i*PrOH	50	72	92:8
8	dioxane	50	42	90:10
9[c]	*t*AmylOH	30	35	90:10
10	*t*AmylOH	30	74	90:10
11	*t*AmylOH	40	>99	92:8
12	heptane	30	>99	90:10

[a] **7a** (0.5 mmol), **6** (0.005 mmol), solvent (1 mL), NaO*t*Bu (5 mol%), 3 h, 30–50 °C, 30 bar H_2. In all cases, the *R* enantiomer is favored. [b] Yield determined by GC analysis using hexadecane as an internal standard. [c] Used as purchased—not dried.

the catalyst is also active in non-dried solvents (Table 1, entries 5 and 9). Using optimal conditions, it was possible to run the model reaction at 30–40 °C, reaching 92:8 e.r. and quantitative yield (Table 1, entries 11 and 12; see the Supporting Information for further optimizations).

To establish the general applicability of the chiral manganese pincer catalyst **6**, the hydrogenation of different aliphatic ketones was studied (1 mol% **6**, 5 mol% KO*t*Bu, 30 bar H_2, 40 °C, 4 h, *tert*-amyl alcohol). As shown in Figure 3, for the smallest cyclic aliphatic substrate cyclopropyl methyl ketone (**7b**), the e.r. decreased to 85:15, while cyclopentyl methyl ketone (**7c**) gave 87:13 e.r. at high conversion. In the case of cyclohexyl ethyl ketone, lower activity and selectivity were observed (**7d**).

On the other hand, 4-acetyltetrahydropyran (**7e**) showed high conversion and gave a good e.r. of 90:10. Similarly, different cyclic ketones with a conjugated double bond were

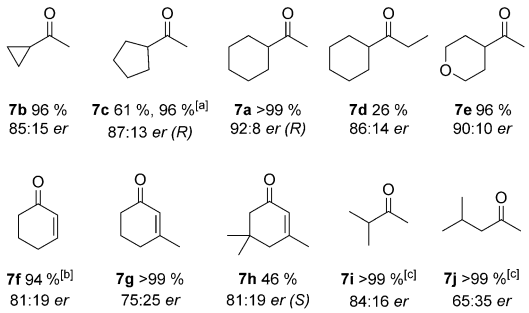


Figure 3. Manganese-catalyzed hydrogenation of aliphatic ketones. General conditions: Substrate (1 mmol), **6** (1 mol%), KO*t*Bu (5 mol%), *tert*-amyl alcohol (2 mL), 4 h, 40 °C, 30 bar H_2. Conversion was determined by GC using hexadecane as an internal standard. [a] 4 h, 80 °C. [b] **6** (2 mol%), toluene (2 mL), 4 h, 50 °C. 6% cyclohexanol. [c] **6** (2 mol%), *tert*-amyl alcohol (2 mL), 4 h, 80 °C.

smoothly reduced (Figure 3, **7f–h**). Notably, catalyst **6** is highly stereo- and chemoselective. Within this substrate class, 2-cyclohexen-1-one gave the highest e.r. value of 81:19. In addition, acyclic aliphatic ketones were tested using 2 mol% catalyst loading at 80 °C. Both substrates (**7i** and **7j**) gave full conversion; however, 3-methyl-2-butanone showed good selectivity (84:16 e.r.), while for 4-methyl-2-pentanone, a lower enantiomeric ratio (65:35) was observed.

Next to aliphatic ketones, we tested the hydrogenation of aromatic ketones. Surprisingly, the parent compound acetophenone (Figure 4, **9a**) gave only low enantioselectivity (59:41 e.r.) even under mild conditions (0.5 mol% **6**, 30 bar,

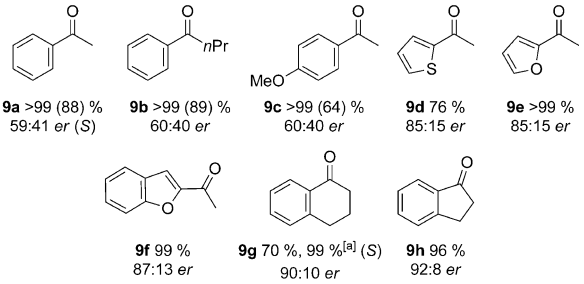
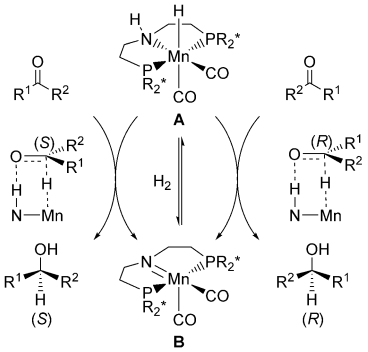


Figure 4. Manganese-catalyzed asymmetric hydrogenation of aromatic ketones. General conditions: substrate (1 mmol), **6** (1 mol%), KO*t*Bu (5 mol%), 1,4-dioxane (2 mL), 4 h, 30 °C, 30 bar H_2. Conversion was determined by GC using hexadecane as an internal standard (Yields of isolated product in parentheses). [a] At 60 °C.

30 °C, 1 h; see the Supporting Information). Similar results were observed for substituted acetophenone derivatives like butyrophenone or 4-methoxyacetophenone (**9b**,**c**). In contrast, the catalyst showed an increased selectivity for heteroaromatic substrates (**9d–f**) like 2-acetylthiophene or 2-furylmethylketone (85:15 e.r.). To our delight, α-tetralone and α-indanone (**9g**,**h**) as acetophenone analogues were also reduced to the corresponding alcohols with e.r. values up to 92:8, whereas the reaction of α-tetralone needed a slightly elevated temperature (60 °C) for complete conversion.

On the basis of the above discussed experimental results, gas-phase B3PW91 DFT computations were carried out to elucidate the enantioselective hydrogenation mechanism. Computational details are given in the Supporting Information. On the basis of our previous work,[11c,e] we propose an outer-sphere mechanism with the neutral PNP amine complex **A** and the corresponding amido complex **B** as the active catalysts (Scheme 3).[11j] The potential-energy surfaces are given in the Supporting Information. The computed and X-ray determined structural parameters of the cationic fragment of complex **6** are in excellent agreement (Table S1 in the Supporting Information).

Our computations show that the hydride complex **A** is very stable towards CO dissociation (> 42 kcal mol^{-1}). The concerted H_2 elimination from **A** to **B** has a Gibbs free energy barrier of 20.3 kcal mol^{-1} and is slightly endergonic (0.8 kcal mol^{-1}), thus indicating facile reversibility and a well-balanced equilibrium between **A** and **B** under H_2 atmosphere, close with those of ethyl-, isopropyl-, and cyclohexyl-substituted PNP Mn complexes.[11e]



Scheme 3. Proposed mechanism for ketone hydrogenation (PR_2*: chiral phospholane ligand in the *R* configuration).

Next we used cyclohexyl methyl ketone (**7a**), cyclopentyl methyl ketone (**7c**), and α-tetralone (**9g**) to test the enantioselectivity. On the basis of these prostereogenic ketones, the asymmetric induction derives from the approach of the ketone group perpendicular to the N-H and Mn-H groups in the *cis* position with either the *re* or *si* enantioface (Scheme 3); and the different steric interaction between the ketone substituents and methyl groups of the chiral phosphorus ligand in *R* and *S* configurations should be the origin of asymmetric induction. The energy difference between the transition states of the *R* and *S* configurations determines the enantiomeric ratio. Compared with the stepwise mechanism of benzaldehyde hydrogenation by non-chiral Mn PNP complexes with isopropyl groups on the phosphorous center,[11c] a concerted and strongly asynchronous transition state was located for all substrates, and this is further confirmed by the intrinsic reaction coordinate (IRC) calculations.

For the hydrogenation of cyclohexyl methyl ketone (**7a**), we found an enantiomeric ratio of 97:3 for (*R*)-1-cyclohexylethan-1-ol (Gibbs free energy barrier of 31.4/33.5 kcal mol^{-1} for the *R*/*S* transition states). For the hydrogenation of cyclopentyl methyl ketone (**7c**), the computed enantiomeric ratio is 97:3 for (*R*)-1-cyclopentylethan-1-ol (Gibbs free energy barrier of 31.4/33.5 kcal mol^{-1} for the *R*/*S* transition states). For the hydrogenation of α-tetralone (**9g**), we found an enantiomeric ratio of 97:3 for (*S*)-α-tetralol (Gibbs free energy barrier of 33.5/35.6 kcal mol^{-1} for the S/R transition states). Although the computed enantiomeric ratios are higher than the experimentally determined data (92:8, 87:13, and 10:90, respectively), the experimentally observed sense of induction is qualitatively reproduced.

To understand the origin of these energy differences, we dissected the energy of the *R*/*S* transition states. As explained in the Supporting Information (Table S5), the strain-energy difference of the catalyst between the *R*/*S* transition states dominates the energy difference for the hydrogenation of cyclohexyl methyl ketone (**7a**) and cyclopentyl methyl ketone (**7c**). For the hydrogenation of α-tetralone (**9g**), the strain-energy differences of both catalyst and substrate between the *R*/*S* transition states contribute to the strain energy. Further analysis into the root-mean-square deviations of the atomic positions of the catalyst in the *R*/*S* transition states reveals that the C16 methyl group undergoes stronger deformation

than the C10 methyl group for the hydrogenation of cyclohexyl methyl ketone (**7a**) and cyclopentyl methyl ketone (**7c**), while just the opposite phenomena were found for the hydrogenation of α-tetralone (**9g**; Figure S31).

Full conversion was observed for cyclohexyl methyl ketone (**7a**, > 99 %), while a lower conversion for cyclopentyl methyl ketone (**7c**, 61 %) and α-tetralone (**9g**, 70 %) was found under 30 bar H_2 pressure. This can be explained by the computed reaction free energies, that is, roughly thermal neutral for cyclohexyl methyl ketone (−1.0 kcal mol^{-1}), and endergonic for the aromatic one (2.9 kcal mol^{-1}). The endergonic property for α-tetralone hydrogenation indicates that the dehydrogenation reaction is favored both kinetically and thermodynamically over the hydrogenation reaction. One can expect that ketone rather than alcohol is favored under stoichiometric condition. High H_2 pressure is thus needed to shift the equilibrium to alcohol.

In addition, the computed barriers of ketone hydrogenation (30–36 kcal mol^{-1}) are much higher than the barrier of H_2 elimination from amine complex **A** to amido complex **B** (20.3 kcal mol^{-1}). This indicates that high H_2 pressure is necessary to maintain the stability of the active catalyst **A**, which is in line with the experimental conditions (30 bar H_2).

In conclusion, we describe a new type of chiral manganese pincer complex and demonstrate its applicability for the reduction of various ketones. In comparison to the manganese pincer catalyst, which was recently developed by Clarke for the asymmetric hydrogenation of aromatic ketones, our reported system preferentially reduces aliphatic ketones with high enantioselectivity. The mechanistic studies confirmed an outer sphere mechanism, whereas the calculated stereochemistry is in line with the experimental data.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric hydrogenation · chiral alcohols · chiral pincer ligands · ketones · manganese

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[17] The absolute stereochemistry of **10c** was determined by comparison with the authentic *S* enantiomer.

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Communications

Asymmetric Catalysis

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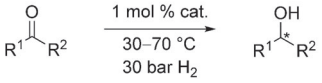
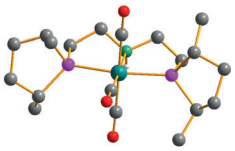
Manganese(I)-Catalyzed Enantioselective Hydrogenation of Ketones Using a Defined Chiral PNP Pincer Ligand





In a pinch: A new type of chiral manganese pincer complex (C gray, H white, Mn blue, N green, O red, P magenta) was developed and applied for the reduction of aromatic and aliphatic ketones. The asymmetric hydrogenation of several prochiral ketones with molecular hydrogen in the presence of this complex proceeds under mild conditions (30–40 °C, 4 h, 30 bar H_2).

