Manganese(I)-Catalyzed (Asymmetric) Reduction of Carbonyl Bonds

Cumulative Dissertation

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Statement of Authorship

I hereby affirm that I have written the present work by myself without outside assistance. No other resources were utilized than stated. All references as well as verbatim extracts were quoted and all sources of information were specifically acknowledged.

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Summary

This dissertation reports the synthesis of diverse non-noble metal complexes for the (asymmetric) reduction of predominantly ketones and esters to the corresponding alcohols. Mainly pincer ligands coordinated to a manganese(I) metal center were used while corresponding noble metal analogues already have demonstrated good activities in different reductions of organic compounds. Thereby, manganese(I) was used as a metal center because of its high abundance, low price and only minor toxicity in comparison to other noble metals. In addition, different bidentate PN-ligands were synthesized and tested for the reduction of esters.

For the reduction of esters, the results obtained with Mn PNP pincer complexes were compared to analogous iron complexes regarding their reactivity and selectivity. In agreement with earlier results, the investigated Et_2PNP manganese pincer complex has the highest activity by providing a comparable selectivity with respect to the iron pincer complex. Surprisingly, the manganese complexes which were coordinated to bidentate PN-ligands have shown higher activities comparable to noble metal complexes.

Regarding the asymmetric reduction of ketones, a new chiral pincer ligand was synthesized and the corresponding metal complexes with manganese, iron, rhenium, and ruthenium were prepared and fully characterized. All of them were compared to each other regarding their activity, selectivity, and especially their enantioselectivity. Herein, the chiral manganese(I) pincer complex delivered the best enantioselectivities, particularly for the reduction of aliphatic ketones.

Zusammenfassung

Die vorliegende Dissertation beschäftigt sich mit der Synthese neuartiger nicht edelmetallbasierender Metallkomplexe für die katalytische Anwendung in der asymmetrischen Reduktion von prochiralen Ketonen sowie der Reduktion von Estern zu den entsprechenden Alkoholen. In den katalytischen Untersuchungen fanden hauptsächlich Pincer-Liganden Anwendung, wobei für die Reduktion von Estern, durch die in der Literatur bekannten hohen Aktivitäten, auch verschiedene bidentate PN-Liganden und deren Komplexe in ihrer Reaktivität getestet wurden. Bei der Komplexsynthese lag das Hauptaugenmerk stets auf der Verwendung von Mangan als Metallzentrum, welches aufgrund der relativen Häufigkeit, des niedrigen Preises und der geringen Toxizität eine gute Alternative zu bereits bekannten Edelmetallsystemen bietet. Des Weiteren stand der Vergleich der Komplexe im Hinblick auf die Selektivtität und Reaktivität zu den bereits bekannten Fe-Pincer Komplexen im Vordergrund, wobei letztere bereits eine gute

Anwendbarkeit im Bereich der Ester-Reduktion gezeigt haben. Während der Untersuchungen zeigte sich insbesondere der Et_2PNP Mangan Pincer Komplex als geeignet für die untersuchte Reduktion. Darüber hinaus konnte gezeigt werden, dass die Aktivität von Mangan-Komplexen mit bidentaten PN-Liganden vergleichbar zu denen bekannter Edelmetallkatalysatoren ist. Für die asymmetrische Reduktion der Ketone wurden neben der Untersuchung eines Mangan-Komplexes auch Vergleiche der Reaktivität und Selektivität mit analogen Eisen, Ruthenium und Rhenium-Komplexen herangezogen. Hierbei erzielte der Mangankomplex die höchste Selektivität unter den getesteten Metallen, während die Edelmetallsysteme deutliche höhere Aktivitäten aufwiesen.

Inhalt

List of Abbreviations

BINAP	2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl	**MHz**	megahertz
Bn	benzyl	**NaO*t*Bu**	sodium *tert*-butoxide
cat.	catalyst	**NMR**	*Nuclear Magnetic Resonance* (Kernspinresonanzspektroskopie)
Cy	cyclohexyl	***o***	*ortho*
δ	chemical shift (NMR)	***p***	*para*
DFT	density functional theory	**Ph**	phenyl
DMSO	dimethylsulfoxide	**ppm**	*parts per million*
ee	enantiomeric excess	**rac**	racemic
equiv.	equivalents	**r.t.**	room temperature
Et	ethyl	**SP**	side product
HSAB	hard and soft acids and bases	***t*-amylOH**	*tert*-amyl alcohol
***i*Pr**	*iso*-propyl	***t*Bu**	*tert*-butyl
IR	infrared	***t*BuOH**	*tert*-butanol
J	coupling constant	***i*PrOH**	*iso*-propanol
KO*t*Bu	potassium *tert*-butoxide	**THF**	tetrahydrofuran
L-Dopa	levodopa L-3,4-dihydroxyphenylalanine	**TMS**	trimethylsilyl
Me	methyl		

Units of Measurement

The International System of Units (SI) is utilized throughout this work to measure experimental or theoretical quantities. All derived units and their expression in terms of the SI base units are given below.

Quantity	**Unit**	**Name**	**Conversion to SI base units**
Frequency	MHz	megahertz	1 MHz = 10^6 s^{-1}
	Hz	hertz	1 Hz = $1s^{-1}$
Length	Å	Ångström	1 Å = 10^{-10} m
Temperature	°C	degree celcius	T/K = T/C° - 273.15)
Volume	mL	millilitre	1 mL = $1cm^3$ = 10^{-6} m^3
Energy	kJ	kilojoule	1 kJ = $10^3 m^2 \cdot$ kg$\cdot$ s^{-2}
	calorie	calorie	1 cal = 4.2 Joules
Time	h	hour	1 h = 3600 s
	min	minute	1 min = 60 s

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1 Target and Motivation

Noble metal complexes have been well known for several decades and stand out due to their high activity for various chemical reactions. Nevertheless, the development of new catalysts, and especially new ligand systems, remains an important field in academia as well as in industry. Thereby, the focus shifts more and more towards the synthesis of non-noble metal complexes. Due to their high natural abundance, complexes of metals such as iron, cobalt and manganese are of great interest. An additional advantage of these metals is their often comparably lower toxicity compared to noble metals. Since the millennium, primarily iron metal pincer complexes have been used in homogeneous catalysis instead of Ru, Rh, and Ir analogues. Even though the iron complexes showed good activities in a variety of transformations, they still had a lower performance compared to their noble metal counterparts. In the context of this thesis, we were now interested in the synthesis of analogous manganese-based pincer complexes and their reactivity regarding the reduction of esters into the corresponding alcohols, which plays an important role in the synthesis of pharmaceuticals, flavors and fragrances.

Another strategy to synthesize alcohols is the reduction of ketones. This transformation is especially interesting for industry and academia, when prochiral ketones are reduced in an asymmetric manner to the corresponding alcohols by chiral complexes. Hence, we were especially interested in applying a chiral pincer-type catalyst, since only a few chiral iron pincer complexes were described at the beginning of this work for the asymmetric hydrogenation of ketones. Thereby, only one of them displays a good activity, while the desired enantiomerically enriched alcohol was produced with moderate selectivity. For this reason, we were interested in synthesizing new chiral pincer ligands and the corresponding non-noble metal catalysts. These shall then be tested regarding their activity and selectivity within the asymmetric hydrogenation of ketones.

2 Introduction – Homogeneous Catalysis

Catalysis in general, and especially acid or base catalyzed reactions, have been known since the sixteenth century.[1] The term “catalysis” was introduced in the nineteenth century by the Swedish chemist J. J. Berzelius, who defined it as the “*power which seems definitely to consist, in a faculty of bodies, by their simple presence, and without any chemical participation, to rouse up the play of certain affinities which at that temperature remained inactive, so as to determine, in consequence of a new arrangement of the elements of the compound…The substance which produces the decomposition undergoes no alteration; nor does it become an element of the new compound, and therefore it operates by an inherent power… I Hence will name it the catalytic force of the substances, and I will name decomposition by this force catalysis.*”[2] The term catalysis was subsequently further developed by diverse chemists. In 1902 Oswald described a catalyst in more familiar terms, which would still be used today. He wrote that a catalyst is a substance that increases the rate at which a chemical system reaches its equilibrium without having an influence on the position of the equilibrium. It participates in the chemical reaction but is not itself consumed and is in some cases able to direct a reaction towards certain products.[3]

Table 1. Comparison of homogeneous and heterogeneous catalysis.[3]

Parameter	Catalysis	
	Homogeneous	Heterogenous
Active Centers	All the metal atoms	Surface atoms only
Concentration	Low	High
Catalyst structure	Definite	Indefinite
Catalyst stoichiometry	Definite	Indefinite
Catalyst variability	Very high	Little
Catalyst regeneration	Complicated	Easy
Reaction conditions	Mild	Harsh (high Temp. and pressure)
Activity	High	Low
Determination of catalyst composition	Rather complicated	Easy
Stability	Low	High
Deactivation through poisoning	Difficult	Common

Today, catalysis is a major subject of chemistry research in academia and industry, especially for the synthesis of e.g. pharmaceuticals, fine chemicals, agrochemicals and plastics.[4] Traditionally, the field of catalysis is divided into two main parts: homogeneous and heterogeneous catalysis.[3] Both can be distinguished by the physical state of the reaction mixture. Whilst the former takes place in one homogeneous phase, the latter consists of at least two phases (for a comparison see Table 1).[5] This thesis focusses on homogeneous catalysis, which is still less applied in industry, but is becoming increasingly prevalent, especially for the synthesis of fine chemicals. This is mainly due to the greater difficulty in regeneration and extraction of homogeneous catalysts from reaction solutions in most cases. For industrial applications, in particular, this recycling has a strong economic and ecological impact.[3] Nevertheless, the investigation of new homogeneous catalysts and their mechanistic studies is a rapidly expanding field of research. The driving force behind this development is largely, due to the different type of interaction between homogeneous catalysts and the substrates. Consequently, homogeneous catalysts can be assumed to be more rationally developed compared to heterogeneous alternatives.

The field of homogeneous catalysis can be divided into different subgroups, depending on the nature of the active catalyst species: acid-base catalysis, catalysis by metal ions, organometallic catalysis, organocatalysis and bio-catalysis. These subgroups were again applied for diverse fields of different reactions. Herein, the work concentrates on organometallic catalysis, which can be considered the most important area in homogeneous catalysis. In this case, a transition metal is coordinated by an organic ligand which is able to influence the metal center sterically and/or electronically. This circumstance allows the synthesis of tailor-made catalysts with predictable features for certain types of reactions, e.g. hydrogenation, hydroformylation, carbonylation, decarbonylation, oxidation reactions, etc.

The following chapters will deal with homogeneous hydrogenation reactions of carbonyl bonds, especially, by using novel achiral, as well as chiral pincer complexes.

2.1 Hydrogenation Catalysis of Carbon-Oxygen Bonds

Homogeneous hydrogenation reactions using metal complexes are one of the most explored fields in the area of homogeneous catalysis and describe the reduction of unsaturated multiple bonds (e.g. C=C, C=O or C=N multiple bonds) using molecular hydrogen.[6] Due to the usage of molecular hydrogen, this method becomes more advantageous with respect to costs and waste formation compared to classical stoichiometric reducing agents, e.g. with metal hydrides like $NaBH_4$.[7] In addition, stoichiometric reducing agents typically have a lack of chemoselectivity when being applied to multi-functionalized substrates.

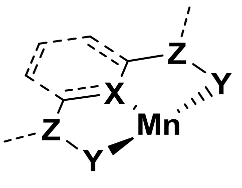
This work is predominantly focused on the hydrogenation of C-O multiple bonds under homogenous conditions. Indeed, the reduction of C-O double bonds is a fundamental reaction in the production of fine and industrial chemicals, while the feasibility of the reduction of different carbonyl bonds depends on the nature of the substrate and its electrophilicity.[8] Thus, aldehydes and ketones are relatively easy to reduce in comparison to esters or carboxylic acids regarding their lower electrophilicity.

Until now, ruthenium[9–13] based complexes are still some of the most efficient homogeneous hydrogenation catalysts beside rhodium[14], iridium[15] and palladium[16] (platinum group metals). The previous research has pointed out that low-valent complexes stabilized by tridentate phosphorous ligands offer the best activity regarding the activation of hydrogen. Therefore, the proceeding research is still focusing on this motif, especially by synthesizing so called pincer complexes, which will also be the main focus of this thesis (see chapter 2.2).

During the last years, the number of implemented platinum group metal catalyzed processes has been in decline, owing to their high price, in conjunction with their high toxicity. Especially, within the production of pharmaceuticals, noble metal traces must be kept within a small ppm range.[17] Thus, the removal of noble metal residues from the product can make a process unprofitable. For that reason, since the start of the twenty-first century, researchers in academia and industry pay more and more attention to the development of non-noble metal catalysts. Intense focus was on first row transition metals like iron, cobalt and nickel and especially iron pincer complexes, which in some cases showed comparable activities and selectivities to their noble metal analogues.[18,19,20] Furthermore, during the last three years, manganese-derived pincer complexes have attracted the attention of the catalytic community, despite the first catalysts being published in 1996.[21,22,23] Nevertheless, manganese is generally a cheap, earth abundant and biocompatible alternative to precious metals. However, it should be recognized that for most catalysts, especially asymmetric catalysts, the price of the chiral ligand determines the overall catalyst costs.

2.2 Hydrogenation Catalysis with Achiral Pincer Complexes

Pincer type complexes were first introduced in the late 1970s by Shaw and van Koten, whereas the term "*pincer*" was coined by van Koten in 1989.[24] Nowadays, they represent a privileged class of homogeneous catalysts for numerous organic reactions as well as in (bio)inorganic chemistry and material science.[9,25]



X: N, NH, C, B, S, P
Y: PR_2, NR_2, SR, OR, NHC
Z: CH_2, NR, O

Figure 1. General structure of manganese pincer complexes.[22]

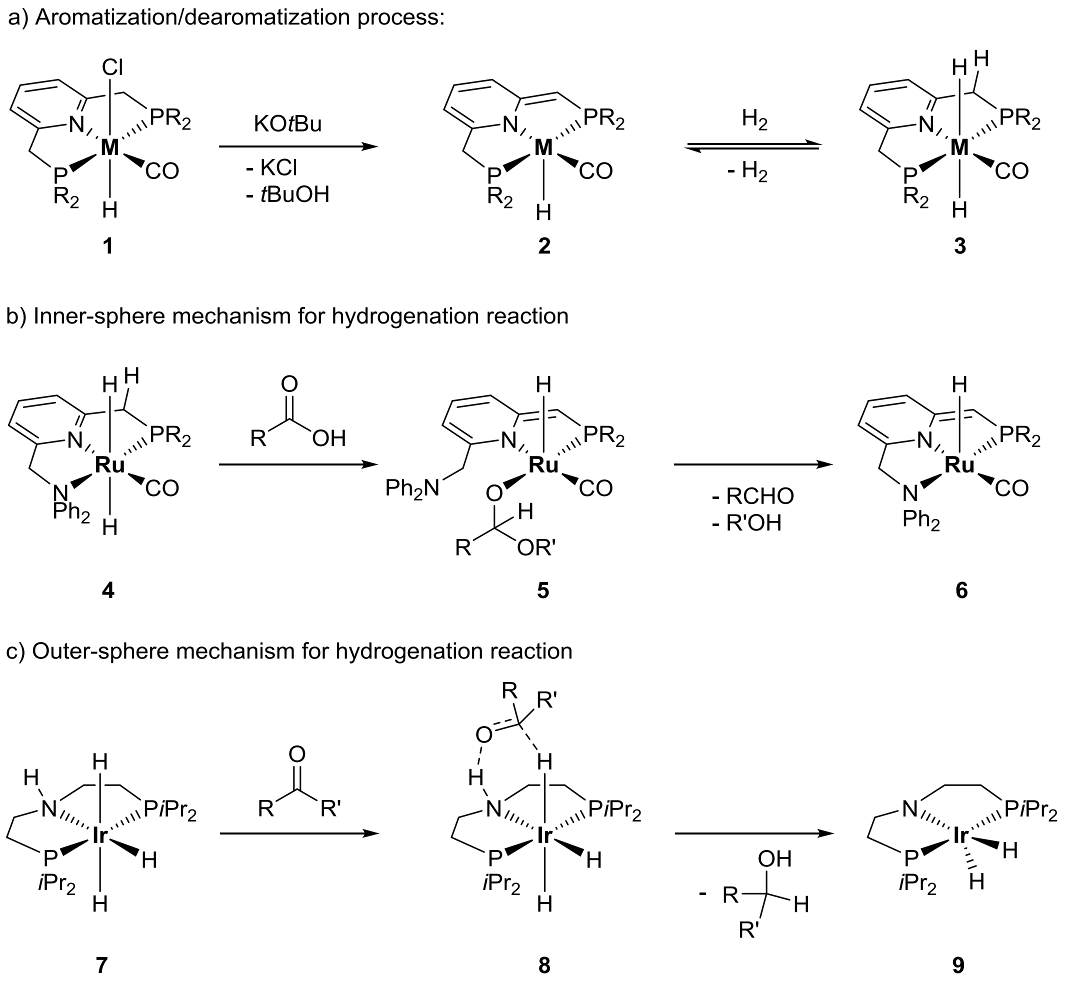
In general, a pincer complex consists of a metal center which is mostly meridionally coordinated by a tridentate ligand (see Figure 1), forming five-[26] or six-membered[27], or even hybrids of five- and six-membered chelate rings.[28] The complexes and ligands can often be synthesized in a few steps and the latter can be easily tuned with respect to their electronic and steric effects to the metal center by changing the donor atoms **Y** and/or **X** or the substituents **R** at the donor atoms.[26,29] An additional possibility of modifying the backbone occurs by changing **Z**, which allows implementation of chirality or an additional steric hindrance.

In most cases, the donor atoms **Y** are two-electron donors, such as phosphorous or sulfur, as representative soft donors or e.g. nitrogen as a hard donor, with respect to the HSAB-concept. Having all these different motifs in account, diverse combinations of e.g. neutral, anionic, Lewis acidic and basic, arene, heteroaromatic and carbene donor sites are possible and known. For an easier differentiation of the various pincer complexes, the different ligand systems were named after their coordinating atoms e.g. PCP-, PNP-, SNS-ligands etc.

The first pincer ligands were mostly ECE type ligands consisting of an *ortho*-disubstituted aryl ring covalently bound via a M-C σ-bond and two *ortho* substituents. These *ortho* substituents contain donor atoms (N, P or S) which form a dative bond to the metal center.[30] In consequence, the geometry perfectly fits to the square planar coordination of d^8 metal centers (e.g. Rh^I, Ir^I, Ni^{II}, Pd^{II}) and the square pyramidal or Y-shaped coordination of d^6 metal centers (e.g. Ru^{II}, Rh^{II}). Different pincer type complexes based on these noble metals and especially with Ir and Pd have been intensively studied for a variety of catalytic transformations.[9–13,15,16,31] In addition, the resulting complexes have a high thermal stability as well as a hampered cyclometallation.[32] Nowadays, other diverse coordination modes and also an unexpected flexibility of the tridentate ligands can be observed. Thus, a mono- as well as bidentate or facial coordination of the pincer ligands in dependence of the donor atoms was reported, thus proving that a hemilability of some ligands also takes place.[33]

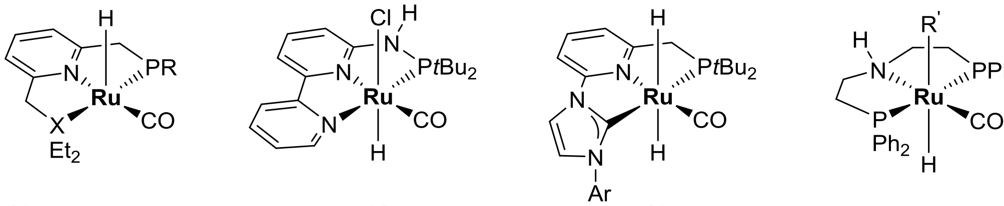
In the first reported metal pincer complexes, the ligand itself did not directly participate in the catalytic reaction. It was normally used to change the steric hindrance, as well as the electronic properties, of the metal center by modification of the ligand. Through a substitution of the monoanionic C-*ipso* donor atom by different heteroatoms, e.g. N, ligands were directly cooperated into the catalytic cycle by interacting with the substrate and without changing the oxidation state of the metal center (non-innocent ligand character).[34,35] One famous example for this so called metal-ligand cooperation is shown in Scheme 1 displaying an aromatization/dearomatization process which occurs at the pyridine based backbone of pincer complex **1**. The pyridine backbone is dearomatized by base and will be again aromatized by the activation of H_2 or dehydrogenation of a H-OR, H-NR_2, or H-C bond.[11,34,36] Thereby, the bond activation process is often assumed to be reversible because of the quite similar energy levels of the aromatized and dearomatized complex.

Further on, the bond activation can take place in an inner- or outer-sphere mechanism. While the first one is presented for the hydrogenation reaction in Scheme 1b by having an aromatization/dearomatization process,[37] the outer-sphere mechanism is illustrated by a metal-ligand cooperation via metal-amide/metal-amine bond (Scheme 1c).[38]



Scheme 1. Metal ligand cooperation as well as inner-[37] and outer-sphere[39] mechanisms.

While the reduction of ketones by e.g. Ru pincer catalysts was mostly applied using transfer hydrogenation conditions,[12] the first reduction of a C=O multiple bond via hydrogenation was published in 2006 by Milstein. He was using a ruthenium-based pincer complex (Figure 2, complex **10a/b**) for the reduction of esters with good activities for this reaction.[37] Before this publication only a few homogeneous systems for the hydrogenation of predominantly activated esters were known.[40] Following this seminal work, diverse Ru pincer complexes were published afterwards in which the "Ru-Macho"-one of Saito and co-workers is the most prominent example, which was utilized for a number of other reactions.[41] It is the aliphatic Ru PNP pincer complex **13a** which is highly active for the hydrogenation of ketones in methanol and is nowadays commercial available.



10a X = P, R = *i*Pr
10b X = N, R = *t*Bu

Milstein

11

Huang

12

Song

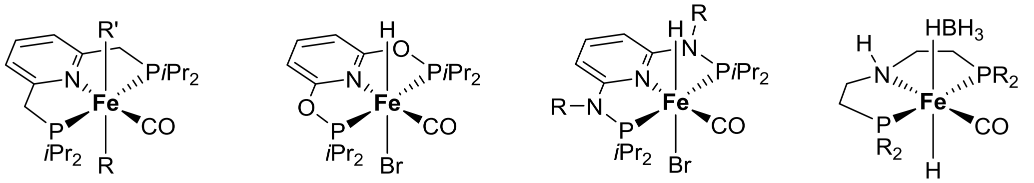
13a R' = Cl
13b R' = HBH_3

Saito

Figure 2. First noble metal pincer complexes for the reduction of esters.

Since the turn of the millennium, research regarding pincer complexes has shifted towards the usage of non-noble metal complexes.[42] These metals are predominantly more abundant, inexpensive and have a lower toxicity in comparison to the precious metals. At the beginning, the main focus was on iron catalysts.[18,43] Thus, many achiral iron(II) catalysts with pincer ligands were described for various applications in the field of hydrogenation catalysis, having mainly a pyridine,[20,44,45–48] or secondary amine[49,50,51] unit in the backbone.[23]

In 2011, Milstein and co-workers developed several new Fe pyridine based PNP pincer catalysts (**14a-c**) for the reduction of various aliphatic and aromatic ketones. Complex **14c** is a dihydride species which enables the reaction without any addition of base.[46,48] The same group also published the reduction of aldehydes with **14b**[52] while later on the diphosphinite PONOP pincer complex by Hu (**15**) has a higher functional group tolerance by being less active (10 mol% of **15**).[45] Additional iron pincer complexes by Kirchner and co-workers (**16a/b**) were presented with high reactivity regarding the hydrogenation of aldehydes with a TON up to 80.000 for the N-Me catalyst **16b**.[47,53]



14a R = Br, R' = Br
14b R = Br, R' = H
14c R = H, R' = HBH_3
14d R = H, R' = H

15

16a R = H
16b R = Me

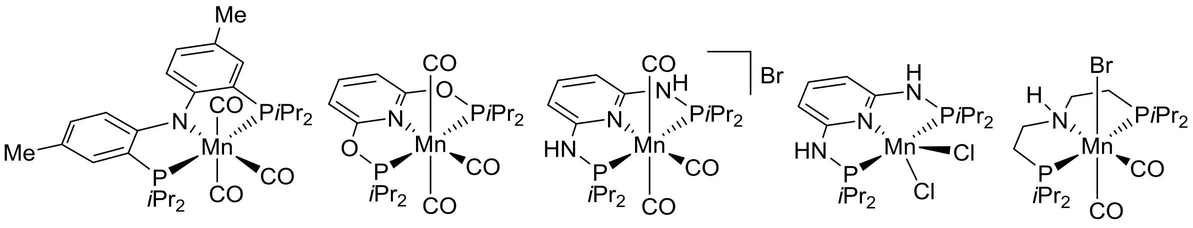
17a R = *i*Pr_2
17b R = Cy_2
17c R = Et_2

Figure 3. Iron pincer complexes for the hydrogenation of esters.

The field of ester hydrogenation by iron pincer complexes was not explored until 2014, when Milstein and co-workers published the first iron pincer catalyzed hydrogenation of activated trifluoroacetic esters to the corresponding alcohols (Figure 3, **14d**).[54] In addition, our group and Guan described, independently, hydrogenations of non-activated esters with PNP iron pincer complexes (Figure 3, **17a-c**).[50,55] Since then, an improved second generation iron pincer complex having ethyl substituents at the phosphorous atoms was synthesized.[56] The influences on the reactivity for the reduction of methyl benzoate by different steric substituents at the phosphorous was further investigated by Langer and co-workers while the main focus was the hydrogenation of amides.[51] Among these catalysts, **17c** was the most active one by reducing the model compound methyl benzoate in 6 h at 60 °C, 30 bar H_2, in THF, with 1 mol% catalyst. Besides this substrate, different aromatic and aliphatic esters, including diesters and lactones were hydrogenated.

In contrast to iron, manganese, as the most abundant transition metal after iron and titanium, was basically not explored, especially for hydrogenation reactions, until 2016.[57] Contrary to this, manganese compounds have a lot of applications in oxidations and coupling reactions.

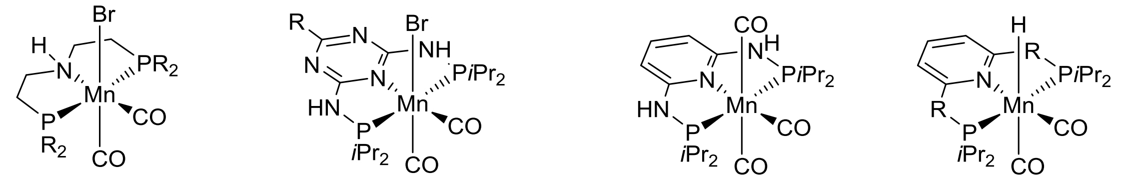
The first manganese-based pincer type complex based on bis(imino)pyridine dates back to the turn of the millennium but most examples were not tested for catalytic reactions, or were not active at all.[58] The first manganese PNP pincer-type complex (**18**) has been reported jointly by the groups of Ozerov and Nocera, who synthesized different diarylamido-based PNP-supported manganese tricarbonyl coumpounds (Figure 4).[59] Inspired by the successful catalytic application of different iron PNP pincer complexes, a series of these manganese pincer complexes were further investigated very recently by Boncella and Tondreau.[60] Starting from $[MnBr(CO)_5]$ and different PONOP, PNP and PNNNP pincer ligands, they prepared the corresponding carbonyl bromide complexes **19**, **20** and **22** as well as the high-spin manganese(II) chloride complex **21**. Kirchner and co-workers also used $MnCl_2$ for the complex synthesis in analogy to the previously described iron PNNNP pincer complexes achieving complex **21**. Unfortunately the characterized complex catalyzed only the oxidative homo-coupling of aryl Grignard reagents.[61]



18 **19** **20** **21** **22a**

Figure 4. First manganese PNP pincer complexes.

During the following years, several hydrogenation reactions of different types of C-X multiple bonds with various kinds of manganese pincer complexes were published by the groups of Kempe, Kirchner, Milstein and our group (Figure 5).[62–64,65,66]



22a R = *i*Pr
22b R = Cy

23a R = C_6H_5
23b R = HN-C_3H_5
23c R = CH_3
23d R = $N(C_2H_5)_2$

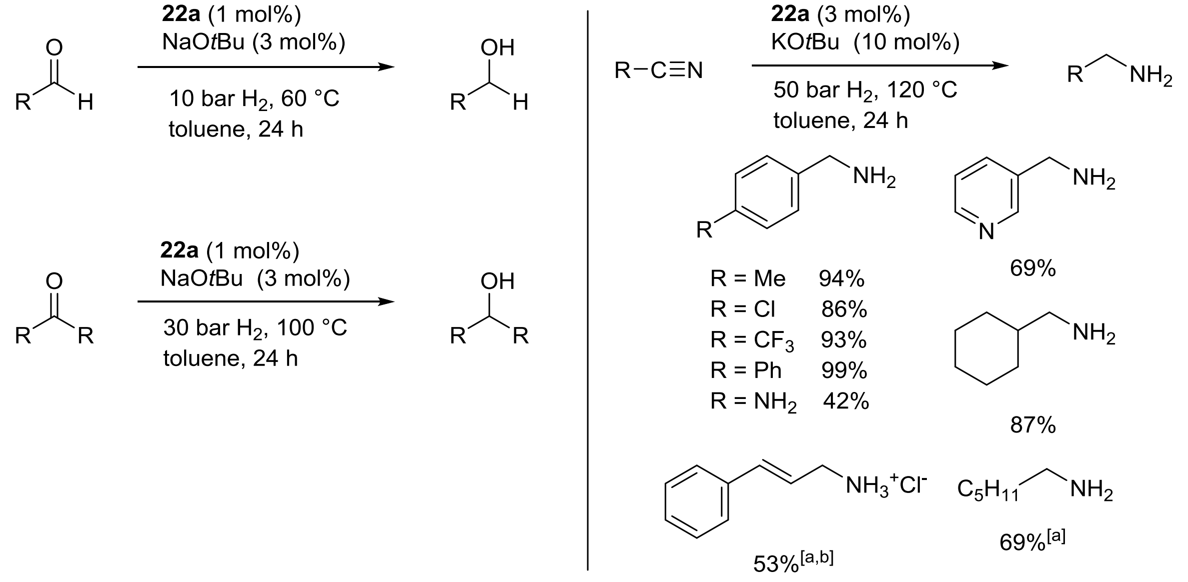
24

25a R = NH
25b R = NMe
25c R = CH_2

Figure 5. Different pincer complexes for the hydrogenation of C-X multiple bonds.

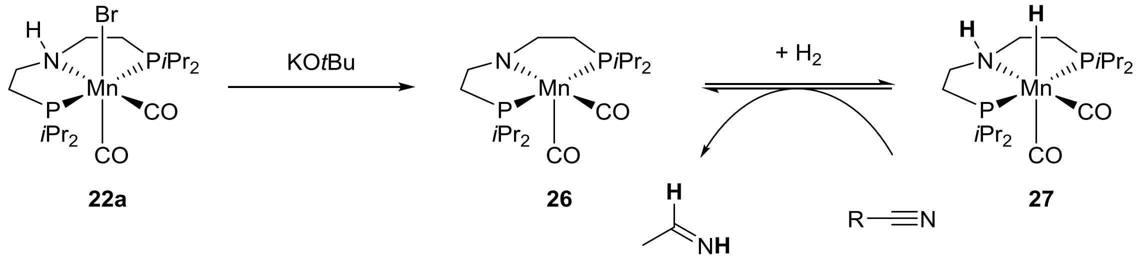
All these pincer complexes were synthesized like the previously mentioned complexes by Boncella and Tondreau by treating the respective ligand with [$MnBr(CO)_5$] for several hours under different conditions.

The first successful hydrogenation using a manganese pincer catalyst was described by our group consisting of an aliphatic PNP backbone including different substituents at the phosphorus atom (**22a** - *i*Pr, **22b** - Cy).[63] While both complexes **22a** and **22b** were able to reduce nitriles, aldehydes and ketones, **22a** is the more active catalyst for the reduction of nitriles with a wide applicability for aromatic, benzylic and aliphatic nitriles as well as for dinitriles. In addition, terminal alkenes were also tolerated. Therefore, **22a** was also used for the reduction of aldehydes and ketones (Scheme 2). Surprisingly, all of these complexes seem to be relatively stable against air in the solid state.



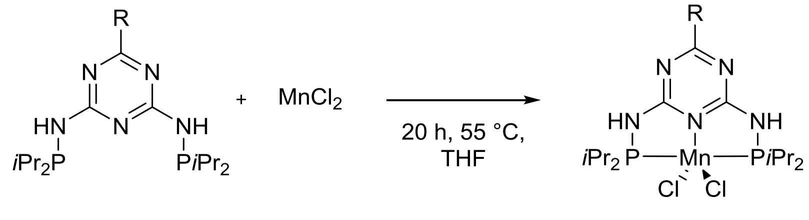
Scheme 2. Catalytic applications of **22a** and **22b**. Reaction conditions for reduction of nitriles: substrate (0.5 mmol), complex **22a** (3 mol%, 0.015 mmol), KO*t*Bu (10 mol%, 0.05 mmol), toluene (1 mL), 24 h, 120 °C, 50 bar H_2. Isolated yields are given. [a] 36 h. [b] 25% of the corresponding saturated amine was formed.

On the basis of DFT calculations, an outer-sphere mechanism for the hydrogenation reaction was proposed. Apparently, initially the corresponding amido complex **26** is formed by treating the pre-catalyst **22a** with base. Afterwards, in the presence of hydrogen the formation of a hydride complex **27** takes place, which could be proven by NMR and IR spectroscopy. This hydride complex reduces the nitrile in two consecutive cycles by a simultaneous hydride transfer at each step.



Scheme 3. Proposed outer-sphere mechanism for nitrile hydrogenation.

Besides this work, Kempe and co-workers published, at the same time, diverse PN_5P pincer type complexes (**23a-d**) which were active pre-catalysts for the reduction of aldehydes and ketones.[64] The most efficient catalyst **23b** was able to hydrogenate ketones with a higher activity, compared to the previously mentioned catalyst. **23a** catalyzed a diverse spectrum of different substituted aromatic ketones with a high functional group tolerance including diaryl ketones and aldehydes by using a catalyst loading from 0.1 to 1 mol%. Under these conditions the successful reduction of linear and cyclic aliphatic ketones was also demonstrated. As a consequence of the milder conditions, an improved selectivity for unsaturated ketones was obtained whereby terminal as well as internal alkenes were not reduced.



28a R = C_6H_5
28b R = HN-C_3H_5

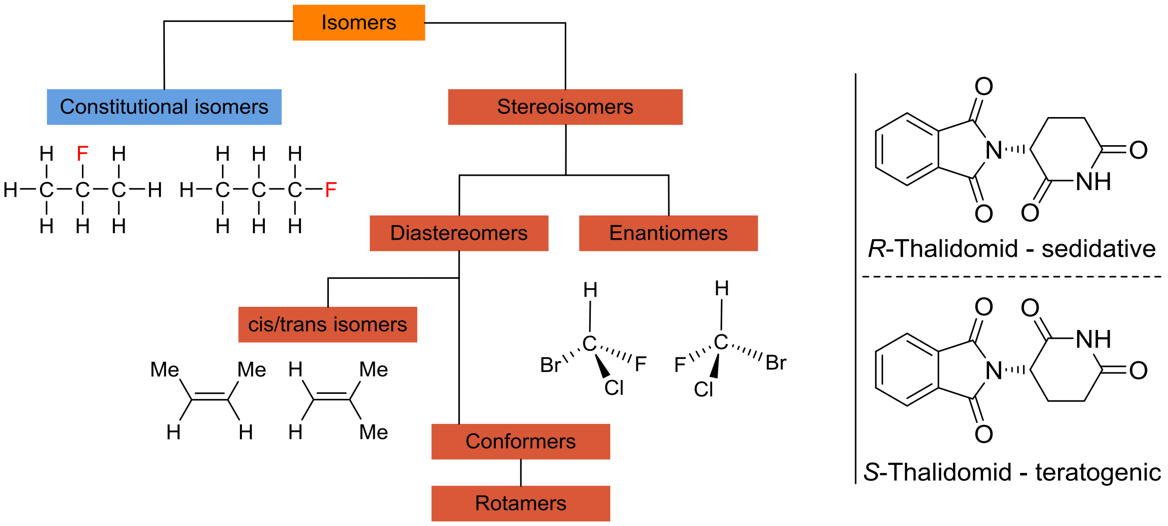
Scheme 4. Synthesis of the manganese dichloro complexes of **28a** and **28b**.

Kempe and co-workers also tested the catalytic activity of the corresponding dichloro manganese(II) complexes **28a/b** synthesized using the ligand and $MnCl_2$ as a metal precursor (Scheme 4). However, no catalytic activity of these two complexes could be observed for the reduction of acetophenone. Also by reducing the Mn(II) metal center to Mn(I) the reduced alcohol could not be detected. As a result they concluded that for further reductions manganese in the oxidation state of +1 combined with carbonyl ligands are necessary.

The PN_3P tricarbonyl manganese pincer complex **24**, published by Sortais and co-workers in 2017, was less active regarding the hydrogenation of ketones (5 mol% cat., 130 °C, 24 h), in comparison to the examples already discussed.[67] By NMR studies, they confirmed the formation of **25a** under the harsh conditions through a CO dissociation. Nearly at the same time, Kirchner and co-worker described the direct use of **25a** as catalyst for the hydrogenation of ketones and aldehydes.[66] Interestingly, a pronounced chemoselectivity towards aldehydes with turnover numbers up to 10400 could be shown by using mild conditions. Only low catalyst loadings from 0.05 to 0.1 mol% were needed for the reduction of a broad range of aldehydes at room temperature.

2.3 Asymmetric Hydrogenation Catalysis

Two molecules are behaving in an asymmetric fashion if they have an unsymmetrical arrangement of atoms in their molecular structure. One of the simplest examples is present if one tetrahedral carbon atom is attached to four different substituents.[68] This carbon atom is forming a chiral center which is considered as asymmetric carbon atom and can be present in two different absolute configurations, for which the descriptors *S* and *R* are used. The abbreviations are attributed to the Latin words *rectus* (right) and *sinister* (left) and were assigned by the Cahn-Ingold-Prelog rules.[69] If only one chiral center is present in a molecule, the resulting two structures are mirror images to each other, known as *enantiomers*. The presence of more than one chiral center leads to diastereomers, which are stereoisomers without being mirror images of each other (see Scheme 5).



Scheme 5. Different types of isomerism (left) and both isomers of *Contergan* (right).[70]

In general, enantiomers do have the same physical properties, apart from their interaction with polarized light which is reverse to each other. However, a different behavior can occur in the interaction with other chiral molecules, e.g. with respect to their biological/medical activity. This can result in one isomer being biologically active, whereas the other does not have any activity, or is even toxic. One of the most famous examples is the pharmaceutical *Contergan*® (Thalidomide) which was sold in the 1950s and ‘60s. Herein, one of the isomers has a sedative effect while the other is teratogenic (see Scheme 5).[71] This contrast in properties led to the necessity for especially the pharmaceutical, and the flavor and fragrance industries to synthesize enantiomerically pure compounds for initial tests regarding the biological activity of both enantiomers, or required whole synthesis of compounds/pharmaceuticals to be performed in entirely enantiopure fashions.[72]

The first success in this area was achieved by resolving a racemic mixture of two enantiomers by e.g. crystallization of diastereomeric adducts or by using an enantiomerically enriched starting material which was often part of the chiral pool originating from natural compounds.[73] This approach is still used in industry today. Alternatively, an auxiliary which promotes the reactions into a favored enantiomer could be applied. Unfortunately, these methods have a couple of drawbacks. In the first example, only a maximum yield of 50% can be achieved, whereas for the latter, stoichiometric amounts of a chiral precursor are necessary.

In contrast to this, asymmetric catalysis is able to promote the conversion of a prochiral substrate to a chiral product with preference for the formation of one major enantiomer.[74] Consequently, by using a chiral catalyst the overall yield can be increased, and a high amount of product can be formed with only small amounts of catalyst. In addition, the utilization of an enzymatic transformation is possible to increase the efficiency of enantioselective syntheses. Drawbacks of this method are the requirement of definite reaction conditions, in addition to a limited compatability of enzymes to a broad substrate scope.[75]

In conclusion, there is an increasing interest in the development of asymmetric catalysts with the aim to synthesize enantiomerically pure chiral compounds for the pharmaceutical industry, for agrochemicals, flavors, fragrances and other materials for which these types of transformations are important.[76]

One of the major breakthroughs regarding asymmetric catalysis was the development of rhodium containing asymmetric complexes by Knowles and co-workers at Monsanto in the 1970s. The first catalysts were able to hydrogenate prochiral olefins to the corresponding enantiomerically pure alkanes. One of the most famous examples regarding chiral catalysis is their publication of L-Dopa synthesis which is used for the treatment of Parkinson's disease. In addition the development of the *BINAP* ligand (see Figure 6) by Noyori and co-workers led to one of the most versatile ligands in homogeneous catalysis.[77] In consequence, the results of Knowles and Noyori regarding their work on asymmetric catalytic hydrogenations, as well as the results of Sharpless on asymmetric catalytic oxidations, were honored with the Noble Prize in 2001, thus underlining the importance of this field.[78]

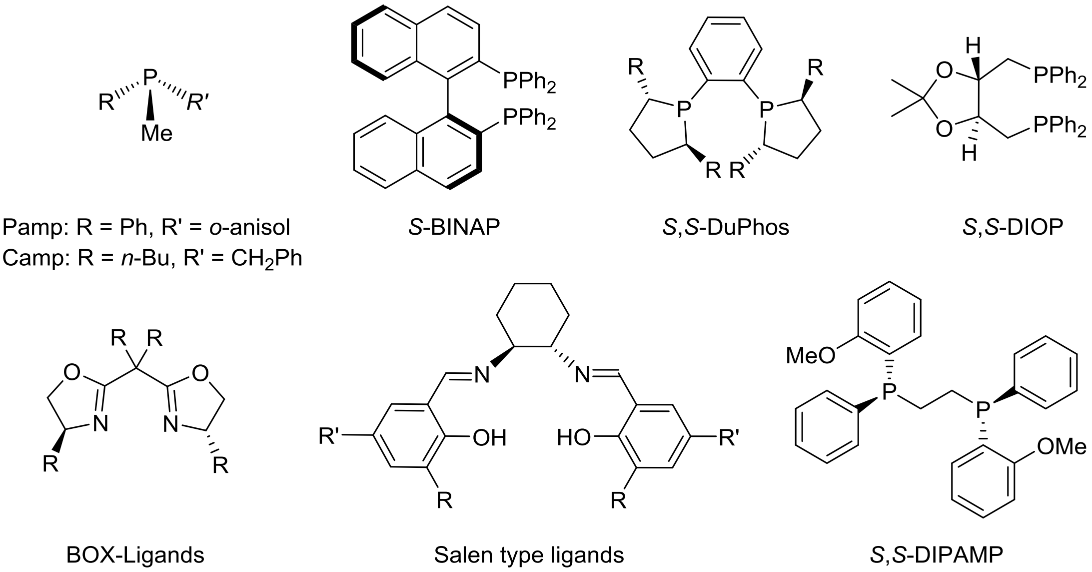

Pamp: R = Ph, R' = *o*-anisol
Camp: R = *n*-Bu, R' = CH_2Ph
S-BINAP
S,*S*-DuPhos
S,*S*-DIOP
BOX-Ligands
Salen type ligands
S,*S*-DIPAMP

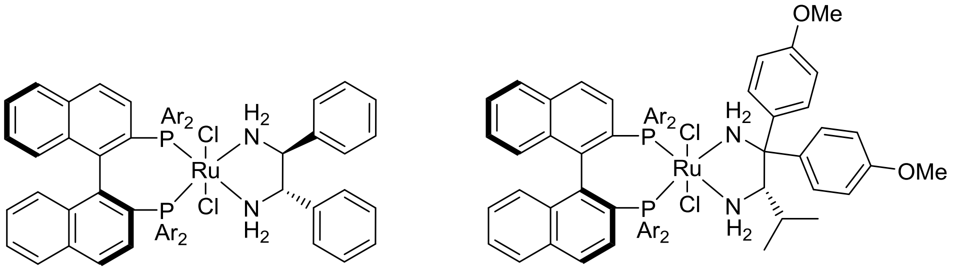
Figure 6. Different prominent chiral mono- and bidentate ligands.[79,80]

Overall, a tremendous number of chiral ligands and resulting complexes were known but only a few were regularly used in industry.[80–82] Some of the most important ligands can be seen in Figure 6. Starting with predominantly monodentate ligands (phosphonates, phosphoramidites, phosphites), nowadays the most promising catalysts are homogeneous metal complexes bearing bidentate, C_2-symmetric ligands, consisting of a chiral backbone or a chiral phosphorous.[83]

As metal centers mainly noble metals like Ru, Rh, Pd, Os and Ir were used. The coordinating heteroatoms are usually P or N, whereas for early transition metals, mostly O or N is coordinated to the metal. An extensive overview of some state-of-the-art hydrogenation catalysts for diverse functionalized ketones can be found in the literature.[68] Overall, especially for the hydrogenation of particularly non-functionalized and aliphatic ketones, only a few examples are known.[81] Thus, the development of chiral organometallic complexes for more efficient, operationally convenient and widely applicable chiral phosphines continues to be an important and challenging field in asymmetric catalysis.[8,84]

2.4 Asymmetric Hydrogenation with Chiral Pincer Complexes

For chiral pincer complexes, a wide applicability in academia has been found showing good selectivities, as well as activities, for different types of organic reactions (reductions, borylations, alkynylation, allylation of carbonyl compounds, aldol- and Mannich-reactions, hydrophosphination and –amination).[85] Predominantly NCN or PCP ligands were used, which have an aromatic backbone as well as two chiral centers at the side arms. By having a precise look on complexes for the hydrogenation of ketones with tridentate ligands, the number of known systems decreases dramatically, even more when the reduction of aliphatic prochiral ketones is considered.



29

trans-RuCl$_2$[(*S*)-binap][(*S*,*S*)-dpen]

30

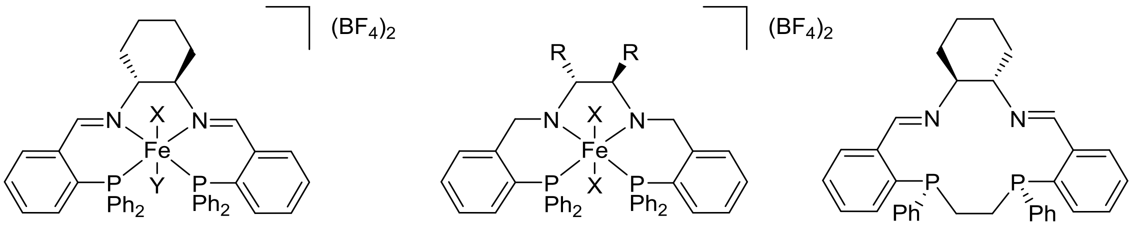
trans-RuCl$_2$[(*S*)-binap][(*S*)-diapen]

Figure 7. One of the most effective P_2/N_2 catalysts.

One of the earliest classes of chiral ligands were phosphine-based and especially diphosphine ligands played an important role in the development of asymmetric hydrogenation reactions of ketones. A kind of second-generation BINAP-Ru system was published by Noyori in 1995. Besides the usual BINAP ligand, he additionally coordinated a diamine to the ruthenium center resulting in a P_2/N_2 ligand system (see Figure 7).[86,87] These complexes have shown a dramatically increased efficiency caused by the donor-acceptor bifunctional ability, the high acidity of the NH_2 nitrogen atom, and the higher nucleophilicity of the hydrogen atom at the Ru metal center during catalysis. Thus, the transfer of the hydride and the amine proton to the substrate is preferred. Unfortunatley, for different metal complexes these ternary P_2/N_2-ligands seem to be less stable under hydrogenation conditions by losing the diamine moiety.[88,89] Therefore, the idea was to incorporate the NH_2 group into the phoshine ligand to counteract against the decoordination by having a tridentate ligand and to take a benefit of the positive effect of the NH group for the hydrogenation.[89,90]

A first example regarding the synthesis of such a chiral noble metal pincer complex was published by the group of Clarke in 2007 using ruthenium as a metal center.[91] This research was continued by other groups using different noble metals like Ir[89,92] and Os[93]. Nevertheless, the reduction of especially aliphatic ketones still remains challenging.

Since the millennium, the field of asymmetric hydrogenations by academia and industry has focused on finding non-noble metal catalysts for the asymmetric reduction of prochiral ketones.[87,94] The first breakthrough was published by Morris and co-workers in 2008 by synthesizing different tetradentate PNNP-ligands (Figure 8, **31**/**32**) competing with other non-noble chiral catalyst. For example, a broad range of macrocycles (e.g. **33**) were tested coordinated to an iron metal center and have shown good activities and enantioselectivity especially for a broad range of aromatic ketones.[95] Nevertheless, also the corresponding tetradentate ligands were further investigated for diverse applications, especially on asymmetric transfer hydrogenation reactions.[96,97]



X = CH_3CN

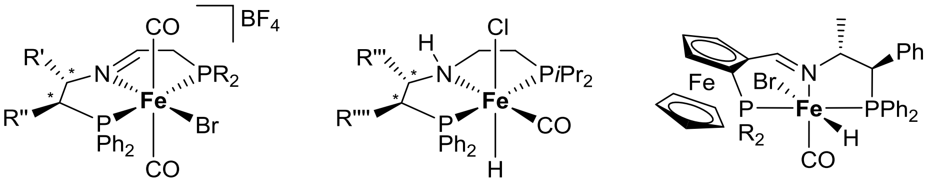
31a Y = CH_3CN
31b Y = CO
31c Y = *t*BuCN

32 X = CH_3CN

33

Figure 8. First iron based asymmetric (transfer) hydrogenation pincer catalysts.

In 2014, Morris and co-workers published the first chiral iron PNP complex (Figure 9, **34**) which was applied for asymmetric hydrogenation (see Figure 9).[98] Aromatic, as well as aliphatic prochiral ketones were converted to the corresponding alcohols but only with moderate to good enantioselectivities. Especially for the latter ones, only *ee* values up to 46% were achieved by testing four different substrates. A drawback of this system is the necessary activation of **34** using six equiv. of $LiAlH_4$, as well as ten equiv. of base during the reaction.



34

35

36a R = *i*Pr (*R*,*R*,S_{Fc})
36b R = Ph (*R*,*R*,S_{Fc})
36c R = Cy (*R*,*R*,S_{Fc})

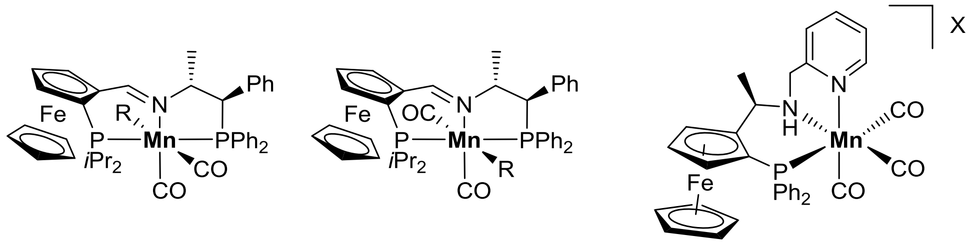
Morris - 2014

Morris - 2017

Morris - 2016

Figure 9. Different chiral iron pincer complexes.

During our research, Morris was able to improve the described system by directly synthesizing complex **35** which can then be used without pre-activation by $LiAlH_4$.[99] While the activity of **35** remains more or less constant, the selectivity was increased for aromatic substrates up to 96% *ee*. The attempt of increasing the enantioselectivity further on by using a planar chiral ferrocene unit, in combination with a centro chiral aliphatic unit as a scaffold in the backbone of the ligand (see complexes **36a-c**), were not successful.[100] The investigated reduction of aromatic ketones worked under milder conditions but the resulting chiral alcohols have shown only *ee* values up to 81% by using **36a**. Interestingly, the diastereomer of **36a** with an (S,S,S_{Fc}) configuration did not show any selectivity.



37a R = Br
37b R = H

37c R = Br
37d R = H

38a X = Br
38b X = BARF

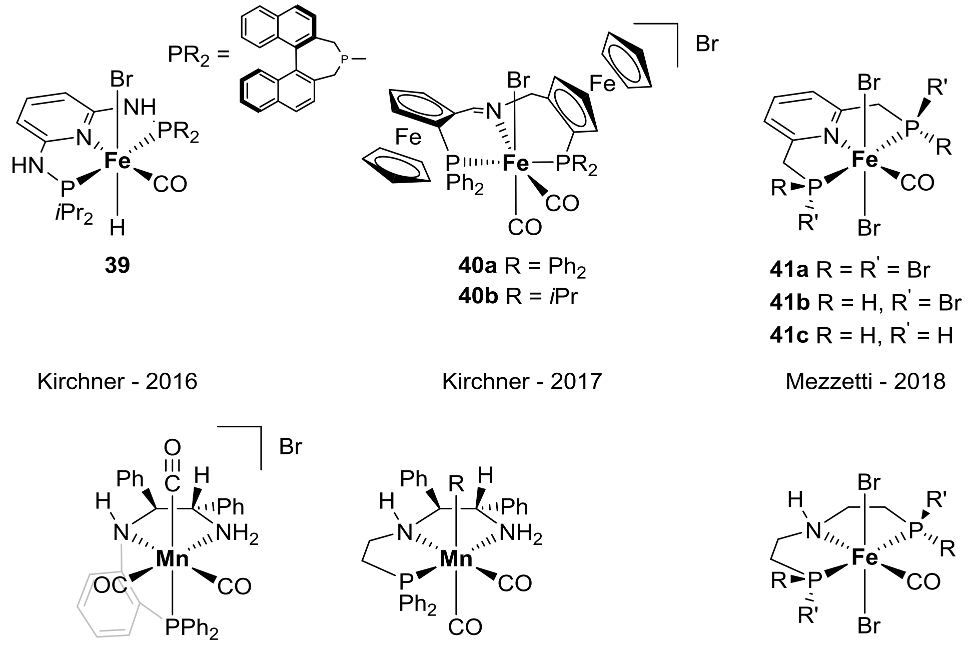
Kirchner - 2017

Clarke - 2017

Figure 10. Different ferrocene based manganese pincer complexes for the reduction of ketones.

Using the same ligand, Kirchner and co-workers studied the behavior of the analogous manganese pincer complex **37a-d** (Figure 10).[101] Surprisingly, the major diastereomer **37a**, as well as the diastereomeric hydrides **37b** and **37c**, displayed a high activity in the transfer hydrogenation of prochiral aromatic ketones (1 mol% cat., 4 mol% KO*t*Bu, *i*PrOH, r.t., 5-16 h) and led to enantioselectivities of up to 85% *ee*. Interestingly, they were able to reduce 3,3-dimethyl-butan-2-on to the corresponding alcohol with 74% *ee* but no further aliphatic ketones were tested. By using a quite similar ligand motif (complex **38a/b**) the group of Clarke described the first chiral PNP ligand which is facially coordinated to the metal center.[102] Herein, the hydrogenation of different acetophenone derivatives was displayed under moderate conditions (1 mol% cat., 10 mol% KO*t*Bu, 50 °C, 50 bar H_2, 16 h) with enantioselectivities up to 97% *ee*.

Two further attempts by the group of Kirchner to synthesize an enantioselective non-noble metal pincer complex were less successful for the asymmetric hydrogenation of ketones.[103] Complex **39** was successfully tested for the hydrogenation of acetophenone and differently substituted derivatives but no enantioselectivities of the corresponding alcohols were discussed. On the other hand, complexes **40a/b** were not active regarding the hydrogenation of prochiral ketones at all. The first P-stereogenic PNP pincer complexes **41a-c** published by Mezzetti and co-workers in 2018 showed only low enantioselectivities for the tested reduction of acetophenone (49% *ee*) with **41b**.[104] By calculating the transition states and having a further look on the mechanism of the hydrogenation process they concluded that the pyridine backbone is too flexible to achieve good selectivities. Based on calculations, they have postulated that with an aliphatic backbone (complex **42a-c**), higher *ee* values should be achievable, based on a stronger CH/π interactions between the substituents of the coordinating phosphorous and the aromatic ring system of the substrate acetophenone.[105] Unfortunately, the additional synthesized P-stereogenic analogues **42a-c** did not show any increased enantioselectivity which demonstrates the difficulty of computational methods to predict enantioselective reactions.



39

40a R = Ph_2
40b R = *i*Pr

41a R = R' = Br
41b R = H, R' = Br
41c R = H, R' = H

Kirchner - 2016

Kirchner - 2017

Mezzetti - 2018

43

44a R = Br
44b R = HBH_3
44c R = OEt

41a R = Cy ; R' = Me
41b R = *t*Bu; R' = Me
41c R = Me ; R' = Ph

Morris - 2018

Mezzetti - 2018

Figure 11. Chiral pincer complexes by Kirchner, Morris and Mezzetti.

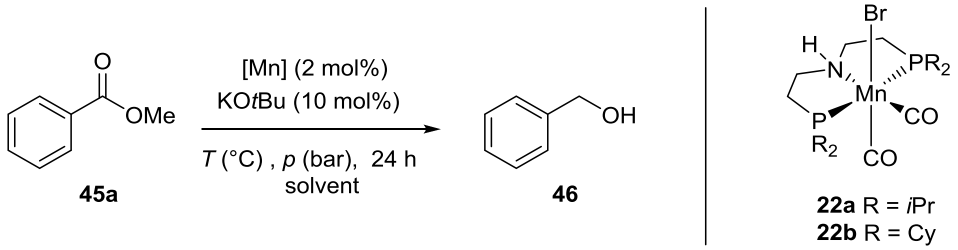
The latest results were published by Morris and co-workers describing the asymmetric transfer hydrogenation of aromatic ketones with well-defined PNN Mn(I) complexes (**43** and **44a-c**).[97] Thereby, the ligands were previously reported and derived from (S, S)-DPEN but were not be tested for complex synthesis. While the facial coordinated pincer complex **43** was not active in the transfer hydrogenation of acetophenone, **44a** fully converted acetophenone to 1-phenylethanol at 80 °C using 1 mol% cat., 2 mol% KO*t*Bu and *i*PrOH as solvent. If the borohydride complex **44b** is used, the addition of base could be avoided. Unfortunately, for both complexes (**44a** and **44b**) only low enantioselectivity of up to 53% *ee* could be achieved, while the mechanism of the transfer hydrogenation was described in more detail.

3 Results and Discussion

3.1 Hydrogenation of Esters by Manganese Pincer Complexes

As demonstrated in the introduction, Kempe and co-workers and our group and were able to characterize the first manganese(I) pincer complexes for the reduction of nitriles, ketones and aldehydes.[63,64] In addition, the group of Kempe found that the usage of manganese in the +2 oxidation state is not active for these kinds of reductions. Our attempts focused on the reduction of esters using different aliphatic manganese pincer complexes.[62] Thereby, with complex **22a** and **22b**, only low product yields were obtained for this reaction (Table 2, entries 4 and 5), although a higher catalyst loading of 3 mol% (Table 2, entry 6) was applied in comparison to the analogous iron pincer complexes (Table 2, entries 1-3).

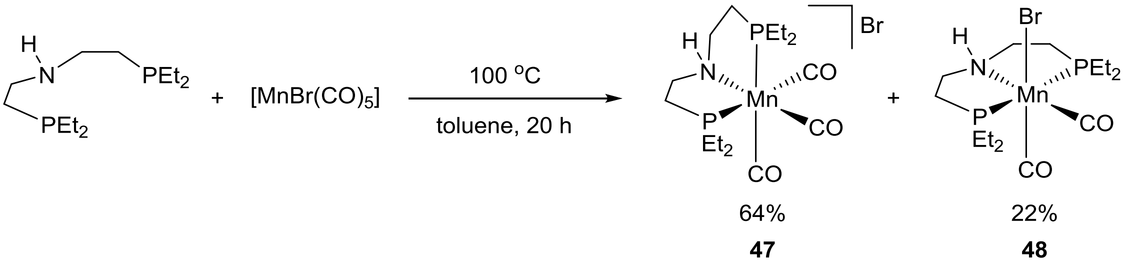
Table 2. Mn-catalyzed hydrogenation of methyl benzoate with different catalysts.

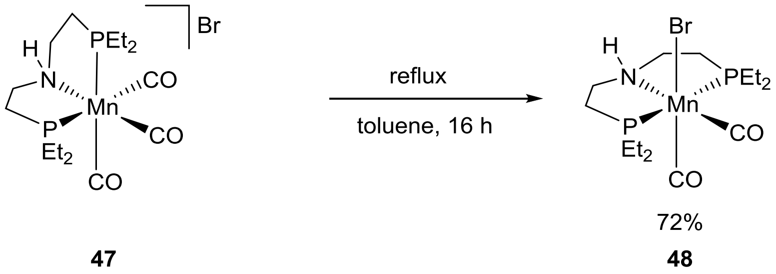


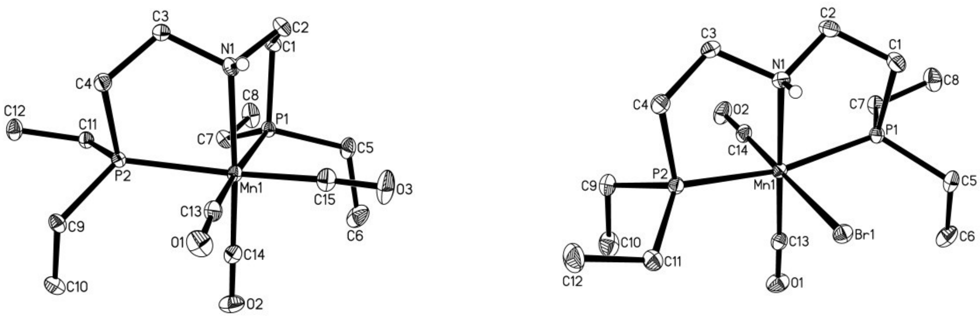
Entry	Catalyst	Solvent	*p* [bar]	T [°C]	Yield[a] [%]
1[56]	**17a**	THF	30	60	50
2[56]	**17b**	THF	30	60	30
3[56]	**17c**	THF	30	60	99
4	**22a**	toluene	30	100	6
5	**22b**	toluene	30	100	2
6[b]	**22a**	toluene	80	120	38
7	**47**	toluene	30	100	82
8	**47**	1,4-dioxane	30	100	93
9	**47**	1,4-dioxane	10	100	51
10	**47**	1,4-dioxane	30	110	97
11	**47**	1,4-dioxane	30	80	46
12	**48**	1,4-dioxane	30	110	97

Reaction conditions: **45a** (0.5 mmol), catalyst (0.01 mmol), solvent (1 mL), KO*t*Bu (10 mol%), 24 h, 80-110 °C, 10-30 bar H_2. [a] Yield determined by GC analysis using hexadecane as an internal standard. [b] 3 mol% **22a**.

In one of our previous studies using iron pincer catalysts, a considerable increase of the activity by using less bulky substituents at the phosphorous atom was observed (Table 2, entries 1-3). Thus, the conversion of methyl benzoate could be increased from 30% to full conversion by changing the cyclohexyl substituents with an ethyl group. We were then interested whether this kind of behaviour is also observed in the case of manganese based pincer catalysts. Therefore, we synthesized the corresponding Et_2PNP pincer ligand and reacted it with $[MnBr(CO)_5]$ (Scheme 6). Interestingly, the main product (64% yield) was a tricarbonyl cationic pincer complex in which the pincer ligand is facially coordinated to the metal center. The compound was not soluble in toluene and thus, could be isolated easily whereas the coordination mode was clarified by X-ray crystal structure analysis (Scheme 6). The observed configuration was surprising, since PNP pincer complexes, such as **22a** and **22b**, as well as related Fe, Ru, Os or Ir pincer complexes, usually have a *trans*-orientation for the two phosphorous atoms. The expected meridional configuration (complex **48**) was only achieved with a yield of 22%.







Scheme 6. Molecular structures of complexes **47** (left) and **48** (right). Only the cation of **47** is presented. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms except of that attached to nitrogen are omitted for clarity.

To get a better understanding of this unusual coordination mode, we calculated the relative energy of the cationic tricarbonyl complexes with two P-ligands in the *cis* (**3**$^+$-*cis*) and in *trans* (**3**$^+$-*trans*) positions. Thereby, the *trans*-isomer is more stable by 7.9 kcal/mol than the *cis*-isomer resulting in the assumption that complex **47** is the kinetically stable product. Accordingly, we were able to improve the formation of catalyst **48** by increasing the reaction temperature. As a consequence, by refluxing the reaction mixture for 20 hours, **48** could be achieved as the main product but only with a higher amount of side products. Alternativley, it was possible to convert **47** by refluxing it additional 16 h after isolation in toluene. The resulting pure complex **48** was isolated with yields up to 72%.

Our initial catalytic tests with complex **47** using the benchmark reaction of methyl benzoate revealed a significantly enhanced activity and gave benzyl alcohol in 86% yield under the same conditions as **22a** and **22b** (Table 2, entry 7). After optimization, both Et_2PNP pincer complexes (**47** and **48**) provided the same activity giving nearly quantitative yield in 1,4-dioxane at 110 °C, 24 h, 10 mol% KO*t*Bu and 30 bar H_2 (Table 2, entry 10 and 12). In addition, by studying the progress of the reaction (Figure 12) for both complexes, the same reaction profile was observed, which led to the assumption that both catalysts are forming the same active species. Unfortunately, several attemps to clarify the catalytically active species by X-ray structure analysis were unsuccessful.

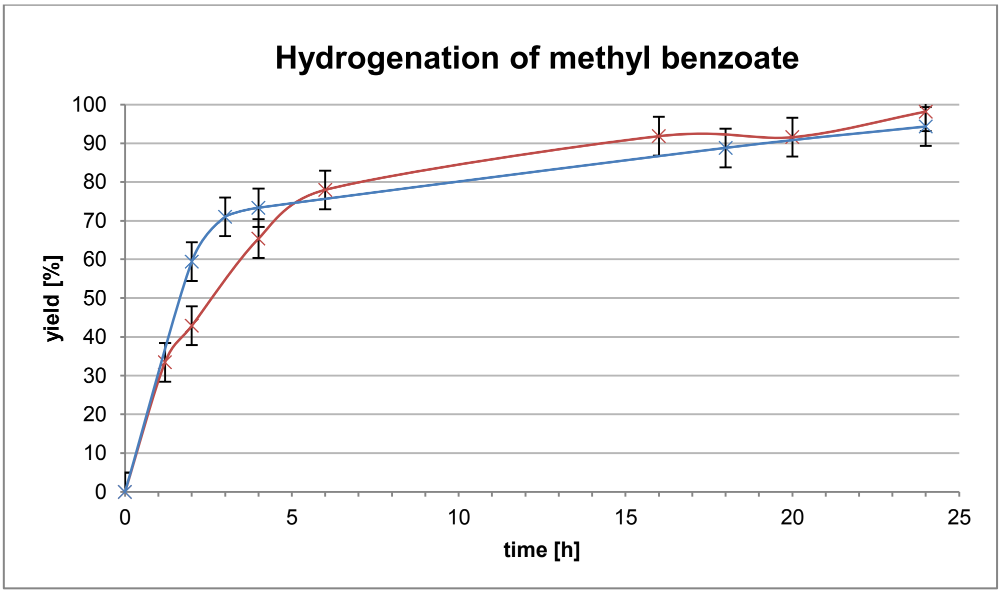


Figure 12. Yield vs. time diagram for the hydrogenation of methyl benzoate. Complexes **47** (red line) and **48** (blue line). Reaction conditions: methyl benzoate (0.5 mmol), **47** or **48** (0.01 mmol), 1,4-Dioxane (1 mL), 110 °C, 30 bar H_2. Yield determined by GC analysis using hexadecane as an internal standard. The repetition of the experiments (three times) led to an abbreviation of ± 5% of the yield.

However, by treating both complexes with three equiv. of base, the same amido complex with a chemical shift of 91.06 ppm in the ^{31}P NMR was detected, as well as the identical hydride complex which seems to be in an equilibrium of two isomers. The formation of two hydride isomers was already observed for different iron pincer complexes in which the hydride is arranged *cis* or *trans* to the N-H proton.[106]

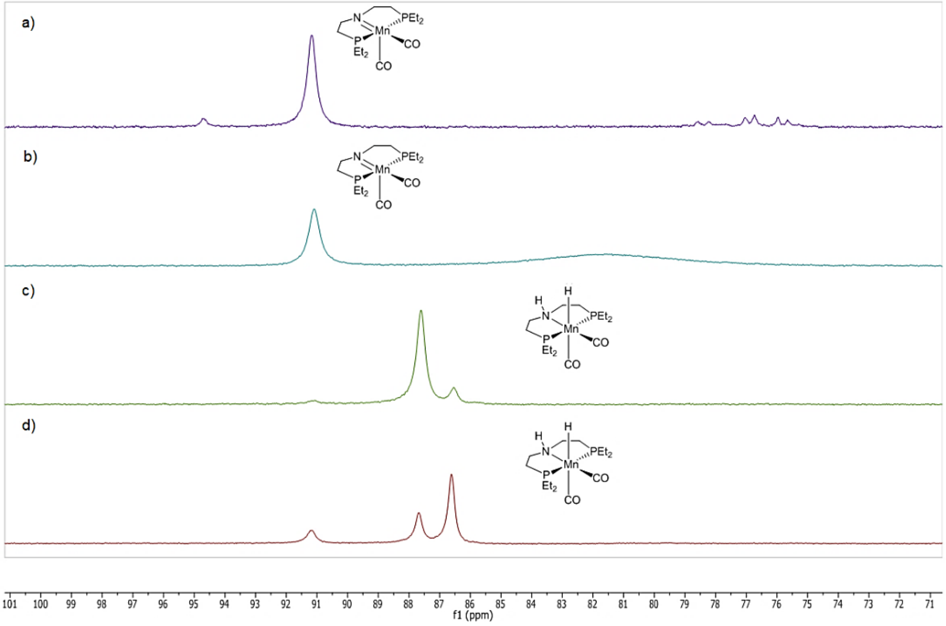
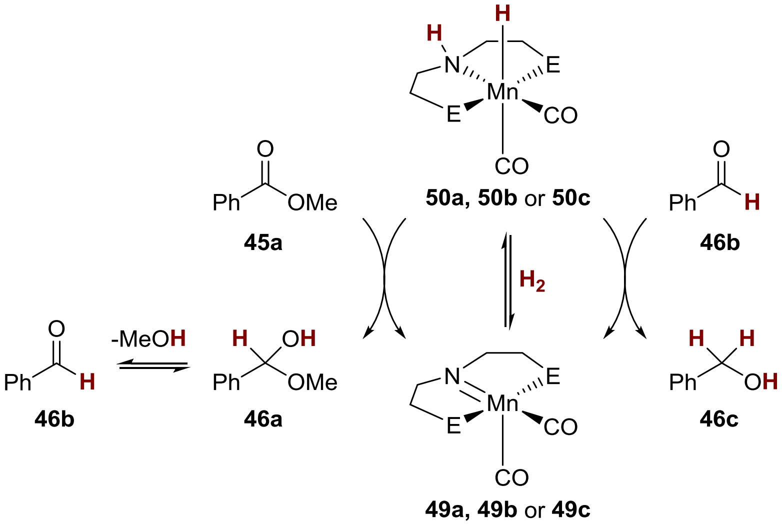


Figure 13. ^{31}P NMR of amido and hydride complex of **47** and **48**. a) Amido complex of **47**. b) Amido complex of **48**. c) Hydride complexes of complex **47**. d) Hydride complex of complex **47** after 40 h.

In order to elucidate the reaction mechanism and to understand the different performance of the active species of **22a**, **22b** and **47**, B3PW91 DFT computations were carried out. The *in situ* formed hydride complexes were very stable towards CO dissociation by forming a well-balanced equilibrium for the concerted H_2 elimination to the respective amido complexes. In all complexes the barrier of H_2 elimination is around 20 kcal/mol and the reactions are slightly exergonic by 0.2-1.5 kcal/mol.



Scheme 7. Proposed mechanism for the Mn-catalyzed ester hydrogenation using methyl benzoate as a representative substrate.

On the basis of the computations, an outer-sphere mechanism was postulated (Scheme 7) in which methyl benzoate **45a** is reduced in two cycles via the formation of the corresponding hemiacetal **46a**. A stepwise process was identified for the first cycle (**45a** to **46a**), whereas the hydrogen atoms are transferred stepwise as a hydride from the manganese center and as a proton from the nitrogen ligand to **50a** (**50b** or **50c**) resulting in amido complex **49a** (**49b** or **49c**) and substrate **46a** which dissociates to methanol and benzaldehyde **46b**. For all catalysts, the first step has a higher barrier than the second step (32.7 vs. 30.1, 34.1 vs. 27.9 and 31.8 vs. 25.8 kcal/mol; respectively, for **50a**, **50b** and **50c**).

After the amido complex is regenerated by addition of H_2, benzaldehyde **46b** is hydrogenated stepwise to benzyl alcohol **46c** in the second cycle, which is again a stepwise process. Here, the first step has a higher barrier than the second step (15.6/11.9, 18.5/13.5 and 15.9/12.8 kcal/mol; respectively, for **50a**, **50b** and **50c**). Based on the energy barriers of both cycles, the initial reduction of the ester seems to be the rate-determining step, while in comparison with each other for the first hydrogenation cycle, **50c /49c** has the lowest barrier followed by that of **50a/49a** and **50b/49b**, which is in agreement with the observed catalytic activity (**50c** > **50b** > **50a**).

Further on, the general applicability of the isolated manganese catalysts was tested for the reduction of various esters including aromatic, aliphatic, diesters and lactones using the optimized conditions of the benchmark reaction using **47**. For the reason that both complexes **47** and **48** have shown identical yields for different tested substrates, only **47** was used for the whole substrate scope because of the easier access of the complex.

Herein, aromatic esters containing electron-donating and electron-withdrawing substituents (Figure 14, **45a-f**), as well as sterically hindered esters (**45g-h**), were hydrogenated with good to excellent yields and full conversion. In addition, electron-rich (**45i**) and electron-poor (**45j**) esters, as well as heteroaromatic substrates (**45l** and **45q**), lactones (**45x** and **45y**) and diesters (**45r** and **45s**), were reduced smoothly in good isolated yields to the corresponding alcohols. Furthermore, in all cases of selective reduction to the corresponding alcohols it proceeded in good to very good yields with the isolated double bond remaining intact when 3-cyclohexene-1-carboxylate **45v**, as well as the bio-based methyl oleate **45u**, were used as substrates. The conjugated ester methyl cinnamate **45t** was converted to the saturated alcohol (93% yield).

The versatility of complex **47** was further demonstrated by the reduction of the flavor and fragrance agent γ-octalactone **45x** which was converted to the corresponding diol in good yield. Notably, the clean reduction of biomass-derived γ-valerolactone **45y** (GVL),[18] which is of actual interest for the concept of a biorefinery, was successfully achieved to give 1,5-pentandiol in excellent yield.

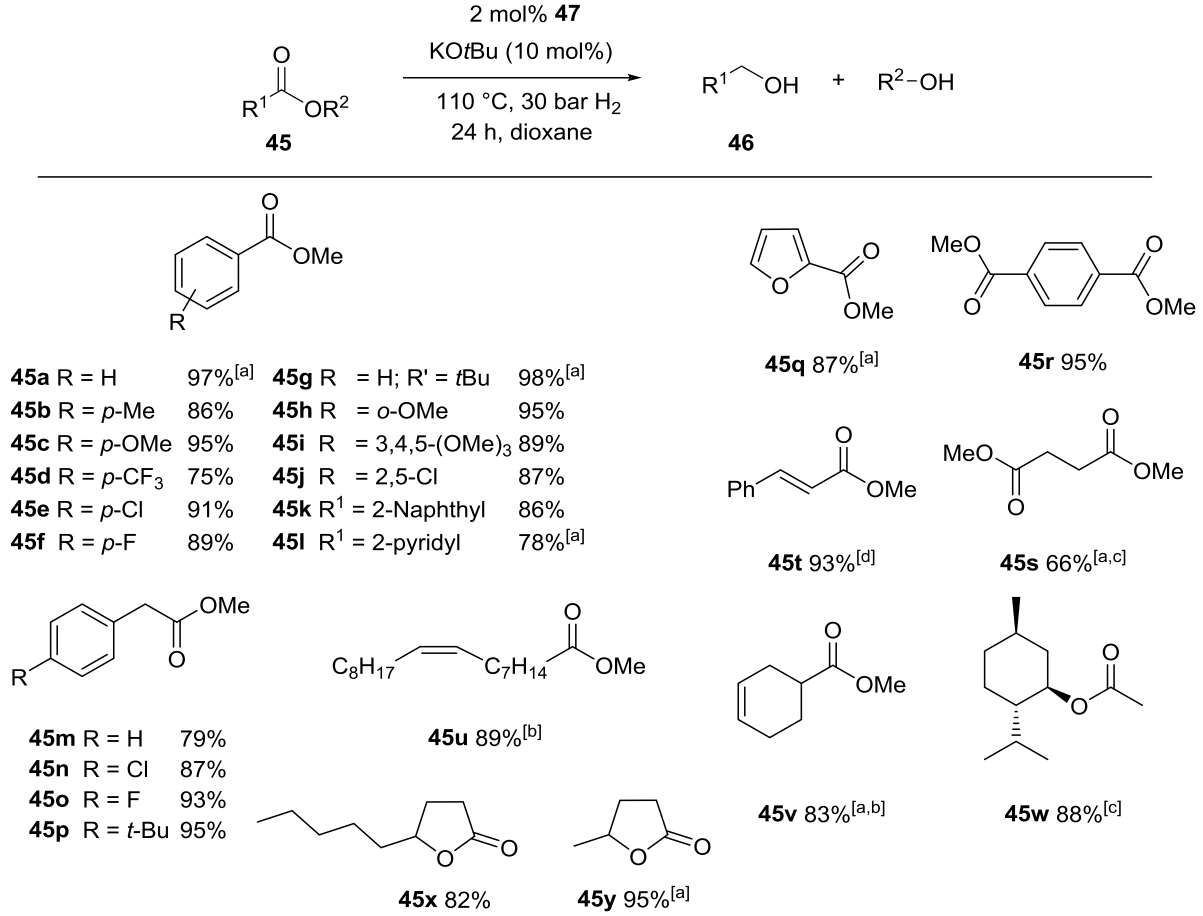


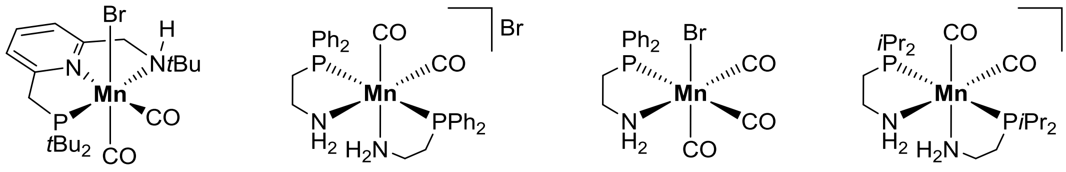
Figure 14. Manganese-catalyzed hydrogenation of aromatic and aliphatic esters. Substrate (1 mmol), **47** (2 mol%), 1,4-dioxane (2 mL), 24 h, 110 °C, 30 bar H_2. Complete conversion was determined by GC analysis. Isolated yield of **45a-y** is given. [a] Determined by GC analysis using hexadecane as an internal standard. [b] 48 h. [c] **47** (3 mol%), 48 h, 120 °C. [d] fully hydrogenated double bond.

In summary, a broad applicability of the aliphatic manganese pincer complexes **47** and **48** could be demonstrated for various ester hydrogenations. Although these complexes were less active than the corresponding iron complexes, they showed high chemoselectivity in the presence of double bonds.

3.2 Hydrogenation of Esters by Manganese Non-Pincer Type Complexes

Besides our described aliphatic pincer complexes **47** and **48**, which were active for the hydrogenation of esters, Milstein defined a lutidine-based manganese pincer complex for the same reaction.[107] Complex **51** was able to hydrogenate aromatic, as well as aliphatic esters, with good yields using only 1 mol% cat., 100 °C, THF, 21-60 h. Unfortunately, in this case KH (2 mol%) is necessary for the activation of the complex. Using KO*t*Bu under the same reaction conditions, lower yields of 38% for the benchmark reaction could be observed. In addition, only the tolerance of external alkynes, as well as cyanide as a substituent was presented. All in all, **51** displays a good alternative to our catalyst system, but is still less active than e.g. the corresponding iron pincer complexes.

To further develop the field of non-noble metal catalysis, three additional novel non-pincer-type manganese complexes (**52-54**) (Figure 15) coordinated by a bidentate aminophosphine ligand were developed.[108]



51 **52** **53** **54**

Figure 15. Lutidine based pincer complex and new non-pincer type complexes for the reduction of ketones.

All complexes were easily synthesized by reacting one or two equivalents of the PN ligand to the corresponding manganese precursor [MnBr(CO)$_5$] in toluene at 100 °C for 24 h. For both complexes **52** and **54** the coordination of the ligands is *cis* to each other while the phosphorous atoms are bound in a *trans* configuration. Compound **53** instead is a neutral complex where the amine and bromine ligands are located *cis* to each other.

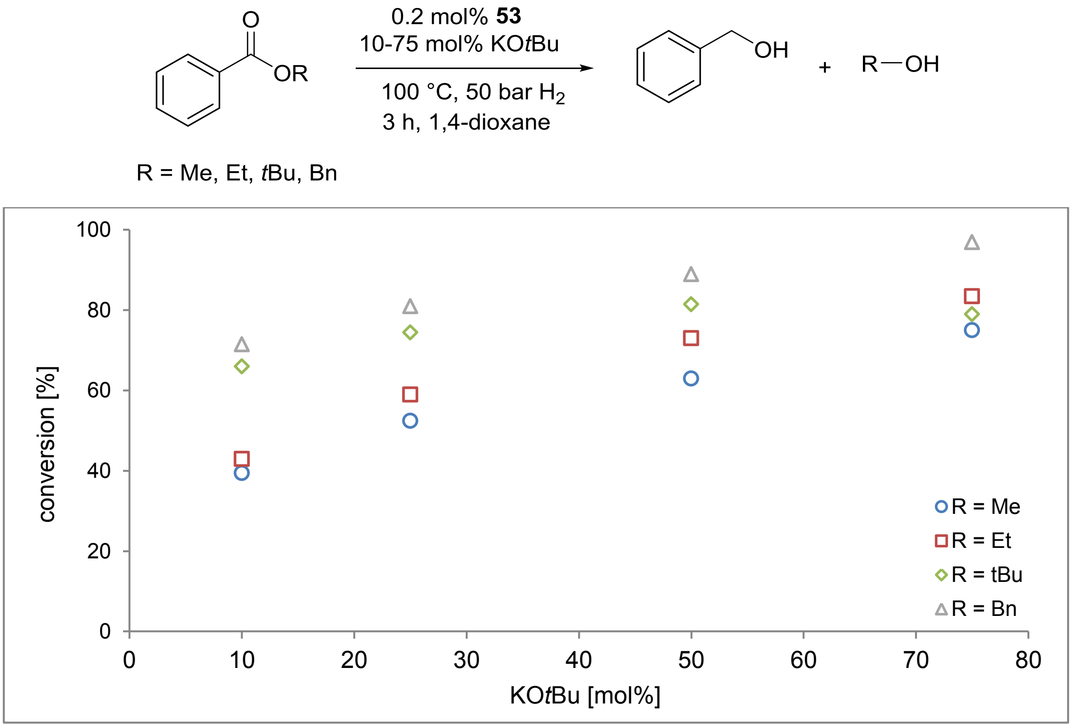


Figure 16. Effect of ester alkoxy group and KO*t*Bu amount on the degree of hydrogenation (equal to sum of the yield of benzyl alcohol, methyl benzyl ether, and 0.5 benzyl benzoate).

The first reductions of methyl benzoate with **52**, **53** and **54** have shown that **53** is the most active catalyst. Unfortunately, by varying the catalyst loading or the reaction temperature we were not able to increase the yields over 70%, which was surprising at the beginning. After optimization, the reactions extend to full conversion when at least 0.75 equivalents of base is added, with respect to the substrate. To understand the role of base, further experiments were executed. Thus, the hydrogenation of different benzyl esters under optimized conditions in dependence on the base concentration was investigated (Figure 16). For all substrates a higher conversion is obtained using higher amounts of base. Thereby the less bulky esters seem to be more influenced than the bulky ones.

In addition, a kinetic profile of the reaction with 0.1 and 0.75 equiv. of base was plotted. Remarkably herein is the limited progress of the reaction by using 0.1 equiv. of base after reaching a conversion of around 20%. Interestingly, after the addition of further 0.65 equiv. of KO*t*Bu the catalyst is reactivated.

In conclusion, with our computational studies we assume a poisoning of the metal complex by the formed methanol during the reduction of the methyl esters. A stable Mn-alkoxide complex is formed, which needs to be activated again by base. This explains the necessity of the high amount of base to achieve full conversion. This kind of product inhibition via metal-alkoxide formation is also well known for P,N-type complexes in catalysis.[109] From computations, it is shown that the regeneration of a bulkier *tert*-butoxide manganese adduct has a lower barrier than the methoxide one, which explains the higher reactivity of the bulkier esters observed during the first experiment.

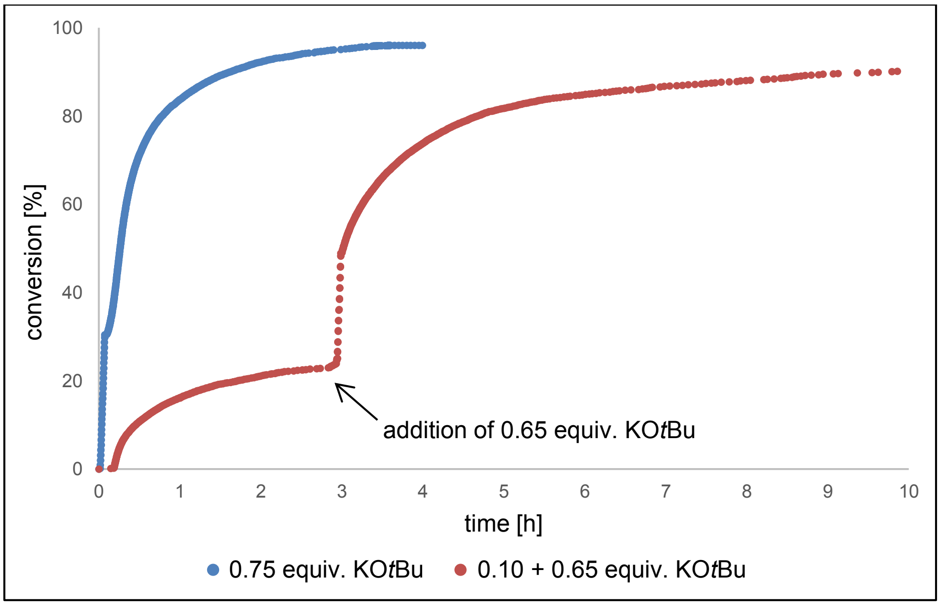
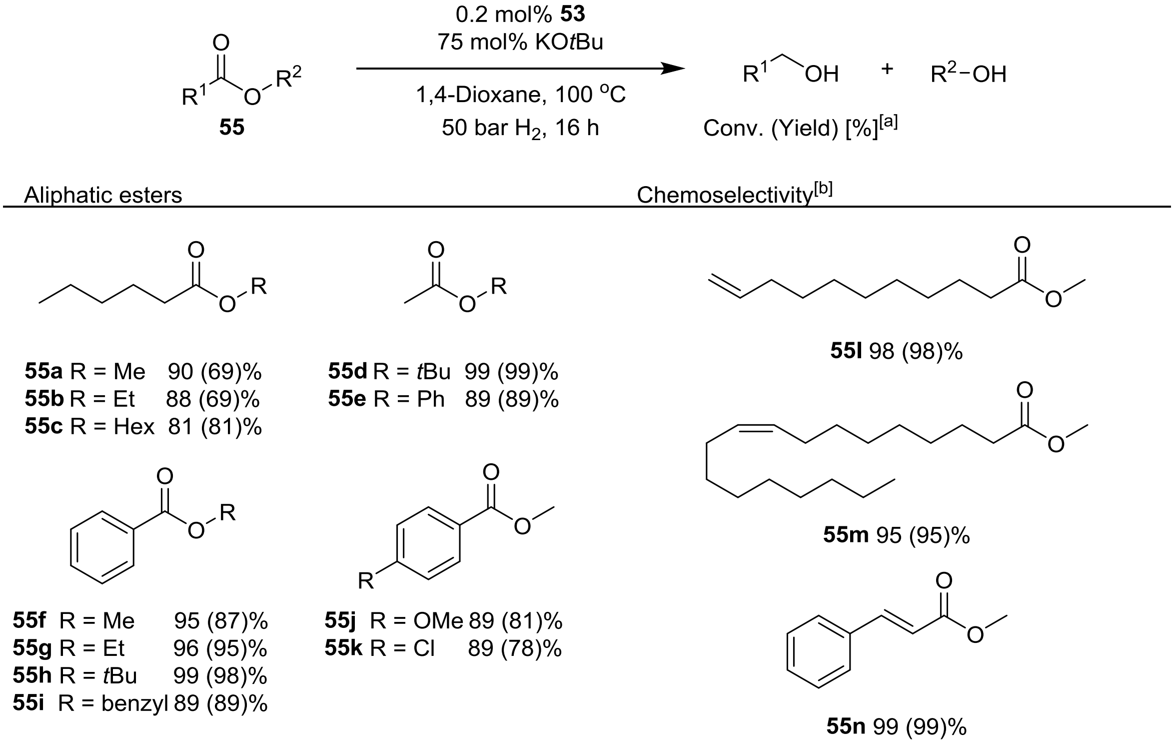


Figure 17. Kinetic traces of methyl benzoate hydrogenation with **53**. Conditions: 15 mmol substrate, 10-75 mol% KO*t*Bu, 0.5 mol% **53**, 28 mL THF, 100°C, 50 bar H_2.

After further optimization of the hydrogenation of methyl benzoate, complex **53** showed an unexpected high activity for the reduction of different esters with a low catalyst loading of 0.2 mol% at 100 °C, 16h, 50 bar H_2, 1,4-dioxane and 0.75 equiv. of KO*t*Bu. During our studies, the reduction of diverse aliphatic and aromatic esters could also be demonstrated (Scheme 8 – **55a-k**). In addition, the chemoselectivity in the presence of C=C double bonds was investigated. While isolated double bonds were not hydrogenated (**55l** and **55m**), methyl cinnamate was fully hydrogenated to hydrocinnamyl alcohol which was already observed using previously described manganese pincer complexes.



Scheme 8. Hydrogenation of different esters by complex **53**. Reaction conditions: 1 mmol substrate, 75 mol% KO*t*Bu, 0.2 mol% **53**, 2 mL 1,4-dioxane, 100 °C, 50 bar H_2, 16 h. [a] Conversion and yield are determined by GC using n-dodecane as internal standard. The yield is given in parantheses. [b] 0.5 mol% cat., 6 h.

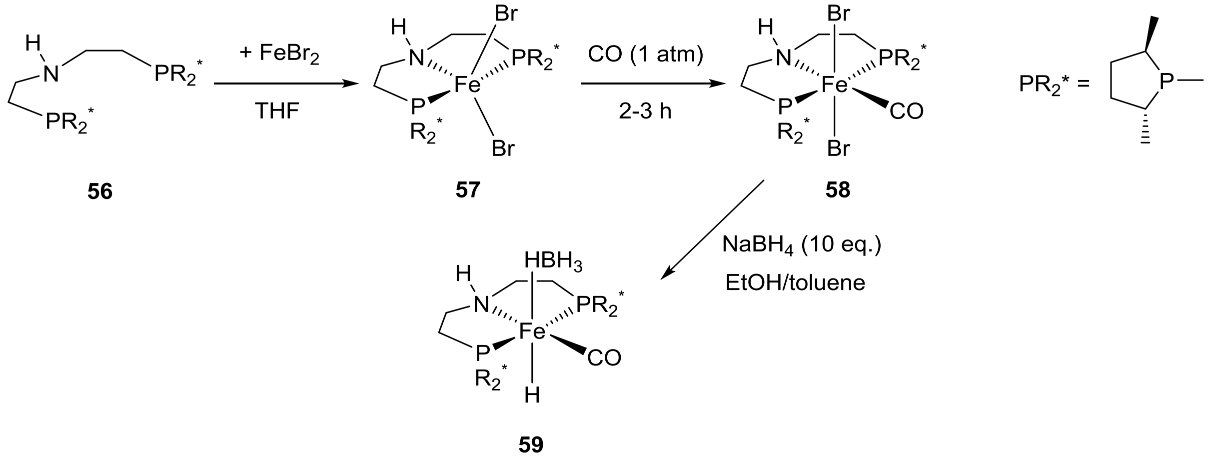
3.2 Hydrogenation of Ketones by Chiral Pincer Complexes[110]

As previously described, the asymmetric reduction of prochiral ketones with non-noble metal pincer complexes was less investigated at the beginning of our studies. Thereby, the state-of-the-art catalysts at this time have the chiral information located at the backbone of the metal complexes. There were no examples known in the literature in which the chiral centers were located at the substituents of the phosphorus atoms, or even having a chiral phosphorous atom present.

Thus, we started to synthesize the chiral pincer ligand bis(2-((2*R*,5*R*)-2,5-dimethyl-phospholano-ethyl))amine **56** which was prepared from the TMS-protected (2*R*,5*R*)-2,5-

dimethylphospholane and the bischloro(diethyl)amine by a modified literature procedure.[111] Inspired by the recent development regarding iron and manganese pincer complexes, we started to prepare different non-noble metal complexes using [MnBr(CO)$_5$] and FeBr$_2$ as precursors.

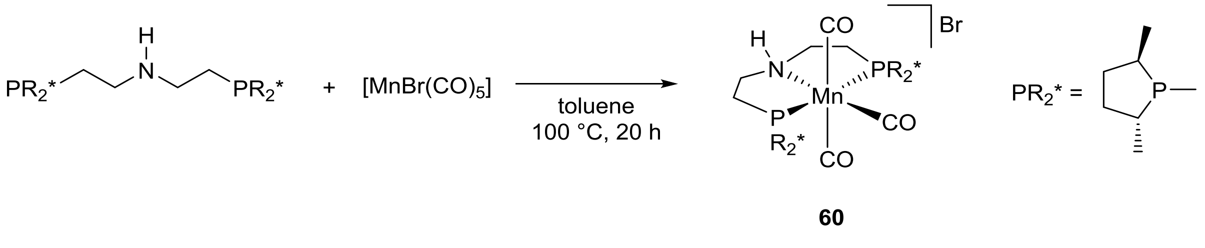
For synthesizing the iron complex **59**, FeBr$_2$ was reacted with the corresponding ligand giving the paramagnetic complex **57**. Without any further work up, **57** was converted by insertion of CO to **58**, displayed by a color change from dark yellow to blue and giving a suitable pre-catalyst for catalysis in good yields.



Scheme 9. Synthesis of chiral iron pincer complexes **58** and **59**.

To avoid an additional activation step by base during the catalytic reaction, the corresponding borohydride complex **59** was prepared in the same way to already known achiral pincer complexes by reacting **58** with 10 equiv. of NaBH$_4$. The investigations of the isolated complex by ^{31}P NMR showed two isomers in which the borohydride is orientated *cis* or *trans* to the corresponding NH proton. Thereby, the minor diastereomer isomerized completely to the major isomer within a few hours.

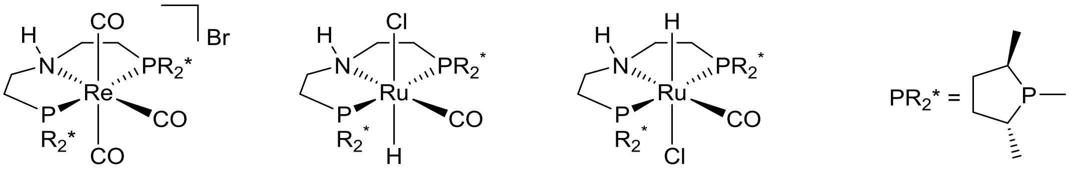
The corresponding chiral manganese catalyst was easily obtained in 72% yield by the reaction of [MnBr(CO)$_5$] with the corresponding ligand (Scheme 10). In this case, an ionic complex **60** is formed with a meridional coordinating pincer ligand as well as three carbonyl groups coordinating *trans* to the metal center.



Scheme 10. Synthesis of **60** by using [MnBr(CO)$_5$] as metal precursor.

As a proof of concept, we additionally synthesized and investigated the corresponding chiral rhenium and ruthenium pincer comples (**61** and **62a/b**) as additional representatives of group 7 and group 8 transition metals in the periodic table. Both precious metals have an increased noble character. One of our early attempts concentrated on the synthesis of the chiral rhenium complex which could be achieved by using [ReBr(CO)$_5$] as a precursor. Herein, the cationic complex **61** was formed, whereas no crystals for a suitable X-ray stucture could be achieved. Thus, it is still unclear whether a *meriodinal* or *facial* coordination occurs at least in the solid state. Some previous work, which was done with Re pincer complexes, indicate that a *facial* coordination is not unlikely and cannot be ruled out.[112]

Furthermore, by refluxing [(C$_6$H$_5$)$_3$P]$_3$Ru(CO)(Cl)H with the chiral pincer ligand in toluene for three hours, a mixture of two diastereomeric Ru-species was detected by ^{31}P NMR and could be isolated. We assume, in analogy to the two iron isomers, that these species belong to complex **62a** and **62b**, whereas **62a** could be separated by crystallization and confirmed by X-ray crystallography.



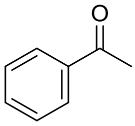
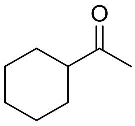
61 **62a** **62b**

Figure 18. Chiral metal pincer complexes with bis(2-((2*R*,5*R*)-2,5-dimethylphospholanoethyl))amine as ligand.

Having these complexes in hand, they were tested for the hydrogenation of acetophenone as well as cyclohexyl methyl ketone to include also an aliphatic ketone as a benchmark substrate. Cyclohexyl methyl ketone was chosen because preliminary tests revealed that the synthesized manganese complex is quite active, as well as selective, for this type of cyclic aliphatic ketone. Under the previously optimized reaction conditions, catalyst **60** gave full conversion, as well as surprisingly high selectivity (83% *ee*), for the aliphatic substrate (Table 3, entry1).

In conclusion, all new catalysts gave full conversion of acetophenone to 1-phenylethanol; although for the rhenium-derived complex **61** a higher temperature was required (Table 3, entry 2 and 3). Unfortunately, the low enantioselectivity using acetophenone could not be improved in the presence of complexes **58**, **59**, **61** or **62a/b** or by changing different reaction parameters, such as solvent, temperature or reaction time. Interestingly, the activity of Ru complex **62a** and the mixture of **62a/b** have the same activity for the benchmark reactions assuming that the same active species is formed. This assumption was proven by the reaction of **62a**, as well as the mixture of isomers with five equiv. of base, whereas the same signals for the corresponding amido species were detected by ^{31}P NMR.

Table 3. Comparison of the different chiral catalysts for the reduction of acetophenone and cyclohexyl methyl ketone.

					
Entry	Cat.	Conv.[a] [%]	*ee* [%]	Conv.[b] [%]	*ee* [%]
1	**60**	>99	18 (*S*)	>99	83 (*R*)
2	**61**	0	-	0	-
3[c]	**61**	>99	6 (*S*)	>99	60 (*R*)
4	**58**	>99	rac.	41	62 (*R*)
5	**59**	>99	rac.	>99	62 (*R*)
6	**62a**	n.d.	n.d.	>99	47 (*R*)[d]
7	**62a/b**	>99	6 (*S*)	>99	47 (*R*)[d]

Reaction conditions: [a] 1 mmol acetophenone, 1 mol% cat., 5 mol% KO*t*Bu, 30 °C, 30 bar, 4 h, 1,4-dioxane (2 mL). [b] 1 mmol cyclohexyl methyl ketone, 1 mol% cat., 5 mol% KO*t*Bu, 40 °C, 30 bar, 4 h, *t*-amyl alcohol (2 mL). [c] 100 °C, 1,4-dioxane (2 mL) for acetophenone and *t*-amyl alcohol (2 mL) for cyclohexyl methyl ketone. [d] in EtOH.

Surprisingly, better catalytic performance was obtained for the aliphatic substrate cyclohexyl methyl ketone. Nevertheless, to obtain full conversion an increased reaction temperature was required for complexes **59** and **60**. In the case of the two iron pre-catalysts (**58** and **59**) , a moderate enantiomeric excess of 62% was observed. Nearly the same selectivity was achieved using Re catalyst **61**. Interestingly, complex **60** gave the highest enantiomeric excess of 83%, whereas the lowest enantioselectivity of 47% *ee* was reached for the noble metal ruthenium complexes **62a/b** (Table 1, entries 6 and 7). Remarkably, this is one of the few cases where noble metal complexes are less selective compared to their base metal analogues.

To get some further understanding of the different selectivities and activities of the investigated complexes, we followed the reaction profile by a conversion vs. time diagram for the reduction of cyclohexyl methyl ketone (Figure 19). The Re complex **61** was not explored because of its lower activity. For complexes **59** and **60** five hours were needed to obtain full conversion of cyclohexyl methyl ketone, while in the case of **59** a slow activation period was observed. Further investigations have shown that this activation period strongly depends on the solvent used. Thus, in EtOH no further activation period could be detected. The noble metal complexes **62a/b** were the most reactive in this case, giving complete conversion after just half an hour. Thus, we assume that the difference in the energy barrier of the two isomers is not large enough to lead to a selective reaction.

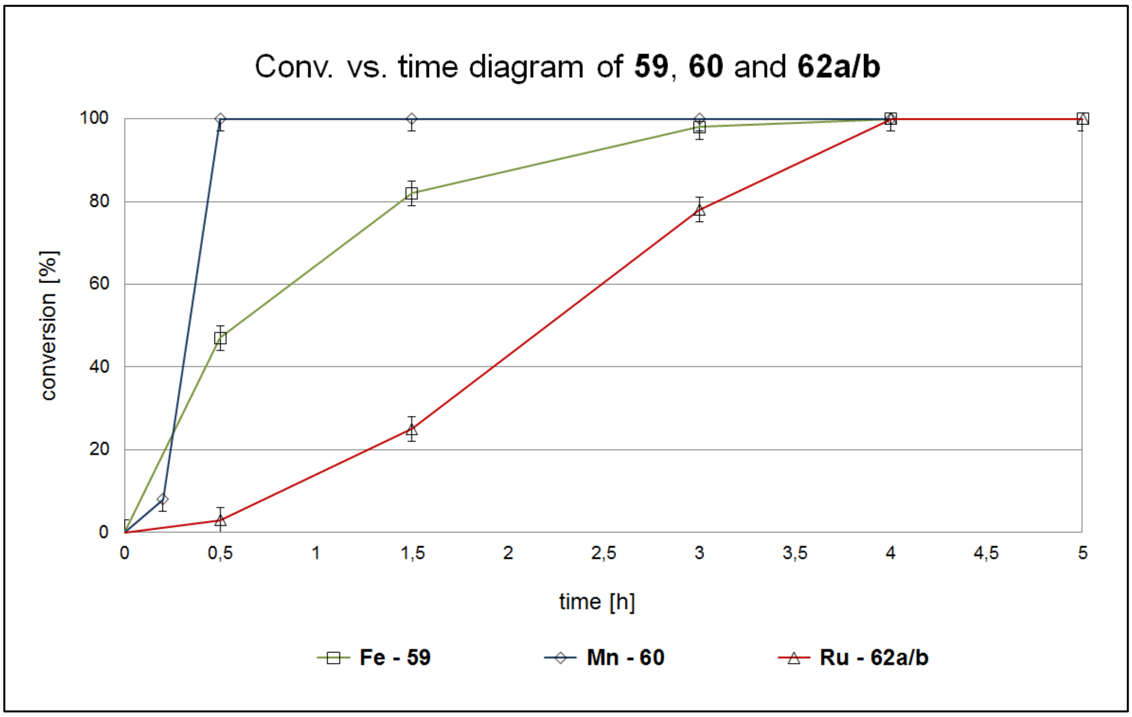
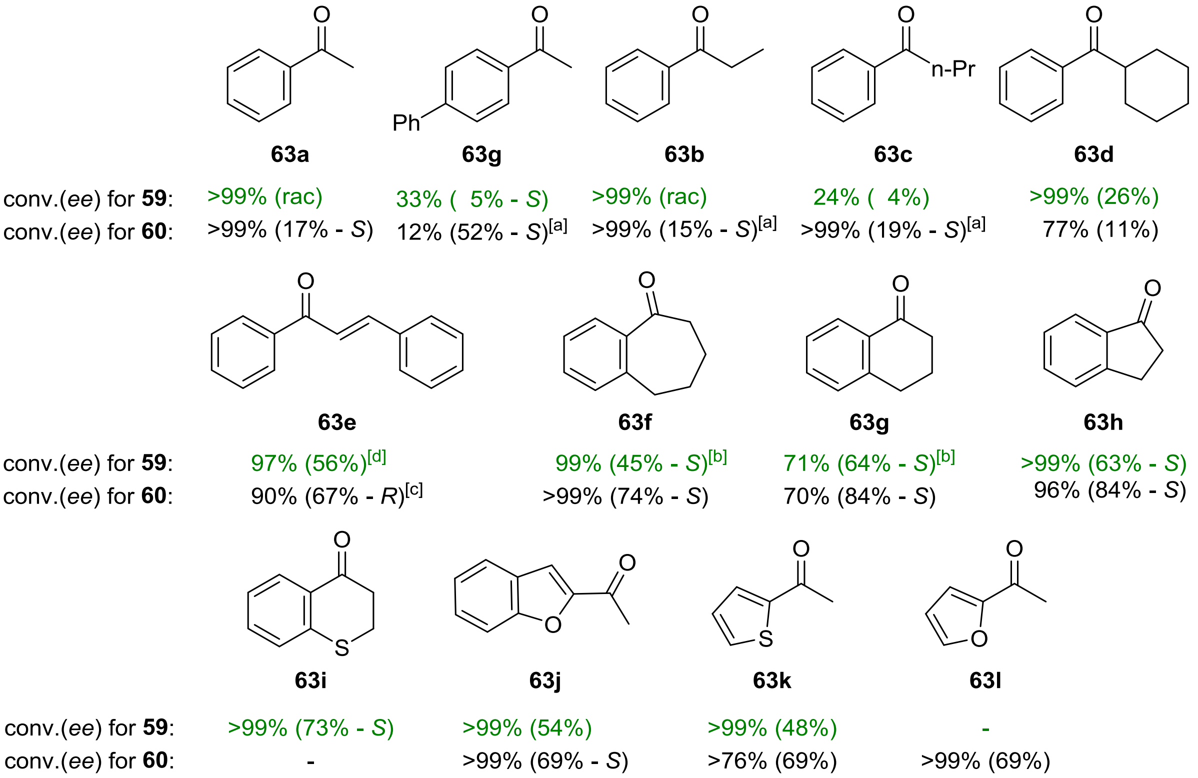


Figure 19. Conversion vs. time diagram for the comparison of the hydrogenation of cyclohexyl methyl ketone with complexes **59**, **60**, and **62a/b**. Reaction conditions: 1 mmol substrate, 1 mol% cat., 5 mol% KO*t*Bu for **60**, and **62a-b**, 40 °C, 30 bar, *t*-amyl alcohol (2 mL). Conversion was determined by GC by using hexadecane as internal standard.

For a further comparision of the chiral pincer complexes, and to elucidate the reaction mechanism for the reduction of prochiral ketones, gas-phase B3PW91 DFT computations were carried out. Herein, a concerted but asynchronous transition state for all investigated substrates with the hydride species of the catalysts is confirmed, where the transfer of Mn-H and N-H to the ketone group takes place in a concerted manner. In contrast, for rhenium a two-step mechanism is found, where the first step is the Re-H transfer to the prochiral carbon center, followed by an intermediate and the second step is the N-H transfer to the oxygen atom of the carbonyl group. Here, the transition state for Re-H transfer is the rate-determining step and is in concurrence with other two-step hydrogenation reactions.[113] Furthermore, the computed enantiomeric ratios were calculated but were determined to be mostly higher than the experimental data. This can be explained by the relatively small difference of the energy barriers. The experimentally observed sense of induction is qualitatively reproduced.

The research of this thesis was mainly focused on non-noble metal catalysis. For that reason, we further investigated the applicability of complexes **59** and **60** in the asymmetric reduction of different prochiral ketones (Figure 20 and 21).



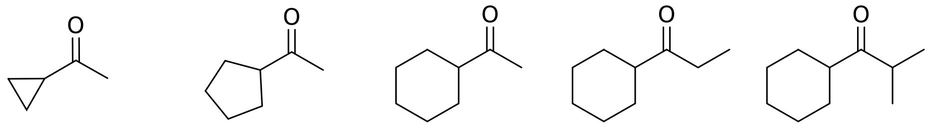
	63a	**63g**	**63b**	**63c**	**63d**
conv.(*ee*) for **59**:	>99% (rac)	33% (5% - *S*)	>99% (rac)	24% (4%)	>99% (26%)
conv.(*ee*) for **60**:	>99% (17% - *S*)	12% (52% - *S*)[a]	>99% (15% - *S*)[a]	>99% (19% - *S*)[a]	77% (11%)

	63e	**63f**	**63g**	**63h**
conv.(*ee*) for **59**:	97% (56%)[d]	99% (45% - *S*)[b]	71% (64% - *S*)[b]	>99% (63% - *S*)
conv.(*ee*) for **60**:	90% (67% - *R*)[c]	>99% (74% - *S*)	70% (84% - *S*)	96% (84% - *S*)

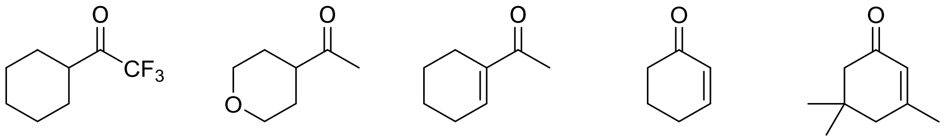
	63i	**63j**	**63k**	**63l**
conv.(*ee*) for **59**:	>99% (73% - *S*)	>99% (54%)	>99% (48%)	-
conv.(*ee*) for **60**:	-	>99% (69% - *S*)	>76% (69%)	>99% (69%)

Figure 20. Asymmetric reduction of prochiral ketones by **59** (upper results) and **60** (lower results). General conditions for **59**: 1 mmol substrate, 1 mol% cat., 30 bar H_2, 3 h, 30 °C, EtOH (2 mL). General conditions for **60**: 1 mmol substrate, 1 mol% cat., 5 mol% KO*t*Bu, 30 bar H_2, 4 h, 30 °C, 1,4-dioxane (2 mL). Conversion was determined by GC using hexadecane as an internal standard. [a] 2 mol% cat., 3 h, 50 °C, EtOH (2 mL). [b] 6 h. [c] 2 mol% cat., 50 °C, 1 h, *i*PrOH (2 mL), 36% 1,3-diphenylpropan-1-ol (10% *ee*). [d] 6% 1,3-diphenylpropan-1-ol.

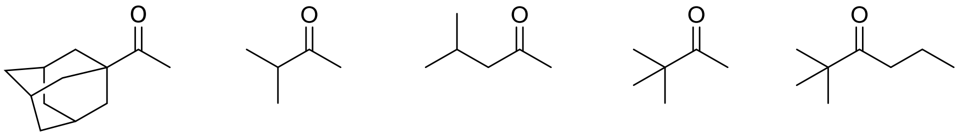
As noticed before, the manganese complex is less active than the iron one which could already be observed in other achiral reactions using this kind of aliphatic PNP pincer ligand as backbone. Interestingly, not only for cyclohexyl methyl ketone but also for most of the investigated substrates, a higher enantioselectivity for the Mn pincer complex **60** was determined. In contrary to these results, for acetophenone and its derivatives, only low enantiomeric excesses, as well as racemic mixtures, were detected (Figure 17, entries **63a-63d**). Different electron-withdrawing or -donating substituents, as well as bulky ones in the *ortho* or *para* position did not have any noticeable influence on the selectivity, nor did bulkier groups like those in **63b** and **63c**. For these substrates only a decrease of the activity was observed. Interestingly, for heteroaromatic ketones (**63i-63l**), as well as bicyclic aromatic hydrocarbons with an α-keto group (**63f-63h**), the enantioselectivity increased dramatically. Thus, up to 73% *ee* was observed for thiochroman-4-on by using **59** and 84% *ee* for the reduction of α-tetralone and inden-1-one, using catalyst **60**.



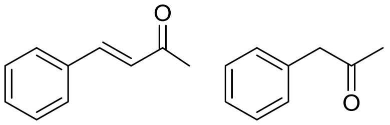
	64a	**64b**	**64c**	**64d**	**64e**
conv.(*ee*) for **59**:	>99% (31%)	>99% (60%-*R*)	>99% (64%-*R*)	-	78% (32%)
conv.(*ee*) for **60**:	96% (70%)	61% (74%-*R*)	>99% (83%-*R*)	26% (71%)	54% (39%)



	64f	**64g**	**64h**	**64i**	**64j**
conv.(*ee*) for **59**:	>99% (16%)	>99% (46%)	97% (64%)[b]	98% (46%)[d]	96% (52%-*S*)
conv.(*ee*) for **60**:	23% (57%)	>99% (79%)	>99% (51%)[a]	94% (52%)[c]	64% (61%-*S*)



	64k	**64l**	**64m**	**64n**	**64o**
conv.(*ee*) for **59**:	65% (>99%)	>99% (57%)	-	17% (32%)	36% (35%)[f]
conv.(*ee*) for **60**:	28% (>99%)	>99% (68%)[e]	>99% (31%)[e]	22% (25%)[e]	3% (48%)[e]



	64p	**64q**
conv.(*ee*) for **59**:	>99% (48%)	>99% (19%)
conv.(*ee*) for **60**:	87% (59%)[g]	-

Figure 21. Reduction of cyclic and branched aliphatic ketones by **59** (upper results) and **60** (lower results). General conditions for **59**: 1 mmol substrate, 1 mol% cat, 30 bar H_2, 6 h, 30 °C, EtOH (2 mL). General conditions for **60**: 1 mmol substrate, 1 mol% cat., 5 mol% KO*t*Bu, 30 bar H_2, 4 h, 40 °C, *tert*-amyl alcohol (2 mL). Conversion was determined by GC using hexadecane as an internal standard. [a] 25% SP. [b] 3% SP. [c] 6% SP. [d] 8% SP. [e] 2 mol% cat., 5 h, 80 °C, *t*-amyl alcohol. [f] 60 °C. [g] 5 mol% NaO*t*Bu, 50 °C, EtOH – 13% of side product: 1-phenyl-3-butanol.

In addition, the reactivity of the new chiral non-noble metal pincer complexes was tested for the hydrogenation of cyclic and branched aliphatic ketones. As presented in Figure 21, the decrease of the ring size in the cyclic part of the ketone (**64a-c**) does not have a significant influence on the activity of the complexes. However, the enantioselectivity dropped down using cyclopropyl methyl ketone (**64a**) and **59** as catalyst.

If the bulkier cyclohexyl ethyl or isopropyl ketone is used, a decreased activity, as well as selectivity, for both complexes is observed (**64d-f**). 1-Cyclohexenyl methyl ketone (**64h**) was reduced with nearly the same enantiomeric excess with both catalysts (51% *ee* and 52% *ee*, respectively), whereas complex **64** was less selective regarding the C=C double bonds and produced a significant amount of cyclohexylethanol (25%). By using cyclohexanone (**64i**), only small amounts of side-products could be detected and good to moderate enantioselectivities of 62% *ee* (complex **60**) and 46% *ee* (complex **59**) were determined. Notably, the bulky substrate adamantyl methyl ketone (**64k**) was hydrogenated with excellent enantioselectivity of >99% *ee* with both complexes, whereas the iron complex **59** still has a higher activity. On the other hand, the reduction of 3,3-dimethyl-butan-2-one (**64n**) was realized with low enantioselectivities of 25% *ee* and 32% *ee*. A variation of the bulkiness of the substituents on the keto group does not cause an improvement of the enantioselectivity (**64l-q**). The best result was obtained for the reduction of 3-methyl-2-butanone with complex **60** giving an enantiomeric excess of 68% (**64l**).

4 Summary and Outlook

The aim of this work was the synthesis of new (chiral) non-noble metal complexes, especially those containing manganese metal centers, for the (asymmetric) reduction of carbonyl bonds. This includes the asymmetric reduction of ketones, as well as the hydrogenation of esters, by different pincer complexes, as well as by non-pincer type complexes for the latter reaction.

In detail, a new achiral Et_2PNP manganese pincer complex was synthesized and efficiently used for the hydrogenation of esters, while already published aliphatic manganese pincer complexes showed only very low reactivities. The applied Et_2PNP pincer complex was *cis* coordinated by additional three carbonyl atoms, resulting in a cationic complex having a bromine counteranion. However, by refluxing this complex in toluene the tricarbonyl complex could be transformed to the neutral species where one CO ligand is exchanged by a bromine anion. Nevertheless, both complexes form the same active species after addition of base and have shown comparable activities regarding the investigated reduction of esters.

As an alternative complex system, we synthesized a bidentate PN ligand, which was tested for the hydrogenation of esters after coordination to a manganese metal center. Three different catalysts were isolated in which one of these complexes had an increased activity compared to the previously discussed pincer complex. Disappointingly, a high amount of base is needed during the reaction due to catalyst inhibition by alkoxide coordination.

The main project of this thesis was the synthesis of a new type of chiral pincer ligand in which the chirality is located at the substituents of the phosphorous atoms at the PNP pincer ligand. The resulting complex, consisting of a phospholane unit at each phosphorus atom, was coordinated to different metals (Mn, Fe, Ru, Re) and the activity, as well as selectivity regarding the hydrogenation of aliphatic and aromatic ketones, was compared with each other. In contrast to other chiral iron and manganese complexes, the new catalysts were highly selective for the reduction of cyclic aliphatic ketones (up to 99% *ee*). Unfortunately, by using acetophenone and analogous derivatives, only racemic mixtures, or very low enantiomeric excesses, were observed, while heteroaromatic and branched aliphatic ketones were reduced with enantioselectivities up to 70% *ee* under relatively mild conditions. The noble ruthenium metal complex instead has a lower selectivity of 47% *ee*, regarding cyclohexylmethyl ketone.

Preliminary studies by choosing a bulky BINAP related group at the phosphorus donor atoms of the PNP pincer ligand results in an inactive iron complex. Related to the higher activity of the investigated ruthenium pincer complex this ligand should be tested coordinated to a ruthenium metal center. In addition, future studies can deal with the use of more bulky substituents at the phospholane unit. Herein, ethyl, *iso*propyl or phenyl groups are conceivable to further increase the enantioselectivity, especially of the aliphatic alcohols. In addition, the usage of an aromatic backbone could be useful to enforce the selective hydrogenation of aromatic substrates through the presence of π-π interactions.

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6 Selected Publications

The following chapter contains the original publications wherein the previously presented research was reported. My contribution to each chapter is outlined in the subchapters:

6.1 Hydrogenation of Esters to Alcohols Catalyzed by Defined Manganese Pincer Complexes

Saravanakumar Elangovan*, Marcel Garbe*, Haijun Jiao, Anke Spannenberg, Kathrin Junge, and Matthias Beller

Angew. Chem. Int. Ed. **2016**, *55*, 15364–15368.

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This manuscript regarding the reduction of ketones was prepared in cooperation with Saravanakumar Elangovan. Both of us were participated in the synthesis of the investigated complexes. In addition I did the testing’s regarding the substrate scope including the product isolation as well as the preparation of the supporting information and the final work concerning the publication of the manuscript. First and second author contributed equally to this publication and my work is about 40%.

Hydrogenation Very Important Paper

International Edition: DOI: 10.1002/anie.201607233
German Edition: DOI: 10.1002/ange.201607233

Hydrogenation of Esters to Alcohols Catalyzed by Defined Manganese Pincer Complexes

Saravanakumar Elangovan[+]*, Marcel Garbe*[+]*, Haijun Jiao, Anke Spannenberg, Kathrin Junge, and Matthias Beller**

Abstract: *The first manganese-catalyzed hydrogenation of esters to alcohols has been developed. The combination of* $Mn(CO)_5Br$ *with* $[HN(CH_2CH_2P(Et)_2)_2]$ *leads to a mixture of cationic and neutral Mn PNP pincer complexes, which enable the reduction of various ester substrates, including aromatic and aliphatic esters as well as diesters and lactones. Notably, related pincer complexes with isopropyl or cyclohexyl substituents showed very low activity.*

The catalytic hydrogenation of esters to the corresponding alcohols is an important basic transformation for organic synthesis, which is also applied in industry for producing flavors, fragrances, and other fine-chemical intermediates as well as monomers for polyesters.[1] Compared to classic stoichiometric reductions, these reactions are advantageous with respect to costs and waste formation.[2] Although many hydrogenations of aldehydes and ketones have been reported, the reduction of carboxylic acids and their esters using H_2 is a more challenging task owing to the lower electrophilicity of the carbonyl carbon atom.[3]

In this respect, the development of more active well-defined homogeneous catalysts for ester hydrogenation is interesting.[4] Notably, in the past decade, several groups from industry (e.g., Firmenich) and academia reported defined metal complexes based on ruthenium,[5] osmium,[6] and iridium[7] for this transformation. However, these expensive and potentially toxic noble metals should ideally be replaced by earth-abundant, inexpensive, and environmentally more benign metals, especially iron and manganese.[8] Whereas in recent years, major developments have been achieved with iron and cobalt complexes both for hydrogenation and dehydrogenation reactions, manganese is much less explored.[9] For example, in 2014, Milstein and co-workers reported the first iron-catalyzed hydrogenation of activated esters to the corresponding alcohols.[10] Furthermore, our group and Guan and co-workers independently described hydrogenation reactions of non-activated esters with PNP iron pincer complexes.[11] Since then, an improved second-generation iron pincer complex[12] and different cobalt complexes[13] have been published for effective ester hydrogenation.

After iron and titanium, manganese is the most abundant transition metal in the Earth's crust. Moreover, most compounds of this latter element show low toxicity, which currently makes it a highly attractive aspirant for the design of new catalysts.[14] In general, manganese catalysts are well known for oxidation reactions whereas reductive transformations were basically unknown until very recently.[15,16] Thus we were very surprised when we discovered that catalytic hydrogenations of aldehydes, ketones, and nitriles can be conducted in the presence of manganese pincer complex **1** whereas Kempe et al. were able to reduce ketones and aldehydes under milder conditions by using a PN_5P ligand.[17] Inspired by these recent developments, we also became interested in manganese-catalyzed ester hydrogenations. To the best of our knowledge, no manganese catalyst has been described for such reductions. Herein, we present the first example of an efficient and selective method for the hydrogenation of various esters into the corresponding alcohols in the presence of molecularly defined manganese complexes (Figure 1).

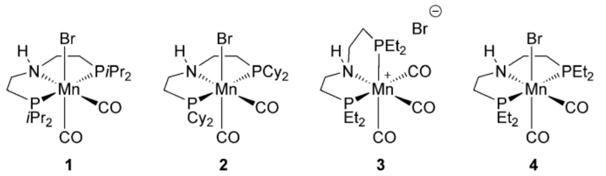

Figure 1. Manganese pincer complexes used in this study.

Initial experiments were performed using methyl benzoate (**6a**) as a benchmark substrate in the presence of 2 mol% catalyst at 30 bar H_2 and 100 °C. Unfortunately, complex **1**, which showed high activity in the hydrogenation of ketones, afforded only very low yields of the desired alcohol (Table 1, entry 1). Similarly, the cyclohexyl-substituted manganese pincer complex **2** proved to be not suitable (entry 2). To improve the catalyst activity, we focused on the synthesis of less hindered manganese complexes. Therefore, reactions of $Mn(CO)_5Br$ with the Et_2PNP pincer ligand were performed. However, in toluene at 100 °C, a mixture of the di- and tricarbonyl manganese complexes **3** and **4** was obtained (**3**: 64 %; **4**: 18 %), which could be isolated and characterized by spectroscopic methods (see the Supporting Information). Interestingly, complex **4** can be formed in higher yield (72 %) when **3** is heated to reflux in toluene for additional 16 h. X-ray

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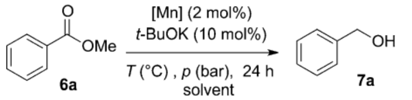
Table 1: Manganese-catalyzed hydrogenation of methyl benzoate (**6a**): Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	p [bar]	T [°C]	Yield[b] [%]
1	**1**	toluene	30	100	6
2	**2**	toluene	30	100	2
3[c]	**1**	toluene	80	120	38
4	**3**	toluene	30	100	82
5	**3**	1,4-dioxane	30	100	93
6	**3**	1,4-dioxane	10	100	51
7	**3**	1,4-dioxane	30	110	97
8	**3**	1,4-dioxane	30	80	46
9	**4**	1,4-dioxane	30	110	97

[a] General reaction conditions: **6a** (0.5 mmol), **1–4** (2 mol%), solvent (1 mL), *t*-BuOK (10 mol%), 24 h, 80–110°C, 10–30 bar H_2. [b] Yield determined by GC analysis using hexadecane as an internal standard. [c] **1** (3 mol%).

analysis of tricarbonyl complex **3** revealed that the Mn center has a distorted octahedral coordination sphere, where both P atoms and the N atom as well as the three CO ligands are located *cis* to each other (Figure 2). This configuration with the two P atoms in *cis* position is surprising as in PNP pincer complexes, such as **1**, **2**, and **4** as well as related Fe, Ru, Os, and Ir pincer complexes, the two P atoms usually adopt a *trans* orientation.

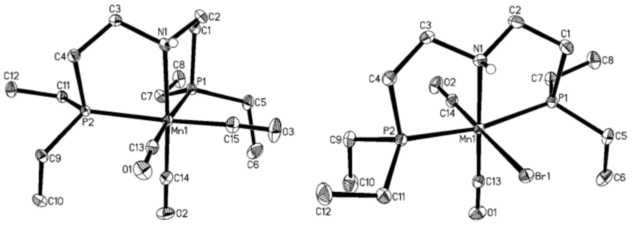


Figure 2. Molecular structures of complexes **3** (left) and **4** (right). Only the cation of **3** is shown. Thermal ellipsoids set at 30% probability. Hydrogen atoms except for those attached to nitrogen omitted for clarity.

To understand this unusual coordination mode, the relative energies of the cationic tricarbonyl complexes with two P ligands in *cis* (3^+-*cis*) and *trans* (3^+-*trans*) position were computed (Figure 3). 3^+-*trans* is more stable than 3^+-*cis* by 7.9 kcal mol^{-1}, indicating that 3^+-*cis* should be the kinetic product. Furthermore, the relative stability of **5**-*cis* and **5**-*trans* from the N–H deprotonation of 3^+-*cis* and 3^+-*trans* was computed. Again, the *trans* complex is more stable than the *cis* isomer by 10.1 kcal mol^{-1}. Furthermore, the energies of CO dissociation from **5**-*trans* and **5**-*cis* resulting in **3b** were computed. CO dissociation from **5**-*trans* is endergonic by 2.4 kcal mol^{-1} whereas CO dissociation from **5**-*cis* is exergonic by 7.7 kcal mol^{-1}.

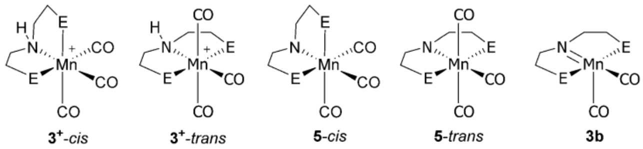


Figure 3. Calculated structures of different manganese complexes. E = P(Et)$_2$.

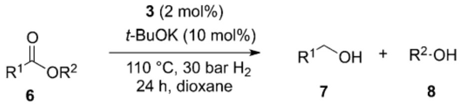
Catalytic tests using **3** in the benchmark reaction revealed a significantly enhanced activity and gave benzyl alcohol in 82% yield (Table 1, entry 4). Even better results were obtained in 1,4-dioxane (93%; entry 5). Interestingly, even at low pressure (10 bar H_2), the desired product was obtained (51%, entry 6). Slightly increasing the temperature to 110°C led to nearly quantitative yield (97%, entry 7). As expected, **4** showed similar activity to that of **3** under the optimized reaction conditions (entries 7 and 9), suggesting that both precursors **3** and **4** form the same active species **3b**. Furthermore, a yield/time analysis showed comparable behavior for complexes **3** and **4** (see the Supporting Information), which supports this hypothesis.

Next, the general applicability of these manganese catalysts was tested for the reduction of various esters, including aromatic and aliphatic esters as well as diesters and lactones (2 mol% catalyst loading, 10 mol% *t*-BuOK, 30 bar H_2, 110°C, 1,4-dioxane). Testing selected substrates with complexes **3** and **4** confirmed that these complexes gave the corresponding products in equal yields.

Esters containing electron-donating and electron-withdrawing substituents were hydrogenated to the corresponding alcohols with moderate to good yields (Table 2, entries 1–7). Furthermore, sterically hindered (**6h**), electron-rich (**6i**), and electron-poor (**6j**) esters as well as heteroaromatic substrates (**6l** and **6m**) were smoothly reduced, and the corresponding products were isolated in good yields (78–95%).

Next, we examined the hydrogenation of benzylic and aliphatic esters under the optimized reaction conditions. In all

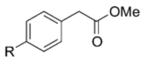
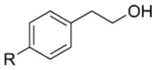
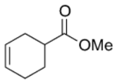
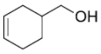
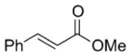
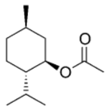
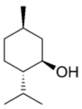
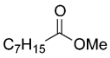
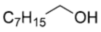
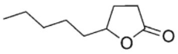
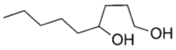
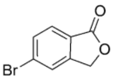
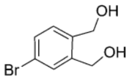
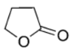
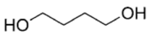
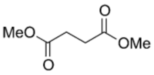
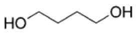
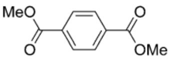
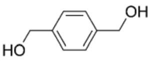
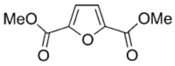
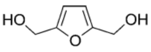
Table 2: Manganese-catalyzed hydrogenation of aromatic esters.[a]



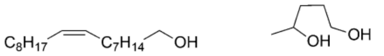
Entry	Substrate	R^1	R^2	Yield[b] **7** [%]
1	**6a**	C_6H_5	Me	97[c]
2	**6b**	C_6H_5	*t*-Bu	98[c]
3	**6c**	*p*-MeC_6H_4	Me	86
4	**6d**	*p*-MeOC_6H_4	Me	95
5	**6e**	*p*-$CF_3C_6H_4$	Me	75
6	**6f**	*p*-ClC_6H_4	Me	91
7	**6g**	*p*-FC_6H_4	Me	89
8	**6h**	2-MeOC_6H_4	Me	95
9	**6i**	3,4,5-(MeO)$_3C_6H_2$	Me	89
10	**6j**	2,5-$Cl_2C_6H_3$	Me	87
11	**6k**	2-naphthyl	Me	86
12	**6l**	2-furyl	Me	87[c]
13	**6m**	3-pyridinyl	Me	78[c]

[a] Substrate (1 mmol), **3** (2 mol%), 1,4-dioxane (2 mL), 24 h, 110°C, 30 bar H_2. [b] Yields of isolated products are given. [c] Determined by GC analysis using hexadecane as an internal standard.

Table 3: Manganese-catalyzed hydrogenation of benzylic and aliphatic esters as well as diesters and lactones.[a]

Entry	Ester	Alcohol	Conv. (yield) [%]
			
1	**9a** R=H		>99 (79)
2	**9b** R=Cl		>99 (87)
3	**9c** R=F		>99 (93)
4	**9d** R=*t*-Bu		>99 (95)
5[b,d]	 **9e**		98 (83)
6	 **9f**		>99 (93)
7[c]	 **9g**		97 (88)
8[d]	 **9h**		92 (71)
9	 **9i**		>99 (82)
10	 **9j**		>79 (57)
11[d]	 **9k**		>99 (88)
12[c,d]	 **9l**		>93 (66)
13	 **9m**		>99 (95)
14[c]	 **9n**		>99 (58)

[a] Substrate (1 mmol), **3** (2 mol %), 1,4-dioxane (2 mL), 24 h, 110 °C, 30 bar H_2. The conversions were determined by GC using hexadecane as an internal standard. Yields of isolated products are given in parentheses. [b] 48 h. [c] **3** (3 mol %), 48 h, 120 °C. [d] The GC yield was determined using hexadecane as an internal standard.



10a 95(89)[a] **10b** >99(95)[b]

Figure 4. Hydrogenation of bio-based carboxylic esters. General reaction conditions: substrate (1 mmol), **3** (2 mol %), 1,4-dioxane (2 mL), 24 h, 110 °C, 30 bar H_2. The conversions were determined by GC analysis using hexadecane as an internal standard. Yields of isolated products are given in parentheses. [a] **3** (3 mol %), 48 h, 120 °C. [b] The GC yield was determined with hexadecane as an internal standard.

cases, selective reduction to the corresponding alcohol proceeded in good to very good yields (Table 3, **9a–9h**). Interestingly, the isolated double bond remained intact when 3-cyclohexene-1-carboxylate (**9e**) or bio-based methyl oleate **10a** (Figure 4) was used as the substrate, whereas the conjugated ester methyl cinnamate (**9f**) produced the saturated alcohol (93 %).

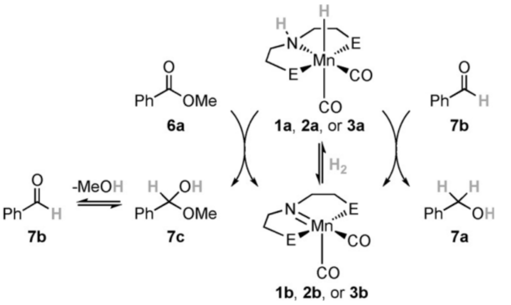
The versatility of complex **3** was further demonstrated for the reduction of lactones and diesters to diols (Table 3, entries 9–14). For example, the flavor and fragrance agent γ-octalactone was converted into the corresponding diol in good yield. Notably, the clean reduction of bio-mass derived γ-valerolactone (**10b**; GVL),[18] which is of actual interest for biorefinery, was successfully achieved to give 1,5-pentanediol in excellent yield (Figure 4). Finally, aromatic and aliphatic diesters were reduced to the corresponding diols in moderate to good yields (Table 3, entries 12 and 14).

To elucidate the reaction mechanism and to understand the different performance of catalysts **1a**, **2a**, and **3a**, which can be obtained from the corresponding precatalysts **1**, **2**, and **3**, B3PW91 DFT computations were carried out (see the Supporting Information). The formation of **3a** was proposed based on the fact that the cationic ethyl complex **3** and the neutral ethyl complex **4** show the same catalytic performance. This assumption was supported by NMR experiments where the active amido species **3b** was observed when precatalysts **3** and **4** were treated with base (see the Supporting Information).

Modelling studies showed that the hydride complexes **1a**–**3a** are very stable towards CO dissociation. Furthermore, a well-balanced equilibrium is established for the concerted H_2 elimination from **1a**–**3a** to the respective amido complexes **1b**–**3b**. For all complexes, the barrier of H_2 elimination is around 20 kcal mol^{-1}, and the reactions are slightly exergonic by 0.2–1.5 kcal mol^{-1}.

On the base of our computations, the following outer-sphere mechanism was postulated (Scheme 1). Methyl benzoate (**6a**) is reduced in two cycles via the corresponding hemiacetal **7c**. A stepwise process was identified for the first cycle (**6a** to **7c**). The hydrogen atoms are transferred in a stepwise process as a hydride from the manganese center and as a proton from the nitrogen ligand in **1a** (**2a** or **3a**), resulting in amido complex **1b** (**2b** or **3b**). In the first step, Mn–H···C transfer results in an intermediate, and the second-step N–H···O transfer results in **7c**. Furthermore, it was found that for all catalysts, the first step has a higher barrier than the second step (32.7 vs. 30.1, 34.1 vs. 27.9, and 31.8 vs. 25.8 kcal mol^{-1}, respectively, for **1a**, **2a**, and **3a**).

Next, hemiacetal **7c** dissociates to give benzaldehyde **7b** and methanol while the amido complex is regenerated by addition of H_2. In the second cycle, benzaldehyde **7b** is



Scheme 1. Proposed mechanism for the manganese-catalyzed ester hydrogenation using **6a** as a representative substrate.

hydrogenated to benzyl alcohol **7a** in a stepwise process. Again, the first step has a higher barrier than the second step (15.6 vs. 11.9, 18.5 vs. 13.5, and 15.9 vs. 12.8 $\mathrm{kcal\,mol^{-1}}$, respectively, for **1a**, **2a**, and **3a**). Based on the energy barriers of both cycles, we propose the initial reduction of the ester to be rate-determining. Comparing the different catalysts for this first hydrogenation cycle, **3a**/**3b** has the lowest barrier followed by **1a**/**1b** and **2a**/**2b**, which is in agreement with the observed catalytic activity (**3** > **1** > **2**).

In conclusion, we have described the first hydrogenation of esters to alcohols that is catalyzed by molecularly defined manganese complexes. This catalytic system enabled the effective and selective hydrogenation of various aromatic and aliphatic esters as well as diesters and lactones. Experimental evidence and DFT calculations showed that the reaction proceeds through an outer-sphere mechanism.

Keywords: alcohols · esters · homogeneous catalysis · hydrogenation · manganese

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6.2 Non-Pincer-Type Manganese Complexes as Efficient Catalysts for the Hydrogenation of Ester

Robbert van Putten, Evgeny A. Uslamin, Marcel Garbe, Chonh Liu, Angela Gonzalez-de-Castro, Martin Lutz, Kathrin Junge, Emiel J. M. Hensen, Matthias Beller, Laurent Lefort, and Evgeny A. Pidko

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Herein I participated in the discussion and interpretation of the experimental data and assisted in the preparation and characterization of the different catalysts. My work as co-author accounts approximately 10% of the publication.

Hydrogenation Catalysts

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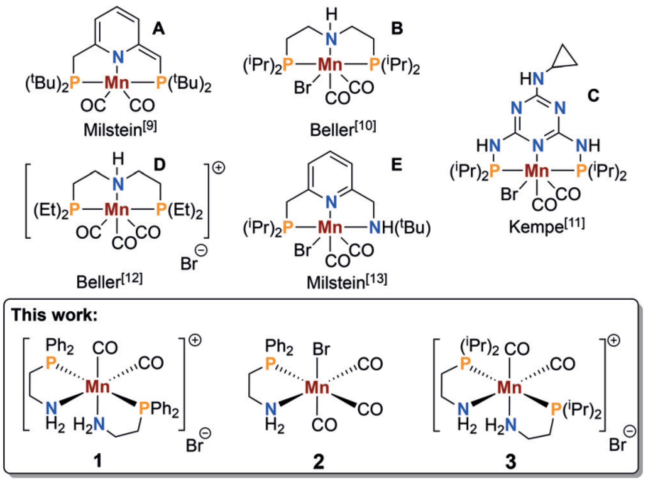
Non-Pincer-Type Manganese Complexes as Efficient Catalysts for the Hydrogenation of Esters

*Robbert van Putten, Evgeny A. Uslamin, Marcel Garbe, Chong Liu, Angela Gonzalez-de-Castro, Martin Lutz, Kathrin Junge, Emiel J. M. Hensen, Matthias Beller, Laurent Lefort, and Evgeny A. Pidko**

Abstract: *Catalytic hydrogenation of carboxylic acid esters is essential for the green production of pharmaceuticals, fragrances, and fine chemicals. Herein, we report the efficient hydrogenation of esters with manganese catalysts based on simple bidentate aminophosphine ligands. Monoligated Mn PN complexes are particularly active for the conversion of esters into the corresponding alcohols at Mn concentrations as low as 0.2 mol% in the presence of sub-stoichiometric amounts of KO^{t}Bu base.*

The reduction of polar carbonyl moieties is a fundamental organic transformation important for the production of a wide variety of bulk- and fine chemicals, such as biofuels, fragrances, and pharmaceuticals. Catalytic processes employing H_2 as the reductant represent an atom-efficient and sustainable alternative to conventional stoichiometric approaches.[1] To date a wide range of versatile and highly active homogeneous ester hydrogenation catalysts based on Ru,[2] Os,[3] and Ir[4] have been described. Driven by economic and environmental considerations, recent efforts have focused on the replacement of the noble-metal component in such catalysts by cheaper, more abundant, and non-toxic metals.[5] Among these, manganese can be regarded as one of the most desirable candidates in view of its low price, rich chemistry, and exceptional biocompatibility.[6] Yet, most examples of non-noble metal homogeneous hydrogenation catalysts are based on Fe[7] and Co,[8] while the respective catalytic chemistry of Mn was not known until very recently. In early 2016 Milstein and co-workers described the first Mn^I-based catalyst **A** for the dehydrogenative coupling of alcohols and amines (Scheme 1).[9a] Later, Kirchner and co-workers showed that this reaction can also be catalyzed by a related Mn^I PNP pincer complex.[9b] Shortly afterwards, the groups of Beller[10] and Kempe[11] independently reported the hydrogenation of ketones with pincer catalysts **B** and **C**. Complex **B** is also active in the reduction of nitriles and aldehydes. Reduction of less-reactive ester substrates remains a challenge for Mn catalysts with only two examples reported to date. Beller and co-workers described aliphatic Mn^I PNP-pincer catalyst **D** that converts esters into alcohols under basic conditions at 2 mol% catalyst loading (110 °C/30 bar H_2/24 h).[12] Milstein and co-workers reported that lutidine-derived Mn^I PNN-pincer catalyst **E** is active at 1 mol%, but requires addition of KH as the base (100 °C/20 bar H_2/50 h).[13] Despite the impressive progress witnessed in recent years in catalytic hydrogenations with non-noble-metal complexes, even the most active examples are efficient only at relatively high catalyst loading of 1–3 mol%, significantly limiting their utility as practical alternatives to the more active Ru-based systems.[14] Herein we report the catalytic hydrogenation of esters with three novel non-pincer-type Mn PN complexes,



Scheme 1. Mn-based (de)hydrogenation catalysts.

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based on simple and easily accessible bidentate aminophosphine ligands. They show good performance at an unprecedented loading of only 0.2 mol%, bringing Mn-catalyzed hydrogenation a step closer to practical implementation.

The use of P,N ligands for Ru-catalyzed ester hydrogenation was first reported by Saudan et al.[15] We prepared complexes **1** to **3** by reaction of $Mn(CO)_5Br$ with 1 or 2 equivalents of the corresponding P,N ligand in toluene at 100 °C for 24 h. The isolated complexes were fully characterized by $^1H/^{31}P$-NMR, ESI-MS, FTIR, elemental analysis, and single-crystal X-ray structure analysis (see Supporting Information). Single-crystal X-ray structure determination revealed the *cis*-coordination of the N-donor groups of the P,N ligands and CO ligands in **1**, with the two phosphine moieties bound *trans* to each other (Figure 1). Their chemical equivalence was also detected in solution by ^{31}P NMR, revealing a single resonance for **1** at $\delta = 79.3$ ppm. Complex **2** contains a single P,N ligand. The amine and Br^- in **2** are bound in a *cis* fashion, providing a favorable environment for heterolytic H_2 activation across the Mn–N moiety.[16]

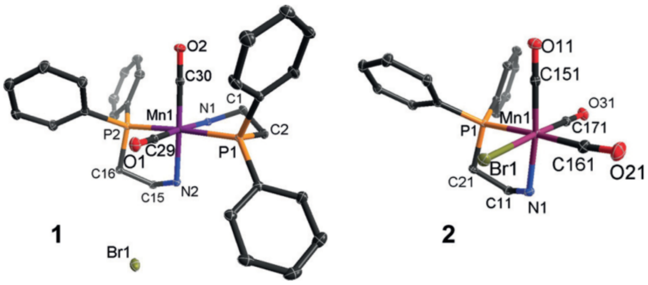
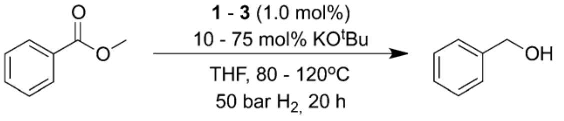


Figure 1. ORTEP diagrams of **1** (left) and **2** (right). Thermal ellipsoids are set at 30% probability. Hydrogen atoms have been omitted for clarity.

Complexes **1–3** are active catalysts for ester hydrogenation. Table 1 summarizes the results of the initial catalytic tests using methyl benzoate as a model substrate. Monoligated complex **2** was found to be considerably more active than **1** and **3** (Table 1, entries 1–3). This is remarkable as the related Ru-PN catalyst is biligated.[15] Reaction at 80–100 °C gave similar benzyl alcohol (BnOH) yields, while the yield decreased substantially at higher temperatures owing to formation of methyl benzyl ether (Table 1, entries 2,4,5). Increasing the amount of KO^tBu led to improved yields (Table 1, entries 6–8). Ultimately, quantitative BnOH yield was obtained with 0.75 equivalents of KO^tBu relative to the substrate (Table 1, entry 8).

Table 1: Hydrogenation of methyl benzoate with **1–3**.[a]

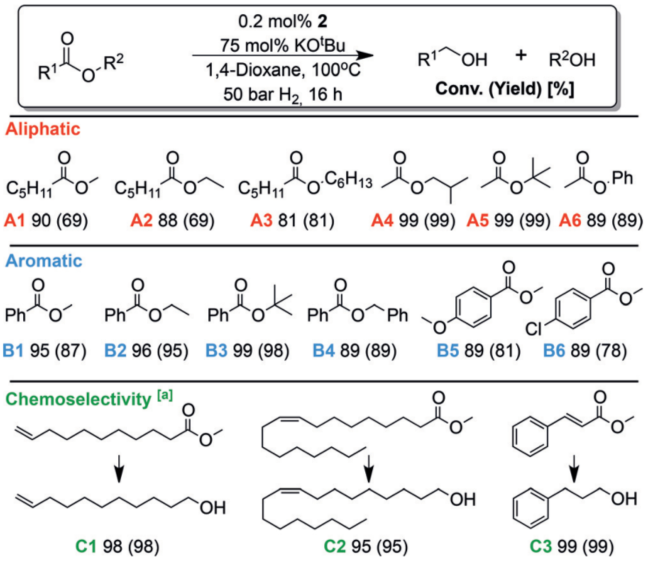


Entry	Catalyst	KO^tBu [mol%]	T [°C]	Conv. [%]	Y_{BnOH} [%][17]
1	**1**	10	100	43	24
2	**2**	10	100	75	66
3	**3**	10	100	13	3
4	**2**	10	80	74	65
5	**2**	10	120	57	43
6	**2**	25	100	86	80
7	**2**	50	100	96	91
8	**2**	75	100	99	98

[a] Conditions: 1 mmol methyl benzoate, 10–75 mol% KO^tBu, 1.0 mol% **Mn**, 2 mL THF, 80–120 °C, 50 bar H_2, 20 h. Yield determined by GC.

After full conversion was achieved, we sought to optimize crucial process parameters such as solvents, bases, reaction temperature and H_2 pressure to enable use of **2** at reduced catalyst loading. With 0.5 mol% of **2** in THF a BnOH yield of 87% could be achieved in just 3 h. Importantly, **2** could also be formed in situ without significant loss of activity, thus eliminating the need for catalyst isolation (Table S1 in the Supporting Information). Mercury poisoning did not evidence inhibition, suggesting the homogeneous nature of catalysis with **2** (Table S1).[18] Replacement of THF for 1,4-dioxane resulted in a higher product yield, while the use of 2-methyl-THF and MTBE led to inferior performance (Table S2). KO^tBu was found to be the superior base for the current catalytic system (Table S3). An increase in temperature and reduction in H_2 pressure resulted in lower BnOH yields (Table S4).

Next, we expanded the scope of the substrates and further decreased the catalyst loading to 0.2 mol%. Under the optimized conditions, **2** was able to convert aromatic and aliphatic esters into their corresponding alcohols in good to excellent yields (Scheme 2). Reduction of hexanoate esters **A1–A3** led to good yields of 1-hexanol with hexyl hexanoate as the only by-product. Interestingly, more sterically hindered esters (**A4–A6**) were almost quantitatively hydrogenated, whereas these are typically more difficult to reduce than their methyl and ethyl analogues.[1] Aromatic benzoate esters with varied steric bulk or electronic properties were all hydrogenated to benzyl alcohol in high yield (**B1–B4**). Similar to aliphatic esters, the reduction of bulky *tert*-butyl benzoate was more efficient than the less-sterically hindered substrates.



Scheme 2. Hydrogenation of various esters with **2**. Conditions: 1 mmol substrate, 75 mol% KO^tBu, 0.2 mol% **2**, 2 mL 1,4-dioxane, 100 °C, 50 bar H_2, 16 h. [a] 0.5 mol% **2**, 6 h.

Hydrogenation of functionalized esters **B5** and **B6** gave high yields of the corresponding alcohols with the functional group being preserved and only trace amount of the methyl ether side products detected by GC-MS. Hydrogenation of unsaturated esters with **2** was fully chemoselective for substrates with the C=C bond distant from the ester moiety, such as fatty acid methyl esters **C1** and **C2**. Methyl cinnamate (**C3**), however, was fully converted into hydrocinnamyl alcohol. No products associated with the Claisen condensation were observed for the enolizable substrates.

To get better insight into the effect of the base in catalysis with **2** we carried out additional catalytic tests using four different benzoate substrates at varied base concentration (Figure 2). For all substrates, the elevated base loading resulted in a higher product yield. The hydrogenation of methyl- and ethyl benzoates was more sensitive to changes in the base concentration than for the *tert*-butyl- and benzyl benzoate substrates. We attribute this to catalyst inhibition by the short-chain alcohols produced in the reaction. This effect is in line with the lower activity achieved with KOMe and KOEt bases (Table S3). Product inhibition via metal-alkoxide formation is well-known for P,N-type complex catalysts and is consistent with both the lower observed rates for methyl- and ethyl esters as well as the increased TON at reduced catalyst loading.[19]

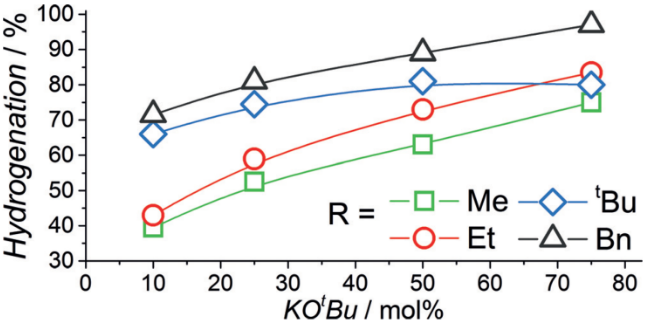


Figure 2. Effect of ester alkoxy group and KO^{t}Bu amount on the degree of hydrogenation (equal to sum of benzyl alcohol, methyl benzyl ether, and $^1/_2$ benzyl benzoate yields).

Dedicated kinetic experiments were next carried out to further study the role of the base (Figure 3).[21] Near-complete hydrogenation was achieved with 0.75 equiv. KO^{t}Bu, while in the presence of 0.1 equiv. base the reaction progress was limited to around 20%. Remarkably, catalytic activity could be instantaneously restored upon addition of 0.65 equiv. KO^{t}Bu. Regardless of the base loading sequence, nearly identical initial rates of about 1100 h^{-1} were observed (see Figure S14). This is consistent with our hypothesis on Mn-alkoxide inhibition, which upon reaction with KO^{t}Bu convert into the catalytically active manganese amide. A similar mechanism of in situ catalyst regeneration has been proposed previously for related Ru-based catalysts.[20]

Next, the reaction mechanism with **2** was studied by density functional theory (DFT) calculations at the PBE0/6-311G(d)//6-31G(d) level (Gaussian09 D.01).[22] Methyl acetate (MeOAc) was chosen as the model substrate. The proposed mechanism, along with the reaction and activation Gibbs free energies for elementary steps, $\Delta G°373K_{solv}$, are summarized in Figure 4. Prior to the catalytic reaction, **2** is activated via a base-assisted hydrogenolysis to produce hydrido complex **I** (see Supporting Information). The cycle starts with an exergonic complexation of MeOAc with **I** to give H-bonded intermediate **II**, which then converts into an activated gem-acetal **III** via a hydride attack with a free energy barrier of 97 kJ mol^{-1}. The addition of H_2 to **III** yields σ-complex **IV**, which after hydrogenolysis produces CH_3OH and CH_3CHO. Methanol elimination gives **VI**, from which the final stage of the catalytic cycle, that is, aldehyde hydrogenation, proceeds. This step is significantly more favorable than the initial ester activation. The first hydride transfer is exergonic by −8 kJ mol^{-1} and shows a free energy barrier of only 29 kJ mol^{-1} (**VI**→**VII**). The resulting alkoxy anion is stabilized by a partial deprotonation of the NH_2-moiety of the ligand, thereby resulting in a trigonal bipyramidal configuration of Mn in **VII**. The interaction with the basic ethoxide facilitates complexation with H_2 to form **VIII** that is followed

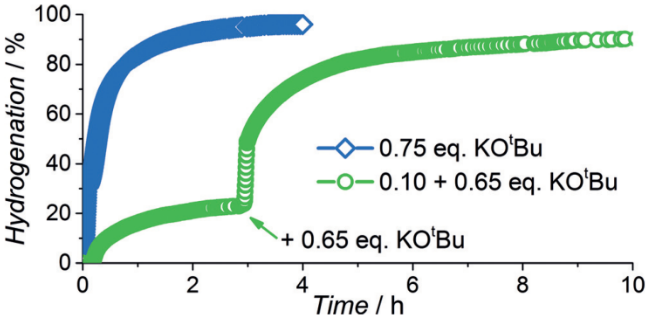


Figure 3. Kinetic traces of methyl benzoate hydrogenation with **2**. Conditions: 15 mmol methyl benzoate, 10–75 mol% KO^{t}Bu, 0.5 mol% **2**, 28 mL THF, 100 °C, 50 bar H_2.

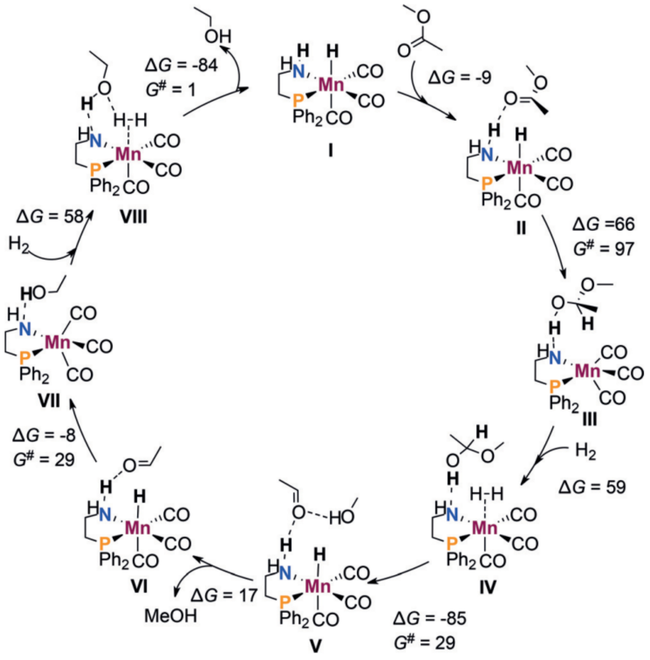


Figure 4. Proposed catalytic cycle for methyl acetate hydrogenation by H_2 and **2** (ΔG and $G^{\neq}$ stand for the reaction and activation Gibbs free energy changes in kJ mol^{-1} at 373 K).

by a barrierless and highly exergonic heterolytic dissociation to produce **I**. The overall free energy barrier for this alkoxide-assisted catalyst regeneration is 59 kJ mol^{-1}, in which the major energy losses originate from the structural distortions upon the formation of σ-H_2 complex **VIII**. The alternative path via ethanol elimination from **VII** followed by the metal–ligand cooperative H_2 activation shows a free energy barrier of about 100 kJ mol^{-1}.

DFT calculations also reveal a competing side-path for the decomposition of **III**, resulting in CH_3CHO elimination and the formation of a stable Mn-alkoxide complex (see Supporting Information). From this point, the formation of **I** requires a base-assisted hydrogenolysis similar to that proposed for the activation of pre-catalyst **2**. This provides additional support for our proposal on catalyst inhibition by stable Mn-alkoxide resting states. In line with the experimental results, the hydrogenolysis of the bulkier Mn-O^{t}Bu adduct shows a much lower energy barrier than Mn-OMe (89 vs. 106 kJ mol^{-1}, respectively).

In summary, we have synthesized and fully characterized three novel Mn P,N ligand complexes, of which monoligated complex **2** is a highly active catalyst for the hydrogenation of aliphatic and aromatic esters. Considering the high catalytic performance and the simple and straightforward preparation, complex **2** holds a great promise as a cheap and practical non-noble metal-based ester hydrogenation catalyst. Based on the complementary experimental and computational results, we provide a mechanistic proposal that points to a potential for further improvement of the Mn-based catalysts under study.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alcohols · esters · homogeneous catalysis · hydrogenation · manganese

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

Marcel Garbe, Kathrin Junge, Svenja Walker, Zhihong Wei, Haijun Jiao, Anke Spannenberg, Stephan Bachmann, Michelangelo Scalone, and Matthias Beller

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The communications dealing with the asymmetric reduction of ketones by a manganese(I) pincer complex was mostly done by myself. I synthesized the chiral pincer ligand and the corresponding complex as well as the optimization of the reaction conditions and the screening of different substrates for the substrate scope. Moreover, I mainly wrote the manuscript as well as the supporting information whereas computations as well as the corresponding part in the manuscript/supporting information were done by Zhihong Wei and Dr. Haijun Jiao. My contribution to this work is approximately 70%.

Asymmetric Catalysis

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

*Marcel Garbe, Kathrin Junge, Svenja Walker, Zhihong Wei, Haijun Jiao, Anke Spannenberg, Stephan Bachmann, Michelangelo Scalone, and Matthias Beller**

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.*

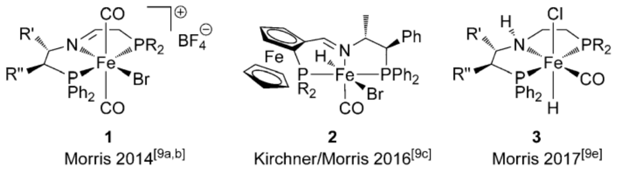
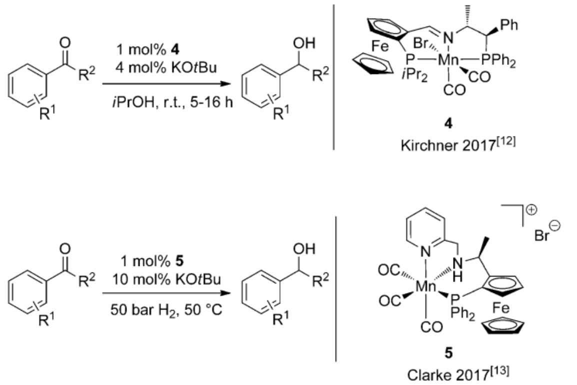


Figure 1. Different iron complexes as enantioselective catalysts for the reduction of prochiral ketones.

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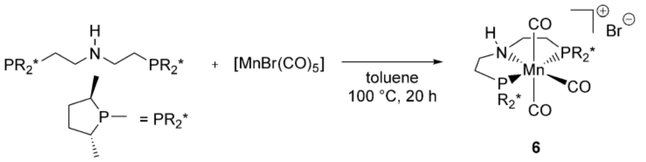
Inspired by the recent developments using homogeneous Mn catalysts,[11,15] we became also interested in Mn-catalyzed asymmetric hydrogenations of (hetero)aromatic and aliphatic ketones. To the best of our knowledge, no manganese catalysts have been described for enantioselective hydrogenations of the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

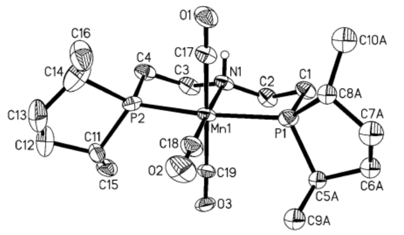
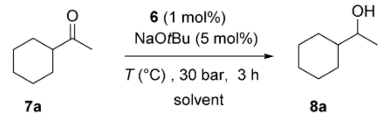


Figure 2. Molecular structure of the cationic fragment of complex **6** (for more details, see the Supporting Information). Displacement ellipsoids corresponds to 30 % probability. Lower occupancy sites and hydrogen atoms except that attached to nitrogen are omitted for clarity. Selected bond lengths [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 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).

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

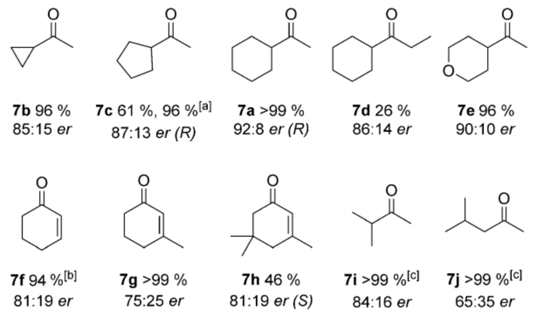


Entry	Solvent	*T*	Yield[b] [%]	e.r. [%]
1	CH_2Cl_2	50	29	88:12
2	heptane	50	> 99	90:10
3	Et_2O	50	63	89:11
4	toluene	50	80	90:10
5[c]	*t*AmylOH	50	> 99	89:11
6	EtOH	50	24	79:21
7	*i*PrOH	50	72	92:8
8	dioxane	50	42	90:10
9[c]	*t*AmylOH	30	35	90:10
10	*t*AmylOH	30	74	90:10
11	*t*AmylOH	40	> 99	92:8
12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

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



7b 96 % 85:15 *er*; **7c** 61 %, 96 %[a] 87:13 *er (R)*; **7a** >99 % 92:8 *er (R)*; **7d** 26 % 86:14 *er*; **7e** 96 % 90:10 *er*

7f 94 %[b] 81:19 *er*; **7g** >99 % 75:25 *er*; **7h** 46 % 81:19 *er (S)*; **7i** >99 %[c] 84:16 *er*; **7j** >99 %[c] 65:35 *er*

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, **7 f–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 (**7 i** and **7 j**) 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, **9 a**) gave only low enantioselectivity (59:41 e.r.) even under mild conditions (0.5 mol% **6**, 30 bar, 30 °C, 1 h; see the Supporting Information). Similar results were observed for substituted acetophenone derivatives like butyrophenone or 4-methoxyacetophenone (**9 b,c**). In contrast, the catalyst showed an increased selectivity for heteroaromatic substrates (**9 d–f**) like 2-acetylthiophene or 2-furylmethylketone (85:15 e.r.). To our delight, α-tetralone and α-indanone (**9 g,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.

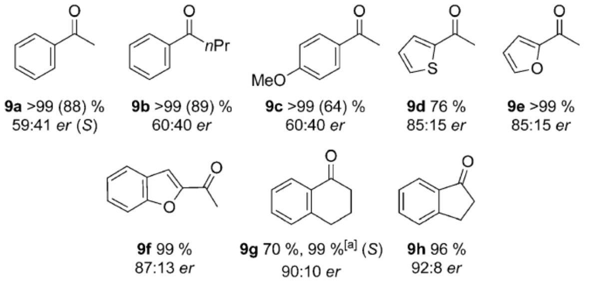
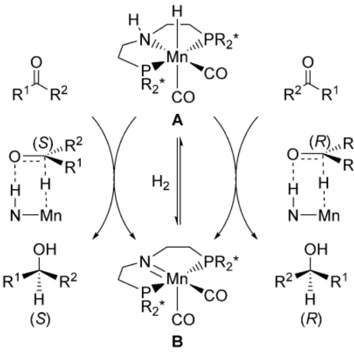


Figure 4. Manganese-catalyzed asymmetric hydrogenation of aromatic ketones. General conditions: substrate (1 mmol), **6** (1 mol%), KO*t*Bu (5 mol%), 1,4-dioxane (2 mL), 4 h, 30 °C, 30 bar H_2. Conversion was determined by GC using hexadecane as an internal standard (Yields of isolated product in parentheses).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

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 (**7 a**), cyclopentyl methyl ketone (**7 c**), and α-tetralone (**9 g**) 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 (**7 a**), 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 (**7 c**), 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 (**9 g**), 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 (**7 a**) and cyclopentyl methyl ketone (**7 c**). For the hydrogenation of α-tetralone (**9 g**), 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 ($-1.0\ \mathrm{kcal\,mol^{-1}}$), and endergonic for the aromatic one ($2.9\ \mathrm{kcal\,mol^{-1}}$). 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 $\mathrm{kcal\,mol^{-1}}$) are much higher than the barrier of H_2 elimination from amine complex **A** to amido complex **B** ($20.3\ \mathrm{kcal\,mol^{-1}}$). 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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6.4 Enantioselective Hydrogenation of Ketones using Different Metal Complexes with a Chiral PNP Pincer Ligand

Marcel Garbe, Zhihong Wei, Bianca Tannert, Anke Spannenberg, Haijun Jiao, Stephan Bachmann, Michelangelo Scalone, and Matthias Beller

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The previous work was further developed and investigated in this update. Herein I have synthesized and characterized all complexes, have done the optimization of the reaction conditions of the iron complex, the corresponding tests regarding the substrate scope together with the comparison of the non-noble metal complexes with the noble metals ones. I additionally assessed all analytical data and mainly wrote the supporting information and the manuscript. My own contribution amounts to approximately 70%.

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Enantioselective Hydrogenation of Ketones using Different Metal Complexes with a Chiral PNP Pincer Ligand

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Abstract: The synthesis of different metal pincer complexes coordinating to the chiral PNP ligand bis(2-((2*R*,5*R*)-2,5-dimethyl-phospholanoethyl))amine is described in detail. The characterized complexes with Mn, Fe, Re and Ru as metal centers showed good activities regarding the reduction of several prochiral ketones. Comparing these catalysts, the non-noble metal complexes produced best selectivities not only for aromatic substrates, but also for different kinds of aliphatic ones leading to enantioselectivities up to 99%*ee*. Theoretical investigations elucidated the mechanism and rationalized the selectivity.

Keywords: Asymmetric Catalysis; Chiral Pincer; Asymmetric Hydrogenation; Prochiral Ketones; Chiral Alcohols

Introduction

Developing chiral organometallic complexes continues to be an important and challenging field in asymmetric catalysis.[1] In this area, enantioselective hydrogenations and transfer hydrogenations are commonly applied for the synthesis of enantiopure alcohols from prochiral ketones leading to building blocks for pharmaceuticals, agrochemicals, as well as flavours and fragrances.[2]

The development of catalysts for asymmetric hydrogenations originated in 1968 when Knowles and Horner published their first systems independently from each other.[3] These catalysts were based on rhodium as a metal center coordinated to chiral phosphine ligands. In the following decades several chiral mono- and bidentate phosphine ligands in the presence of noble metals were established and notable advancements in asymmetric hydrogenations as well as transfer hydrogenations have been achieved by academia and industry.[4] Based on the seminal work of Noyori and the original contributions of Knowles, this area was honoured with the Nobel Prize in 2002.[5] To date, one of the most prominent and powerful catalyst systems for asymmetric reductions is the BINAP-derived ruthenium complex synthesized by Noyori and co-workers.[6] In part, other precious metals such as Rh,[7] Pd,[8] Ir[9] and Os[10] also led to standard protocols for asymmetric reduction of ketones.

Since the turn of the millennium an increasing interest aroused in homogenous catalysis using non-noble metal complexes based on Cu,[11] Co,[12] Ni[13] and Fe[14] combined with different mono-, di-, tri-, or tetradentate ligands. Apart from being less toxic, more abundant, inexpensive and environmental-friendly, these metals might offer different selectivity control and bio-inspired reactivity. Nevertheless, it should be recognized that for most asymmetric catalysis, the price of the chiral ligand determines the overall catalyst costs.

A thorough study on this topic was reported by the group of Morris, who used predominantly chiral PNNP ligands for the (transfer) hydrogenation of ketones.[15] In 2014, they published the first chiral iron PNP complex for asymmetric hydrogenation (Figure 1).[16] Complex **1** showed a high activity for aromatic as well as for aliphatic prochiral ketones but only moderate enantioselectivities up to 46%*ee* were achieved for the latter ones. The catalyst needs to be activated by four equivalents of $LiAlH_4$ and base during the reaction. With the improved Fe pincer complex **2** the pre-

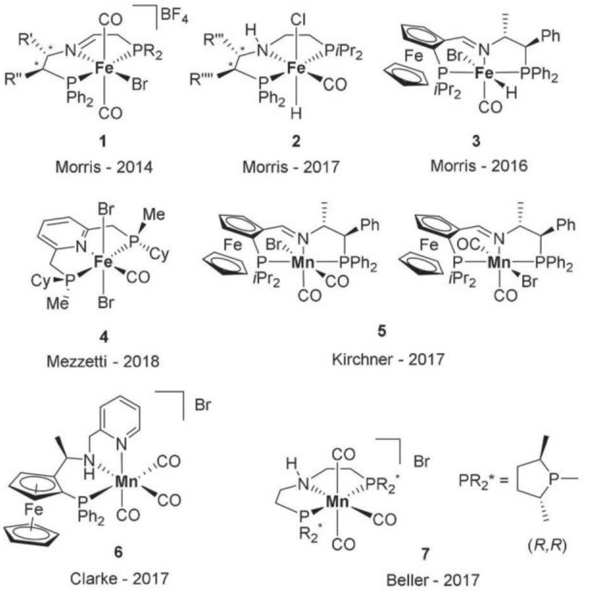


Figure 1. Selected chiral Fe and Mn pincer complexes used for the asymmetric reduction of prochiral ketones.

activation step could be avoided and aromatic prochiral ketones are reduced with *ee* values up to 96%*ee*.[17]

Further pincer ligand backbones were synthesized for iron and manganese complexes by the groups of Morris (**3**), Mezzetti (**4**) and Kirchner (**5**).[18] Whereas **3** and **4** were only studied for the asymmetric reduction of aromatic ketones, **5** was also able to reduce aliphatic substrates with enantioselectivities up to 74%*ee*. In addition, during the preparation of this manuscript Morris and co-workers described asymmetric transfer hydrogenation of ketones with well defined PNN Mn(I) complexes in which the ligands were previously reported and derived from (*S,S*)-DPEN.[19] Only one of the complexes showed moderate activities with enantioselectivities up to 53%*ee* for aromatic substrates while the mechanism of transfer hydrogenation was described in more detail.

Recently, our group reported the synthesis of the chiral bis(2-((2*R*,5*R*)-2,5-dimethylphospholanoethyl))amine ligand[20,21] and the corresponding manganese based complex **7** for the hydrogenation of ketones.[21] While only low selectivities were observed for the reduction of acetophenone and its derivatives some aliphatic ketones especially cyclohexyl methyl ketone gave enantiomeric excesses up to 84%*ee*.

Based on this work, herein we compare in detail the behaviour of different metal pincer complexes coordinating to bis(2-((2*R*,5*R*)-2,5-dimethylphospholanoethyl))amine. Interestingly, non-noble Mn and Fe complexes are superior compared to related Ru and Re catalysts.

Initially, we synthesized the chiral rhenium complex **8** as well as the corresponding ruthenium (**9a** and **9b**) (Figure 2) and iron (**12**) derivatives, which are all reported here for the first time. Analoguouse to the preparation of the manganese complex **7**, [ReBr(CO)$_5$] was reacted with bis(2-((2*R*,5*R*)-2,5-dimethylphospholanoethyl))amine in toluene at 100 °C for twenty hours. After crystallization, **8** was obtained in 69% yield as a grey powder. Furthermore, refluxing carbonylchlorohydridotris(triphenylphos-phine)ruthenium(II) with the chiral pincer ligand in toluene for three hours gave a mixture of two different Ru-species which were detected by ^{31}P NMR. We assumed that these species belong to the isomers **9a** and **9b**, whereas **9a** could be isolated by crystallisation. The structure of **9a** was confirmed by X-ray crystallography (see SI).

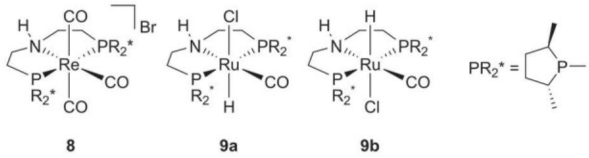
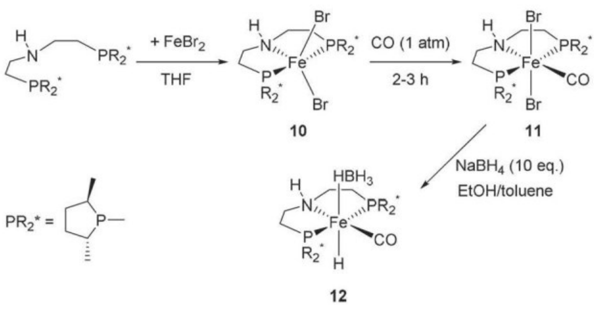


Figure 2. Chiral metal pincer complexes with bis(2-((2*R*,5*R*)-2,5-dimethylphospholanoethyl))amine as ligand.

For the synthesis of the iron complex **12**, FeBr$_2$ was reacted with the corresponding ligand. Next, the resulting paramagnetic complex **10** was converted by insertion of CO to **11**, a suitable pre-catalyst for catalysis.

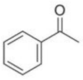
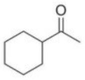
To avoid additional activation steps by base the corresponding borohydride complex **12** was prepared. NMR characterization shows two isomers where the hydride is orientated *cis* or *trans* to the corresponding NH proton.

After synthesizing these complexes, they were tested regarding their activity and selectivity in two benchmark hydrogenations of aromatic (acetophenone) and aliphatic (cyclohexyl methyl ketone) ketones. In preliminary experiments the previously optimized



Scheme 1. Synthesis of chiral iron pincer complexes **11** and **12**.

Table 1. Comparison of the different catalysts for the reduction of acetophenone and cyclohexyl methyl ketone.

					
Entry	Cat.	Conv. [%][a]	*ee* [%]	conv. [%][b]	*ee* [%]
1	**7**	>99	18 (*S*)[21]	>99	83 (*R*)[21]
2	**8**	0	–	0	–
3[c]	**8**	>99	6 (*S*)	>99	60 (*R*)
4	**11**	>99	rac.	41	62 (*R*)
5[d]	**12**	>99	rac.	>99	62 (*R*)
6	**9a**	n.d.	n.d.	>99	47 (*R*)[e]
7	**9a/b**	>99	6 (*S*)	>99	47 (*R*)[e]

Reaction conditions:

[a] 1 mmol acetophenone, 1 mol% cat., 5 mol% KO*t*Bu, 30 °C, 30 bar H_2, 4 h, 1,4-dioxane (2 mL). Conversion was determined by GC by using hexadecane as internal standard.

[b] 1 mmol cyclohexyl methyl ketone, 1 mol% cat., 5 mol% KO*t*Bu, 40 °C, 30 bar H_2, 4 h, *t*-amyl alcohol (2 mL). Conversion was determined by GC by using hexadecane as internal standard.

[c] 100 °C, 1,4-dioxane (2 mL) for acetophenone and *t*-amyl alcohol (2 mL) for cyclohexyl methyl ketone.

[d] No base is needed.

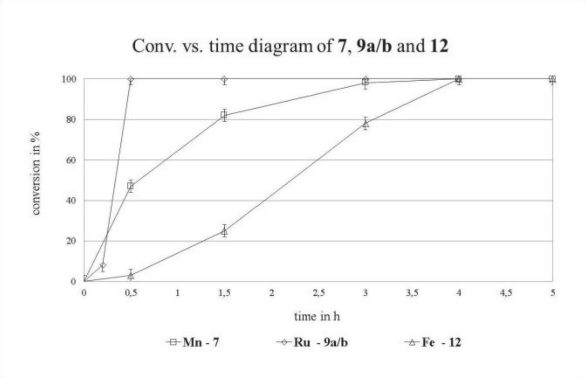
[e] EtOH is used as solvent. In *t*-amyl alcohol a lower enantioselectivity was observed.

conditions of the manganese pincer catalyst system **7** were determined: 1 mol% cat., 5 mol% base, 30 °C, 30 bar H_2, 4 h, 1,4-dioxane for acetophenone and 1 mol% cat., 5 mol% base, 40 °C, 30 bar H_2, 4 h, *t*-amyl alcohol for cyclohexyl methyl ketone.

As shown in Table 1, entry 1, the manganese complex **7** led to full conversion for both substrates and a high enantioselectivity regarding cyclohexyl methyl ketone with 83%*ee*.[21] All new catalysts produced complete conversion of acetophenone, too; although for the rhenium-derived complex **8** a higher temperature was necessary (Table 1, entry 3). As expected, applying the Ru complex **9a** or a mixture of **9a** and **9b** with base, the same activity was observed indicating that the same active species is formed (SI). Unfortunately, the low enantioselectivity using acetophenone could not be improved in the presence of complexes **8**, **9a/b**, **11** or **12**.

In general a better catalytic performance was obtained for the aliphatic substrate cyclohexyl methyl ketone. Nevertheless, to obtain full conversion increased temperature is required using **8**. In this case only a moderate enantiomeric excess of 60%*ee* was observed. Nearly the same selectivity was achieved using the two different iron species **11** and **12** (Table 1, entries 4 and 5), but complex **12** showed a higher activity regarding the reduction of cyclohexyl methylketone. Surprisingly, a low enantiomeric excess (47%*ee*) was observed for the ruthenium complexes **9a/b** (Table 1, entries 6 and 7). Remarkably, this is one of the few cases where noble metal complexes are less selective compared to their base metal congeners.[22]

Next, the activity of the different complexes was investigated in a conversion time diagram for the reduction of cyclohexyl methyl ketone. In general, the Re complex **8** was less selective *vide supra*; hence only the Mn, Fe and Ru complexes **7**, **9a/b**, and **12** were studied in more detail (Scheme 2). Under these conditions, the noble-metal complexes **9a/b** are most reactive giving complete conversion already after half an hour. With complexes **7** and **12** four to five hours were needed, while in case of **12** a slow activation period was observed. For all complexes the enantioselectivity was unaffected over the time.

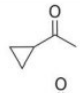
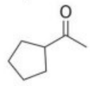
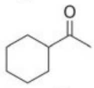
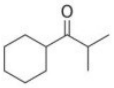
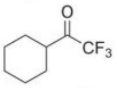
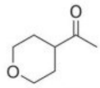
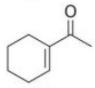
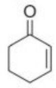
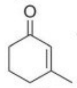
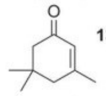
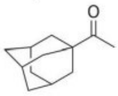


Scheme 2. Conversion vs. time diagram for the comparison of **7**, **9a/b** and **12**. Reaction conditions: 1 mmol substrate, 1 mol% cat., 5 mol% KO*t*Bu (only for **7** and **9a/b**), 40 °C, 30 bar H_2, *t*-amyl alcohol (2 mL). Conversion was determined by GC by using hexadecane as internal standard.

Due to its good activity and enantioselectivity the iron pincer complex **12** was investigated for the hydrogenation of different aromatic and aliphatic prochiral ketones. Therefore the reaction parameters for the asymmetric reduction of aromatic (30 bar H_2, 30 °C, 3 h, EtOH) and aliphatic ketones (30 bar H_2, 30 °C, 6 h – see SI) were optimized and compared to the results of Mn pincer complex **7**.

As shown in Table 2, the decrease of the ring size in the cyclic part of the ketone (Table 2, entries 1–3) does not have a significant influence on the activity of complex **12**, but the enantioselectivity dropped down using cyclopropyl methyl ketone (**13a**) instead of cyclopentyl- or cyclohexyl methyl ketone (**13b** and **13c**). Furthermore, the steric effect of the aliphatic chain in cyclohexyl alkyl ketone was elucidated. In case of cyclohexyl isopropyl or trifluoromethyl ketone (**13d–e**), a decrease of the activity as well as selectivity for both complexes was detected. 4-Acetyltetrahydropyran (**13f**) showed only a moderate

Table 2. Hydrogenation of cyclic aliphatic ketones using complexes **7** and **12**.[a]

Entry	prochiral ketone	Catalyst **7**[a] conv. [%]	*ee* [%]	Catalyst **12**[b] conv. [%]	*ee* [%]
1	 **13a**	96[21]	70	>99	31
2	 **13b**	61[21]	74 (*R*)	>99	60 (*R*)
3	 **13c**	>99[21]	83 (*R*)	>99 [83%][c]	64 (*R*)
4	 **13d**	54	39	78[d] [51%][c]	32
5	 **13e**	23	57	>99	16
6	 **13f**	96[21] [74%][c]	79	>99	46
7[e]	 **13g**	>99 (25%)	51	97 (3%)	52
8[e]	 **13h**	94[21] (6%)	62	98 (8%)	46
9	 **13i**	>99[21]	51	99	55
10	 **13j**	64[21]	61 (*S*)	96 [83%][c,f]	52 (*S*)
11	 **13k**	28	>99 (*R*)	65	>99 (*R*)

[a] General conditions for **7**: 1 mmol substrate, 1 mol% cat., 5 mol% KOtBu, 30 bar H_2, 4 h 40 °C, *tert*-amyl alcohol (2 mL). Conversion was determined by GC using hexadecane as internal standard.

[b] General conditions for **12**: 1 mmol substrate, 1 mol% cat, 30 bar H_2, 6 h, 30 °C, EtOH (2 mL). Conversion was determined by GC using hexadecane as internal standard.

[c] isolated yield.

[d] 60 °C – no conv. at 30 °C.

[e] Conversion to the fully hydrogenated product is given in brackets. Yield of the side product was determined by GC using hexadecane as internal standard.

[f] ~5% of impurities.

value of 46%*ee* for the iron complex (**12**), while the enantioselectivity reached 79%*ee* for complex **7**. In contrast to this 1-cyclohexenyl methyl ketone (**13g**) is reduced with nearly the same enantiomeric excess for both complexes (51%*ee* and 52%*ee*, respectively). Thereby, complex **7** is less selective regarding the C=C double bonds, producing a significant amount of side product (cyclohexylethanol: 25%). Whereas using cyclohexenone (**13h**) only small amounts of side product could be detected and good to moderate enantioselectivity of 62%*ee* (complex **7**) and 46%*ee* (complex **12**) were determined. By using different analogues of cyclohexenone (**13i**–**13j**), the enantiomeric excess could not be increased. Notably, the bulky substrate adamantyl methyl ketone (**13k**) was hydrogenated with excellent enantioselectivity of >99%*ee* with both complexes whereas the iron complex **12** shows still a higher activity.

Furthermore, a number of non-cyclic aliphatic ketones were applied for the asymmetric reduction with chiral Mn and Fe pincer complexes **7** and **12**. The reduction of 3,3-dimethyl-butan-2-one (Figure 3 – **14b**) was realized with low enantioselectivities of 25%*ee* and 32%*ee*. A variation of the bulkiness of the substituent on the keto group does not cause an improvement of the enantioselectivity (see **14a**–**14c**). The best result was obtained for the reduction of 3-methyl-2-butanone with complex **7** giving an enantiomeric excess of 68%*ee* by using **7** as catalyst (**14a**).

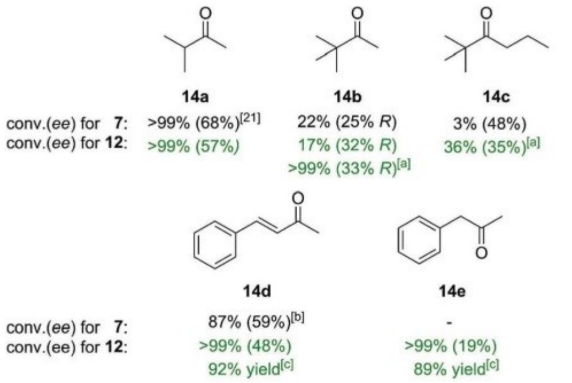


Figure 3. Reduction of non-cyclic aliphatic ketones by **7** (upper results) and **12** (lower results). General conditions for **7**: 1 mmol substrate, 2 mol% cat., 5 mol% KOtBu, 30 bar H_2, 5 h, 80 °C, *t*-amyl alcohol. General conditions for **12**: 1 mmol substrate, 1 mol% cat, 30 bar H_2, 6 h, 30 °C, EtOH (2 mL). Conversion was determined by GC using hexadecane as internal standard. [a] 60 °C. [b] 5 mol% NaOtBu, 50 °C, EtOH – 13% of side product: 1-phenyl-3-butanol. [c] Isolated yield is given.

As mentioned above, the asymmetric reduction of acetophenone and different substituted aromatic derivatives gave only low enantioselectivities (Figure 4 – **15a**–**f**). The highest enantiomeric excess was observed for the reduction of 1-phenyl-1-butanol-4-phenylacetophenone (52%*ee*) using complex **7**. In most cases ketones were reduced to racemic mixtures in the

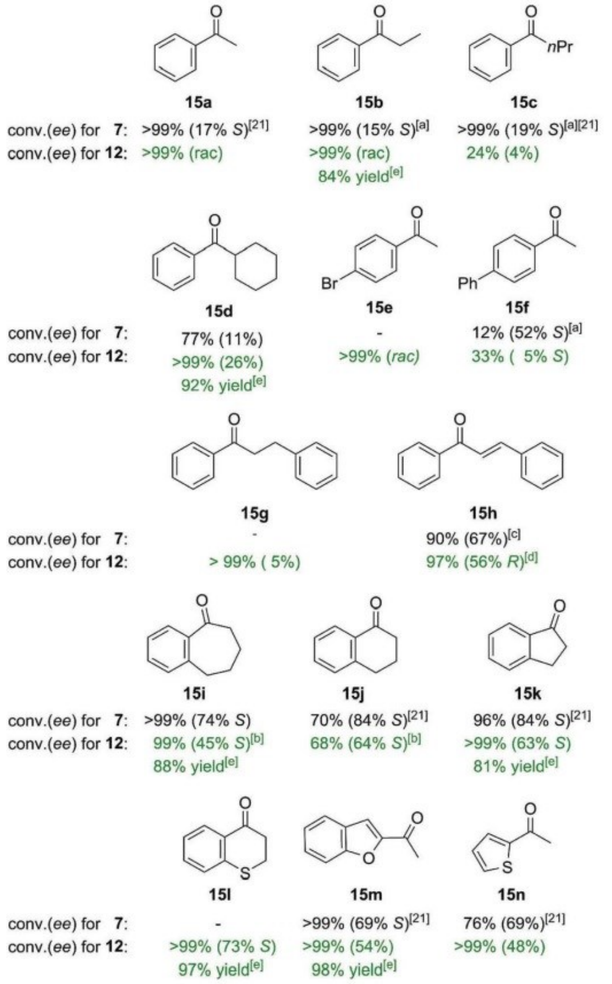
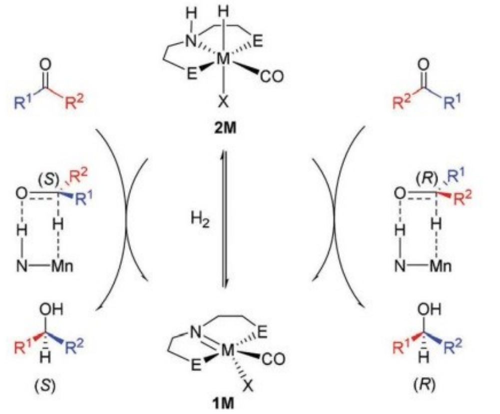


Figure 4. Asymmetric reduction of aromatic prochiral ketones by **7** (upper results) and **12** (lower results). General conditions for **7**: 1 mmol substrate, 1 mol% cat., 5 mol% KOtBu, 30 bar H_2, 4 h, 30 °C, 1,4-dioxane (2 mL). General conditions for **12**: 1 mmol substrate, 1 mol% cat, 30 bar H_2, 3 h, 30 °C, EtOH (2 mL). Conversion was determined by GC using hexadecane as internal standard. [a] 2 mol% cat., 3 h, 50 °C, EtOH (2 mL). [b] 6 h. [c] 2 mol% cat., 50 °C, 1 h, *i*PrOH (2 mL), 36% 1,3-diphenylpropan-1-ol (10%*ee*). [d] 6% 1,3-diphenylpropan-1-ol. [e] Isolated yield is given.



Scheme 3. Proposed mechanism for ketone hydrogenation (E for chiral phospholane ligand in *R,R* configuration; X=CO for M=Mn and Re; X=H for M=Fe and Ru).

presence of **12**. Only, for cyclohexyl phenyl ketone a chiral induction of 26%*ee* was detected. Surprisingly, with benzalacetophenone (**15h**) an enantioselectivity of 67%*ee* was achieved using the chiral Mn based catalyst **7**. Here, slightly elevated temperature (50 °C) was required which decreased the chemoselectivity forming 36% of 1,3-diphenylpropan-1-ol. When the Fe pincer complex **12** is applied for benzalacetophenone only 6% of the side product was detected and the chiral alcohol was obtained in 56%*ee*.

To our delight, for 1-benzosuberol, α-tetralone and α-indanone good *ee* values between 74%*ee* and 84%*ee* were detected with the manganese pincer complex **7**. By using complex **12** slightly smaller enantioselectivities of 64%*ee* (**15j**) and 63%*ee* (**15k**) were achieved. Reducing 1-benzosuberol with **12** the selectivity dropped down significantly to 45%*ee*. We also tested some heterocyclic aromatic ketones (**15l**–**15n**) which were reduced by both catalytic systems with high activities. Again the selectivity of the manganese pincer complex **7** with *ee* values up to 69%*ee* for 2-furyl methyl ketone (**15m**) was slightly better than for the iron catalyst system.

In our previous work,[21] an outer-sphere mechanism (Scheme 3) was proposed for the enantioselective hydrogenation of the Mn pincer complexes **7** based on B3PW91 density functional theory computations. Here, the asymmetric origin comes from the approach of the prochiral ketone group perpendicular to the N–H and M–H groups in the *cis* position with either the *re* or *si* enantioface.

Now, the corresponding Fe, Ru and Re chiral pincer complexes were included in our computation at the B3PW91 level of theory and compared with the experimental results (Figure 5). Therefore, the acti-

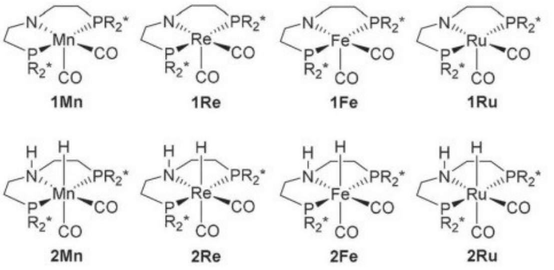
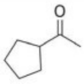
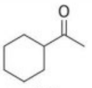
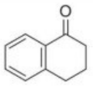


Figure 5. Active catalysts **1M** and **2M** used for the calculated hydrogenation reactions.

Table 3. Comparison of the determined (*er*/Expt) and computed (*er*/DFT) enantiomeric ratio on the basis of the difference (bold and underlined value in kcal/mol; $T=313$ K) of free energy ($\Delta G^{\ddagger}$/TS, kcal/mol) between *R* and *S* transition state configurations.

			
		Mn (**7**)[21]	
$\Delta G^{\ddagger}$/TS	31.3/33.5 (*R*/*S*)	31.4/33.5 (*R*/*S*)	33.5/35.6 (*S*/*R*)
er/DFT	97/3 (*R*; −**2.2**)	97/3 (*R*; −**2.1**)	97/3 (*S*; −**2.1**)
er/Expt	87/13 (*R*; −**1.1**)	91/9 (*R*; −**1.4**)	90/10 (*S*; −**1.4**)
		Fe (**12**)	
$\Delta G^{\ddagger}$/TS	25.5/27.5 (*R*/*S*)	24.3/26.1 (*R*/*S*)	26.6/27.9 (*S*/*R*)
er/DFT	97/3 (*R*; −**2.0**)	95/5 (*R*; −**1.8**)	90/10 (*S*; −**1.3**)
er/Expt	80/20 (*R*; −**0.9**)	81/19 (*R*; −**0.9**)	80/20 (*S*; −**0.9**)
		Ru (**9**)	
$\Delta G^{\ddagger}$/TS	21.0/22.7 (*R*/*S*)	20.5/22.3 (*R*/*S*)	22.4/23.8 (*S*/*R*)
er/DFT	95/5 (*R*; −**1.7**)	95/5 (*R*; −**1.8**)	91/9 (*S*; −**1.4**)
er/Expt	72/28 (*R*; −**0.6**)	73/27 (*R*; −**0.6**)	78/22 (*S*; −**0.8**)
		Re (**8**)	
$\Delta G^{\ddagger}$/TS	29.3/31.1 (*R*/*S*)	29.5/31.5 (*R*/*S*)	29.9/33.6 (*S*/*R*)
er/DFT	95/5 (*R*; −**1.8**)	96/4 (*R*; −**2.0**)	99/1 (*S*; −**3.7**)
er/Expt	80/20 (*R*; −**0.9**)	80/20 (*R*; −**0.9**)	71/29 (*S*; −**0.6**)

vated amido (**1M**) and amine (**2M**) complexes were used as catalysts as well as cyclopentyl methyl ketone, cyclohexyl methyl ketone and α-tetralone as substrates. The computed results are listed in Table 3 (for more details see SI).

In case of **2Mn** as catalyst a concerted but asynchronous transition state was calculated for all three substrates (cyclohexyl methyl ketone, cyclopentyl methyl ketone and α-tetralone), where the transfer of Mn–H and N–H to the ketone group takes place concertedly.[21] Such a one-step mechanism is also found for the reactions using **1Fe** and **1Ru** as catalysts. However, for **1Re** a two-step mechanism is found, where the first step is the Re–H transfer to the prochiral carbon center, followed by an intermediate, and the second step is the N–H transfer for the oxygen atom of the carbonyl group. Because the transition state for Re–H transfer is higher in energy than that of the N–H transfer, it is the rate-determining step. This finding is in conclusion with other two-step hydrogenation reactions.[23]

Firstly, we compared the stability and reactivity with respect to the exchange reaction between **1M** and hydrogen to form **2M** (**1M**+H_2=**2M**). It is found that this exchange reaction is slightly exergonic by 0.82, 2.92, 2.83 and 2.66 kcal/mol, respectively, for **1Mn**, **1Fe**, **1Ru** and **1Re**. The free energy barrier is 19.46, 17.18, 18.48 and 21.74 kcal/mol for **1Mn**, **1Fe**, **1Ru** and **1Re**, respectively. The free energy barrier for the back reaction is 20.28, 20.10, 21.31 and 24.41 kcal/mol for **1Mn**, **1Fe** and **1Ru**, and **1Re**. Such energetic properties are similar with those of the non-chiral counterparts.[23]

A comparison of the enantiomeric ratios and the energy differences of the *R* and *S* transition states for the hydrogenation of cyclopentyl methyl ketone, cyclohexyl methyl ketone and α-tetralone shows a good agreement of the computed enantioselectivity for all three substrates and all four catalysts with the experiment (Table 3). Thus, the *R* isomer is more selective for cyclopentyl and cyclohexyl methyl ketone, while the *S* isomer is more selective for α-tetralone.

Although the computed enantiomeric ratios are larger than the experimentally determined data at the first glance, the energetic difference to differentiate the enantiomeric ratios does not vary too much. For the Mn-based system, for example, the computed energy difference is 2.1–2.2 kcal/mol; while the estimated energy difference from the experimentally determined enantiomeric ratios is 1.1–1.4 kcal/mol, and the largest deviation is 1.1 kcal/mol. The same results are found for the Fe- and Ru-based systems. For the Re-based system, the deviation is 0.9 and 1.1 kcal/mol for cyclopentyl and cyclohexyl methyl ketone, however, a much larger deviation is found for α-tetralone (3.1 kcal/mol).

In addition to the agreement in the enantioselectivity and enantiomeric ratios between theory and experiment; we also found general agreement in the stability between theory and experiment. Thus, the computed free energy barriers of all hydrogenation reactions are higher than the barriers of the hydrogenation elimination of the catalyst [**2M**=**1M**+H_2], indicating that high H_2 pressure is needed to maintain the stability of the catalysts. This finding is supported by the high H_2 pressure in the experiment (30 bar). In case that the barrier of the hydrogenation is lower than that of H_2 elimination, no high H_2 pressure should be needed.

According to the computed barriers, the catalytic activity should follow the decrease order of Ru > Fe > Re > Mn. Experimentally, Ru-based catalysts are most active; however, the comparison of the activity of the Mn and Fe based catalysts depends on the solvent which is used while the Re complex showed the lowest activity.

Since reactions are usually carried out in solution and the large substitutes might have strong van der Waals interactions, one will always question the accuracy and reliability of only gas phase computed results despite of excellent agreement between theory and experiment in stability and reactivity as well as selectivity. Therefore, we computed the Fe-based reaction (**1Fe**+H_2=**2Fe**) considering van der Waals dispersion correction and solvation effects (1,4-dioxane) (B3PW91-SCRF-D3). It is found that including dispersion and solvation correction the barrier (15.05 vs. 17.18 kcal/mol) is lowered and makes the reaction more exergonic (−6.69 vs. −2.92 kcal/mol). The rather large reaction free energy does not support the expected equilibrium. These effects have been observed computationally on other pincer systems.[25]

In addition, we computed the hydrogenation and the enantiomeric ratio of α-tetralone as an example for the consideration of the van der Waals dispersion correction and solvation effect. To our surprise, the computed barrier is rather low (9.72 and 7.37 kcal/mol for the *R* and *S* isomer, respectively); much lower than the gas phase values (27.9 and 26.6 kcal/mol) as well as the barrier of the back reaction (**2Fe** = **1Fe** + H_2) in both gas phase and in solution (20.10 and 21.74 kcal/mol, respectively). These results do not agree with the determined reaction parameters. Here, the high H_2 pressure (30 bar) implies a higher barrier for the hydrogenation than for the H_2 elimination from the catalyst and a stabilizing effect on the catalyst. In case the barrier of the hydrogenation is lower than that of H_2 elimination, no selectivity should be observed. Despite the fact of the lower hydrogenation barriers, the selectivity is not altered by solvation and dispersion correction. On the basis of these results, one should take care about the choice of the method; and benchmark calculations are needed to scale the computed results.[21–23]

Conclusions

In conclusion, we have synthesized different chiral metal pincer complexes using bis(2-((2*R*,5*R*)-2,5-dimethylphospholanoethyl))amine as ligand as well as Ru, Re, Mn and Fe as metal centers. These complexes showed high activities as well as selectivities especially regarding aliphatic ketones. Among all the studied complexes, surprisingly the manganese pincer complex performed best.

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7. Appendix

7.1 List of Publications

1. **“Hydrogenation of Esters to Alcohols Catalyzed by Defined Manganese Pincer Complexes“**

   Saravanakumar Elangovan, Marcel Garbe, Haijun Jiao, Anke Spannenberg, Kathrin Junge, Matthias Beller

   Angew. Chem. Int. Ed. **2016**, *55*, 15364-15368 (DOI: 10.1002/anie.201607233); *Angew. Chem.* **2016**, *128*, 15590-15594 (DOI: 10.1002/ange.201607233).

2. **“A Stable Manganese Pincer Catalyst for the Selective Dehydrogenation of Methanol“**

   Maria Andérez-Fernández, Lydia K. Vogt, Steffen Fischer, Wei Zhou, Haijun Jiao, Marcel Garbe, Saravanakumar Elangovan, Kathrin Junge, Henrik Junge, Ralf Ludwig, Matthias Beller

   Angew. Chem. Int. Ed. **2017**, *56*, 559-562 (DOI: 10.1002/anie.201610182); *Angew. Chem.* **2017**, *129*, 574-577 (DOI: 10.1002/ange.201610182).

3. **“Non-Pincer-Type Manganese Complexes as Efficient Catalysts for the Hydrogenation of Esters”**

   Robbert van Putten, Evgeny A. Uslamin, Marcel Garbe, Chronh Liu, Angela Gonzalez-de-Castro, Martin Lutz, Kathrin Junge, Emiel J. M. Hensen, Matthias Beller, Laurent Lefort, Evgeny A. Pidko

   Angew. Chem. Int. Ed. **2017**, *56*, 7531-7534 (DOI: 10.1002/anie.201701365); *Angew. Chem.* **2017**, *129*, 7639-7642 (DOI: 10.1002/ange.201701365).

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

   Marcel Garbe, Kathrin Junge, Svenja Walker, Zhihong Wei, Haijun Jiao, Anke Spannenberg, Stephan Bachmann, Michelangelo Scalone, Matthias Beller

   Angew. Chem. Int. Ed. **2017**, *56*, 11237-11241 (DOI 10.1002/anie.201705471); *Angew. Chem.* **2017**, *129*, 11389-11393 (DOI: 10.1002/ange.201705471).

5. **“Enantioselective Hydrogenation of Ketones using Defined Metal Complexes with a Chiral PNP Pincer Ligand”**

   Marcel Garbe, Zhihon Wei, Bianca Tannert, Anke Spannenberg, Haijun Jiao, Stephan Bachmann, Michelangelo Scalone, Matthias Beller

   Adv. Synth. Cat. **2019**, in press. (DOI: 10.1002/adsc.201801511).

7.2 Review article

1. **“Homogeneous Catalysis by Manganese-Based Pincer Complexes”**

   Marcel Garbe, Kathrin Junge, Matthias Beller

   Eur. J. Org. Chem. **2017**, 4344-4362 (DOI: 10.1002/ejoc.201700376).

7.3 Patent

1. Stephan Bachmann, Matthias Beller, Marcel Garbe, Kathrin Junge, Michelangelo Scalone (Hoffmann-La Roche Inc.) WO 2018/189060 A1, **2018**.

7.4 Conference Participation

7.4.1 Poster

1. **“Enantioselective Hydrogenation of Ketones using a Defined Chiral PNP Pincer Ligand”**

   Marcel Garbe, Bianca Wendt, Kathrin Junge, Anke Spannenberg, Stephan Bachmann, Michelangelo Scalone, Matthias Beller

   21th *International Symposium On Homogeneous Catalysis*, 8.-13. Juli 2018, Amsterdam, Niederlande.

2. **“New Manganese Pincer Complexes as Hydrogenation Catalysts“**

   Marcel Garbe, Saravanakumar Elangovan, Kathrin Junge, Matthias Beller

   50th *German Catalysis Meeting*, 15.-17. März 2017, Weimar, Deutschland und 19th *JCF Spring Symposium*, 29. März – 1. April 2017, Mainz, Deutschland.

7.4.2 Talk

1. **“Enantioselective Hydrogenation of Ketones using a Defined Chiral PNP Pincer Ligand”**

   Marcel Garbe, Bianca Wendt, Kathrin Junge, Anke Spannenberg, Stephan Bachmann, Michelangelo Scalone, Matthias Beller

   Roche PTDC Technology, Innovation & Science Forum, 06.-07. Juni 2018, Basel, Schweiz.