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Enantioselective Transfer Hydrogenation of Ketones Catalyzed by a Manganese Complex Containing an Unsymmetrical Chiral PNP′ Tridentate Ligand

Afrooz Zirakzadeh,*[a] Sara R. M. M. de Aguiar,[a] Berthold Stöger,[b] Michael Widhalm,[c] Karl Kirchner,*[a]

Abstract: Manganese complexes of the types [Mn(PNP')(Br)(CO)$_2$] and [Mn(PNP')(H)(CO)$_2$] containing a tridentate ligand with a planar chiral ferrocene and a centro chiral aliphatic unit were synthesized, characterized and tested in enantioselective transfer hydrogenations of 13 ketones. The catalytic reactions proceed with conversions up to 96% and e.e. values of up to 86%. The absolute configuration of all products was determined to be (*S*). It has to be noted that the presence of dihydrogen (up to 20 bar) did not affect the reduction. Based on DFT calculations preliminary mechanistic details including the origin of the (*S*)-selectivity are presented. The molecular structure of [Mn(PNP')(Br)(CO)$_2$] was studied by X-ray diffraction.

In recent years, research in the field of hydrogenation catalysis for the synthesis of enantiopure alcohols and amines in the pharmaceutical, fragrance and fine chemical industries for economic reasons as well as the idea of developing green and environmentally friendly catalysts has moved towards developing complexes with non-platinum group metals such as iron and manganese.[1-12] To date, efficient manganese catalysts have been developed by Beller,[10] Milstein[11] and Kempe[12] for hydrogenations and transfer hydrogenations of ketones, aldehydes, nitriles and esters but none of them are enantioselective. Very recently, as part of our continuing search for novel asymmetric hydrogenation catalysts, we reported a group of chiral PNP' pincer ligands with a ferrocene-aliphatic scaffold which were tested in the asymmetric hydrogenation of ketones in the presence of an iron center.[13] Of all the ligands tested, (*R*,*R*,*S*$_{Fc}$)-**1** performed best and the enantioselectivities of up to 81% e.e. were obtained. Hence, we were curious to ascertain whether our new ferrocenyl-containing 6.5.-ring PNP' ligands (Scheme 1) could be transformed into active precatalysts of the type [Mn(PNP')(Br)(CO)$_2$] and [Mn(PNP')(H)(CO)$_2$] for the asymmetric reduction of ketones. Herein, we report the first asymmetric transfer hydrogenations of ketones with manganese complexes of chiral PNP' pincer ligands consisting of a planar chiral ferrocene and a centro chiral aliphatic unit which are connected through an imino nitrogen.

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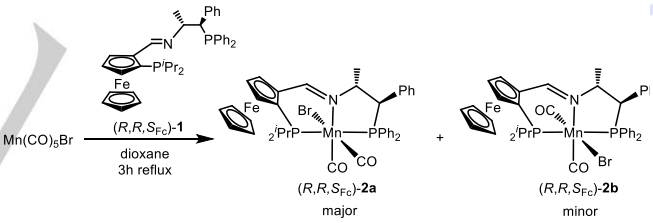
Results and Discussion

Synthesis of (R,R,S$_{Fc}$)-2. Treatment of Mn(CO)$_5$Br with 1.1 equivalents of the ligand (*R*,*R*,*S*$_{Fc}$)-**1** in dioxane afforded the *bis*-carbonyl complex [Mn(PNP')(Br)(CO)$_2$] (*R*,*R*,*S*$_{Fc}$)-**2** in essentially quantitative yield (Scheme 1). The ^{1}H and ^{31}P{^{1}H} NMR spectra of the crude reaction mixture revealed the presence of two isomers (ratio: 4:1). The major isomer (*R*,*R*,*S*$_{Fc}$)-**2a** could be purified by crystallization and its structure was unequivocally determined by X-ray crystallography. A molecular view of (*R*,*R*,*S*$_{Fc}$)-**2a** is depicted in Figure 1 with selected bond distances and angles given in the caption. The ^{31}P{^{1}H} NMR spectrum contained two doublets centered at 54.4 and 86.1 ppm with a $^2J_{PP}$ coupling constant of 97 Hz. In the IR spectrum two strong ν_{CO} absorptions at 2022 and 1927 cm^{-1} were observed.



Scheme 1. Synthesis of [Mn(PNP')(Br)(CO)$_2$] (*R*,*R*,*S*$_{Fc}$)-**2**.

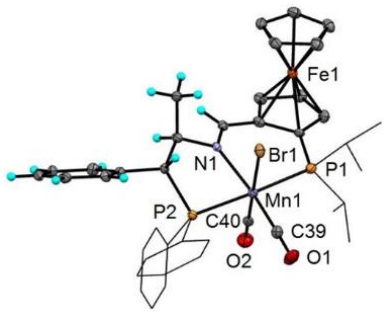


Figure 1. Structural view of (*R*,*R*,*S*$_{Fc}$)-**2a** showing 50% thermal ellipsoids (most H atoms and solvent molecules are omitted for clarity). Selected bond lengths (Å) and bond angles (°): Mn1–Br1 2.5541(8), Mn1–C39 1.778(5), Mn1–C40 1.771(5), Mn1–P1 2.318(1), Mn1–P2 2.281(1), Mn1–N1 2.098(4), P1–Mn1–Br1 92.37(4), P2–Mn1–Br1 91.39(4), P1–Mn1–N1 95.4(1), P2–Mn1–N1 80.1(1), Br1–Mn1–N1 85.6(1), P1–Mn1–P2 173.92(5).

Synthesis of (R,R,S$_{Fc}$)-3. Manganese hydride complexes of the type [Mn(PNP')(H)(CO)$_2$] ((*R*,*R*,*S*$_{Fc}$)-**3**) were synthesized by treatment of (*R*,*R*,*S*$_{Fc}$)-**2a** with $NaBH_4$ in EtOH at room

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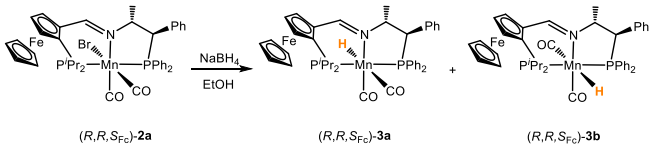
temperature for 2 hours (Scheme 2). The ^{1}H NMR spectrum of (*R*,*R*,S_{Fc})-**3** confirmed the presence of two hydride species in a ca. 6:1 ratio exhibing signals at -3.8 and -4.9 ppm as well-resolved triplets with $^{2}J_{HP}$ coupling constants of 19.7 and 47.0 Hz, respectively. These isomers could not be separated and attempts to obtain crystals suitable for an X-ray diffraction study were unsuccessful. The ^{31}P{^{1}H} NMR spectra revealed two doublets centered at 75.6 and 107.4 ppm with a $^{2}J_{PP}$ coupling constant of 56 Hz for the major isomer and two doublets centered at 83.4 and 109.3 ppm with a $^{2}J_{PP}$ of 57 Hz for the minor isomer. In the IR spectrum the strong bands for the CO stretching frequencies appeared at 1918 and 1853 cm^{-1} for the major isomer. The structures of the two possible *cis*-CO isomers (*R*,*R*,S_{Fc})-**3a** and (*R*,*R*,S_{Fc})-**3b** were established by DFT calculations and are depicted in Figure 2. It was found that (*R*,*R*,S_{Fc})-**3b** is slightly more stable than (*R*,*R*,S_{Fc})-**3a** which may suggest that the latter is the experimentally observed major isomer which, in fact, possess different configuration at the metal center than (*R*,*R*,S_{Fc})-**2a**.



Scheme 2. Preparation of monohydride complexes (*R*,*R*,S_{Fc})-**3a** and (*R*,*R*,S_{Fc})-**3b**.

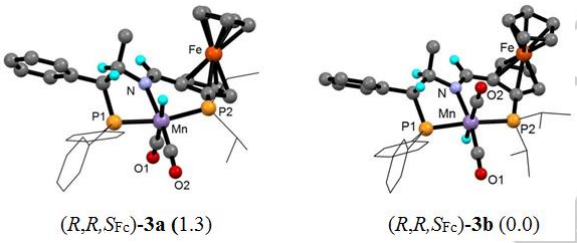


Figure 2. Energies (kcal/mol) for the optimized structures of the two isomers [Mn(PNP')(H)(CO)$_2$] (*R*,*R*,S_{Fc})-**3a** and (*R*,*R*,S_{Fc})-**3b** (most hydrogen atoms omitted for clarity).

Catalysis. The catalytic activities of (*R*,*R*,S_{Fc})-**2a** and (*R*,*R*,S_{Fc})-**3** (as a mixture of (*R*,*R*,S_{Fc})-**3a** and (*R*,*R*,S_{Fc})-**3b**) were investigated in the asymmetric transfer hydrogenation (THY) and asymmetric hydrogenation under transfer hydrogenation conditions (HY) of acetophenone as a function of dihydrogen pressure, amount of base, and substrate-to-catalyst ratio (S/C) in ^{i}PrOH (Table 1). Interestingly, it turned out that dihydrogen does not have any influence on the conversion and the e.e. values. In fact, in the absence of dihydrogen the same conversions and e.e's were found (Table 1, entries 1-6) and, thus, this process clearly proceeds exclusively via transfer hydrogenation. Complex (*R*,*R*,S_{Fc})-**3** as compared to (*R*,*R*,S_{Fc})-**2a** led to a faster THY process and after 2 hours (instead of 5 hours) the product was obtained with 95% conversion and 86% e.e. For both complexes base was necessary and in the absence of base no conversion was observed. Since with (*R*,*R*,S_{Fc})-**2a** and (*R*,*R*,S_{Fc})-**3** similar results were obtained the more easily accessible complex (*R*,*R*,S_{Fc})-**2** was used as precatalyst for substrate screening. All reactions were carried out at room temperature with S/C/base ratio of 100/1/4. It was observed that the product enantiomeric excess was slightly dependent on the reaction time due to product racemization. Therefore, the maximum product e.e. values obtained at the given reaction time are listed together with the corresponding conversion. The results for 13 substrates are provided in Table 2. The best results were obtained with the acetophenone and *para*-substituted acetophenones. In these cases e.e. values of up to 85% were observed at nearly quantitative yield. The influence of *para*-substituents turned out to be small. Moreover, (*R*,*R*,S_{Fc})-**2a** was found to catalyze also the reduction of phenyl ethyl ketone and phenyl benzyl ketone with high conversions and e.e. values of 82-84% (Table 2, entries 8 and 9). In case of 1-tetralone and acetylferrocene a significant drop in conversion and e.e's was observed (Table 2, entries 11 and 12). The absolute configuration of all products was determined to be (*S*).

Table 1. THY and HY results obtained for acetophenone with complexes (*R*,*R*,S_{Fc})-**2a** and (*R*,*R*,S_{Fc})-**3**.[a]

entry	complex	S/C ratio	Pressure (bar)	Base equiv.	Time (h)	% conv.	% e.e.[b]
1	(*R*,*R*,S_{Fc})-**2a**	100/1	0	4	5	95	85
2	(*R*,*R*,S_{Fc})-**2a**	100/1	5	4	5	95	85
3	(*R*,*R*,S_{Fc})-**2a**	100/1	20	4	5	95	85
4	(*R*,*R*,S_{Fc})-**3**	100/1	0	4	2	96	86
5	(*R*,*R*,S_{Fc})-**3**	100/1	5	4	2	96	86
6	(*R*,*R*,S_{Fc})-**3**	100/1	20	4	2	96	86
7	(*R*,*R*,S_{Fc})-**2a**	100/1	0	8	5	95	79
8	(*R*,*R*,S_{Fc})-**2a**	100/1	0	4	5	95	85
9	(*R*,*R*,S_{Fc})-**2a**	100/1	0	2	5	93	85
10	(*R*,*R*,S_{Fc})-**2a**	100/1	0	0	5	–	0
11	(*R*,*R*,S_{Fc})-**3**	100/1	0	8	2	97	81
12	(*R*,*R*,S_{Fc})-**3**	100/1	0	4	2	96	86
13	(*R*,*R*,S_{Fc})-**3**	100/1	0	2	2	93	86
14	(*R*,*R*,S_{Fc})-**3**	100/1	0	0	2	5	-
15	(*R*,*R*,S_{Fc})-**2a**	200/1	0	4	5	80	85
16	(*R*,*R*,S_{Fc})-**2a**	200/1	20	4	5	80	85
17	(*R*,*R*,S_{Fc})-**3**	200/1	0	4	2	89	85
18	(*R*,*R*,S_{Fc})-**3**	200/1	20	4	2	88	85

[a] Reaction conditions: Acetophenone (1 mmol), ^{i}PrOH (5 mL), 25 °C. [b] determined by GC on a Beta DexTM 110 (30 m) column.[14]

Mechanistic and Theoretical Investigations. To gain insight into a possible mechanism of this THY, NMR investigations were carried out by treating complex (*R*,*R*,S_{Fc})-**2a** with ^{t}BuOK in ^{i}PrOH (and 5% THF-d_8) at room temperature. After 2 hours, the formation of the hydride complexes (*R*,*R*,S_{Fc})-**3a** and (*R*,*R*,S_{Fc})-**3b** was observed by ^{1}H and ^{31}P{^{1}H} NMR spectroscopy. In addition, a third minor species was detected in the ^{31}P{^{1}H} NMR spectrum giving rise to doublets centered at 110.2 and 74.0 ppm with a $^{2}J_{HP}$ coupling constant of 70.2 Hz (Figure S10). This species could as yet not be identified.

Based on the experimental findings, the catalytic reaction clearly proceeds via a monohydride complex. Moreover, it seemed likely the hydrogen transfer proceeds through an outer sphere pathway taken into consideration the inertness of bis-carbonyl Mn(I) complexes as found for several related Mn(I) systems utilized in hydrogenation/dehydrogenation reactions recently.[10-12,15-17] Whether or not this reaction proceeds via metal ligand bifunctional catalysis cannot be unequivocally established as yet. Preliminary DFT calculations reveal that the formation of

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the hydride complex (R,R,S_{Fc})-**3a** by reacting the cationic complex $[Mn(PNP')(CO)_2]^+$ (**A**) (formed upon liberation of the bromide ligand of (R,R,S_{Fc})-**2a** in the presence ^{t}BuOK in alcoholic solutions) with isopropoxide is very facile as shown in Figure 3. The hydrogen transfer reaction proceeds in an outer sphere fashion without ligand participation with a barrier of only 4.9 kcal/mol and the reaction is exothermic by -21.5 kcal/mol. The approach of the alkoxide is guided by a weak hydrogen bonding between the acidic C-H bond adjacent to the PPh_2 moiety of the ligand and the oxygen atom of the isopropoxide.

Based on these results, the (*S*)-selectivity of the catalytic reaction may be explained, on the one hand, by hydrogen bonding between the ligand and the oxygen atom of the substrate together with steric restrictions on the other hand. This is demonstrated for acetophenone in Figure 4. In the case of isomer (R,R,S_{Fc})-**3a** (a,b) a *Re*-face approach of the ketone to the hydride ligand is feasible as it minimizes unfavorable steric interactions, while a *Si*-face approach due to steric repulsions between the phenyl substituent of acetophenone and a Cp ring of the ferrocenyl moiety is highly unlikely. Moreover, this reaction is facilitated by a weak hydrogen bonding, which is not possible for isomer (R,R,S_{Fc})-**3b** (c,d). In the case of (R,R,S_{Fc})-**3b**, the steric repulsion allows only for a *Si*-face attack of the ketone. Accordingly, we believe that the key intermediate for the THY process is the hydride complex (R,R,S_{Fc})-**3a**.

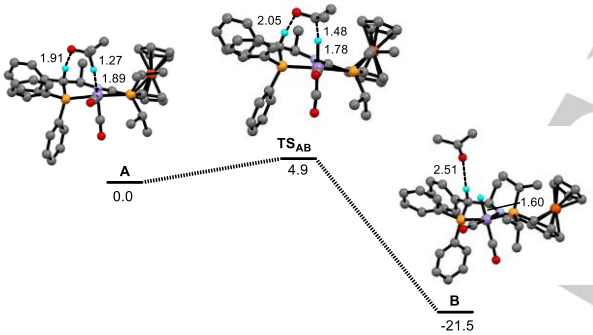


Figure 3. Energy profile (in kcal/mol) for the reaction of the cationic $[Mn(PNP')(CO)_2]^+$ fragment (**A**) with isopropoxide to give the acetone adduct of (R,R,S_{Fc})-**3a** (denoted as **B**) (in ^{i}PrOH as solvent).

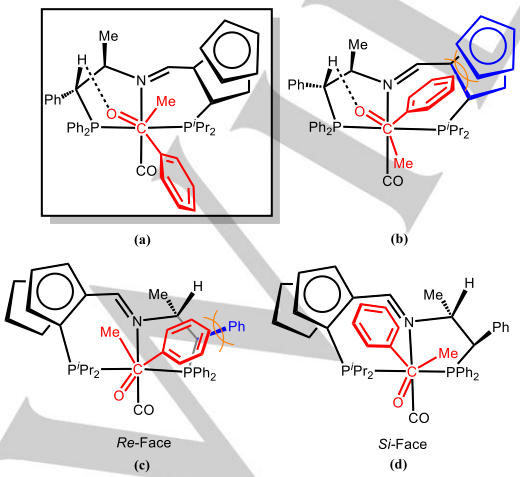
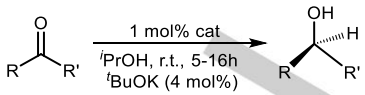
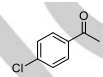
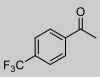
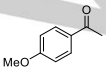
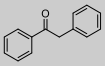
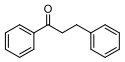
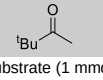


Figure 4. *Re* and *Si*-face addition of acetophenone to the two isomers (R,R,S_{Fc})-**3a** (a, b) (R,R,S_{Fc})-**3b** (c, d). View along the C (acetophenone)-H-Fe-CO axis.

Table 2. THY results obtained with complex (R,R,S_{Fc})-**2a**.[a]



entry	substrate	time (h)	% conv.	% e.e.[b]
1		5	95	85
2		16	73	65
3		16	77	69
4		5	94	83
5		5	90	76
6		5	95	84
7		5	96	85
8		6	93	84
9		6	62	82
10		16	58	79
11		16	60	46
12		16	37	20
13		5	80	74

[a] Reaction conditions: Substrate (1 mmol), catalyst (0.01 mmol), KO^{t}Bu (0.04 mmol), ^{i}PrOH (5 mL), 25 °C. [b] ACP, 2-F-ACP, 2-Cl-ACP, 4-CF_3-ACP, 4-MeO-ACP, 4-Me-ACP, PEK and TETN determined by GC on a Beta DexTM 110 (30 m) column and PBK and DPP determined by HPLC on a Chiralcel OD-H column. AcFc determined by HPLC on a Chiralcel OJ column.[14]

Conclusions. We have developed the first enantioselective transfer hydrogenation of ketones catalyzed by a well-defined Mn-based complex. Key intermediates are two isomeric *bis*-carbonyl Mn(I) hydride complexes of the type $[Mn(PNP')(H)(CO)_2]$ ((R,R,S_{Fc})-**3a**,**b**) which are readily prepared from the corresponding bromide compound $[Fe(PNP')(Br)(CO)_2]$ ((R,R,S_{Fc})-**2a**) upon treatment with $NaBH_4$. These complexes contain a ligand with a planar chiral ferrocene and a centro chiral aliphatic unit. All complexes were tested in the asymmetric transfer hydrogenation of ketones and gave similar conversion and enantioselectivity. Since (R,R,S_{Fc})-**2a** is more readily accessible from a synthetic point of view, transfer hydrogenations of 13 ketones were performed with this catalyst precursor under mild condition at room temperature in the presence of ^{t}BuOK. The catalytic reactions proceed with conversions up to 96% and e.e. values of up to 86%. The absolute configuration of all products was determined to be (*S*). It has to be noted that the presence of dihydrogen (up to 20 bar) did not affect the reduction. Based on

DFT calculations preliminary mechanistic details including the origin of the (*S*)-selectivity are presented. More detailed explorations on the mechanism are in progress.

Supporting Information. Experimental procedure, spectral and complete crystallographic data and technical details in CIF format for (R,R,S_{Fc})-**2a** (CCDC entry 1435577). This material is available free of charge via the Internet at http://pubs.acs.org.

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Keywords: Chiral ligands, Manganese, Hydride complexes, Ferrocenes, Asymmetric transfer hydrogenation.

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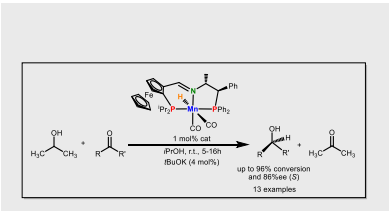

The first enantioselective transfer hydrogenation of ketones catalysed by a well-defined Mn-based complex containing a chiral PNP' pincer ligand with a planar chiral ferrocene and a centro chiral aliphatic unit is reported. The asymmetric transfer hydrogenation reactions procced under mild conditions with conversions up to 96% and e.e. values of up to 86%.

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Title

Enantioselective Tran Hydrogenation of Ketones Catalyzec a Manganese Complex Containing Unsymmetrical Chiral PNP′ Triden Ligand