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Iron-, Cobalt-, and Nickel-Catalyzed Asymmetric Transfer Hydrogenation and Asymmetric Hydrogenation of Ketones

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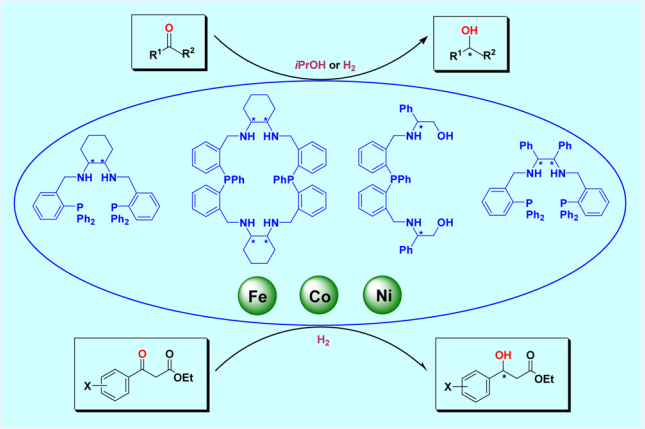
CONSPECTUS: Chiral alcohols are important building blocks in the pharmaceutical and fine chemical industries. The enantioselective reduction of prochiral ketones catalyzed by transition metal complexes, especially asymmetric transfer hydrogenation (ATH) and asymmetric hydrogenation (AH), is one of the most efficient and practical methods for producing chiral alcohols. In both academic laboratories and industrial operations, catalysts based on noble metals such as ruthenium, rhodium, and iridium dominated the asymmetric reduction of ketones. However, the limited availability, high price, and toxicity of these critical metals demand their replacement with abundant, nonprecious, and biocommon metals. In this respect, the reactions catalyzed by first-row transition metals, which are more abundant and benign, have attracted more and more attention.



As one of the most abundant metals on earth, iron is inexpensive, environmentally benign, and of low toxicity, and as such it is a fascinating alternative to the precious metals for catalysis and sustainable chemical manufacturing. However, iron catalysts have been undeveloped compared to other transition metals. Compared with the examples of iron-catalyzed asymmetric reduction, cobalt- and nickel-catalyzed ATH and AH of ketones are even seldom reported. In early 2004, we reported the first ATH of ketones with catalysts generated in situ from iron cluster complex and chiral PNNP ligand. Since then, we have devoted ourselves to the development of ATH and AH of ketones with iron, cobalt, and nickel catalysts containing novel chiral aminophosphine ligands. In our study, the iron catalyst containing chiral aminophosphine ligands, which are expected to control the stereochemistry at the metal atom, restrict the number of possible diastereoisomers, and effectively transfer chiral information, are successful catalysts for enantioselective reduction of ketones. Among these novel chiral aminophosphine ligands, 22-membered macrocycle P_2N_4 exhibited extraordinary enantioselectivities when combined with iron(0) cluster $Fe_3(CO)_{12}$. A broad scope of ketones including aromatic, heteroaromatic, and β-ketoesters can be reduced smoothly with excellent enantioselectivities (up to 99% ee) approaching or exceeding those achievable with the noble metal catalysts. Notably, the chiral iron-based catalyst proved to be highly efficient for both ATH as well as AH of various ketones. Until now, such "universal" catalyst is very rare. Preliminary studies suggest that the AH reaction most likely involved iron particles as the active catalytic species. These research results point to a new direction in developing viable effective nonprecious metal catalysts for asymmetric reduction and probably for other asymmetric catalytic reactions as well.

1. INTRODUCTION

Chiral alcohols are important building blocks used in the pharmaceutical, agrochemical, fragrance, and other fine chemical industries. The catalytic asymmetric reduction of prochiral ketones, especially asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH), is one of the most powerful methods for producing optically active alcohols.[1,2] In both academic laboratories and industrial operations, catalysts based on noble metals such as ruthenium, rhodium, and iridium have typically been used for the asymmetric reduction of ketones. However, the limited availability, high cost, and toxicity of these precious metals demand their replacement with abundant, inexpensive, and nontoxic metals. For this reason, reactions catalyzed by first-row transition metals, which are more rich in supply and environmentally benign, have attracted increasing attention.[3−6] In early 2004, we reported the first ATH of ketones with

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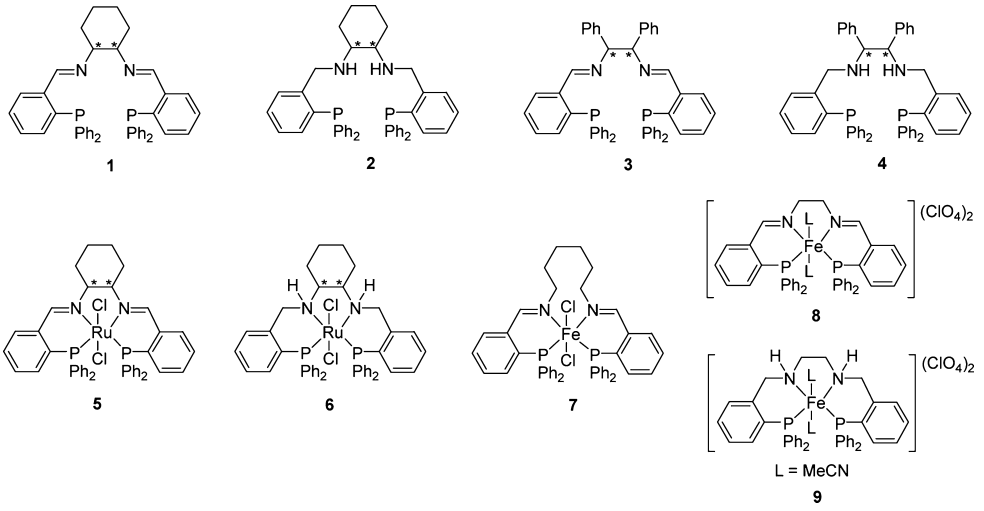

Figure 1. Representative examples of our PNNP ligands and their metal complexes.

catalysts generated in situ from an iron complex and a chiral PNNP ligand, following our previous studies on chiral aminophosphine ligands and their application in asymmetric catalysis.[7] Since 2008, Morris and co-workers have developed a series of well-designed chiral PNNP-Fe(II) complexes and applied them in the ATH of ketones, with excellent catalytic activity.[8−12] Recently, reports on the efficient iron-catalyzed AH of ketones have also appeared.[13−15] However, compared with the successful examples reported for iron-catalyzed asymmetric reduction, cobalt- and nickel-catalyzed ATH and AH of ketones are relatively underdeveloped. In this Account, we highlight our studies of ATH as well as AH of ketones with iron, cobalt and nickel catalysts containing chiral aminophosphine ligands.

2. IRON AND COBALT CATALYSTS CONTAINING A CHIRAL PNNP LIGAND FOR THE ATH OF KETONES

2.1. Design and Synthesis of Chiral PNNP Ligands and Their Metal Complexes

Generally, chiral metal catalysts play a key role in asymmetric catalysis, which act as templates to regulate reactions occurring within the coordination sphere. Chiral catalysts contain various metal centers as well as chiral ligands that realize the induction of the chirality from the catalysts to the products in catalytic processes. Recently, chiral P_xN_y-type ligands that combined the distinctly different characteristics of the phosphorus atoms and nitrogen atoms have been greatly developed. This favorable combination proved to be critical for both catalytic activity and enantioselectivity. The phosphorus atom is a relative "soft" π-acceptor, which may stabilize metal center in a low oxidation state. Whereas the nitrogen atom is a "hard" σ-donor, which produces a weaker coordination to the metal center that easily dissociates in solution to afford a vacant site for substrate coordination.[16] Hopefully, mixed P_xN_y-type ligands can exhibit versatile features compared with those of P,P or N,N ligands.

In 1996, we reported the synthesis of achiral or chiral open-chain PNNP ligands and their ruthenium(II) and iron(II) complexes (Figure 1).[17,18] The tetradentate PNNP systems possess two phosphorus atoms and two nitrogen atoms, which should easily modify the steric and electronic properties of the resulting complexes as well as their catalytic activity. Further, we revealed the structural characteristics of these PNNP ligands using X-ray analysis of single crystals of their ruthenium complexes **5** and **6**. Complex **5** exhibits a distorted-octahedral geometry that approximates C_2 symmetry (Figure 2a). Around

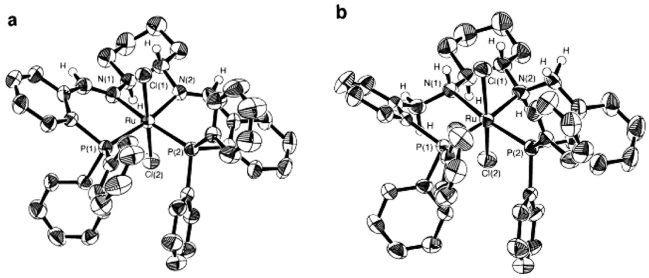

Figure 2. X-ray structure of chiral PNNP-Ru(II) complexes **5** and **6**.

the Ru center, the four equatorial positions are occupied by the tetradentate ligand **1**, and the axial positions are occupied by two chloride atoms. The N,N-ligated five-membered ring has a δ-conformation, which is dictated by the configuration of the chiral PNNP ligand. Complex **6** exhibits a similar near-C_2 geometry, where the four equatorial positions are occupied by the ligand **2** (Figure 2b). Since our previous report, both other research groups and our group have synthesized a series of tetradentate PNNP ligands and their metal complexes, and have widely applied them to various enantioselective catalysis such as asymmetric reduction of polar bonds, oxidative kinetic resolution, asymmetric epoxidation, asymmetric cyclopropanation, and so forth.[7−12,18−31]

2.2. Iron Carbonyl Cluster Catalyst Containing Chiral PNNP Ligands for ATH of Ketones

ATH reactions were developed over recent decades as an alternative to traditional catalytic AH processes in which hydrogen gas is used under pressure. Over this period, ATH has emerged as an attractive method because of its operational simplicity and the easy availability of hydrogen sources.[2,32] For the ATH of ketones, the most efficient and enantioselective catalysts are usually based on ruthenium, rhodium, or iridium. Compared with the excellent chiral mononuclear metal catalysts, chiral metal cluster catalysts have seldom been studied. In 2003,[20] we reported the first successful example of a ruthenium cluster catalyst for the ATH of aromatic ketones after discovering that the chiral mononuclear ruthenium(II) complex (*S*,*S*)-**6** is an effective catalyst with high enantiose-

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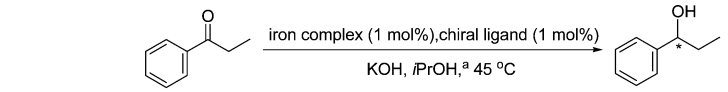
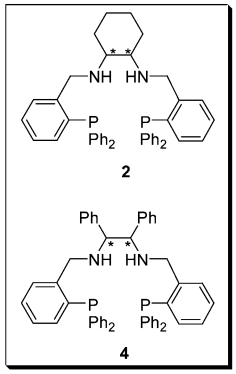
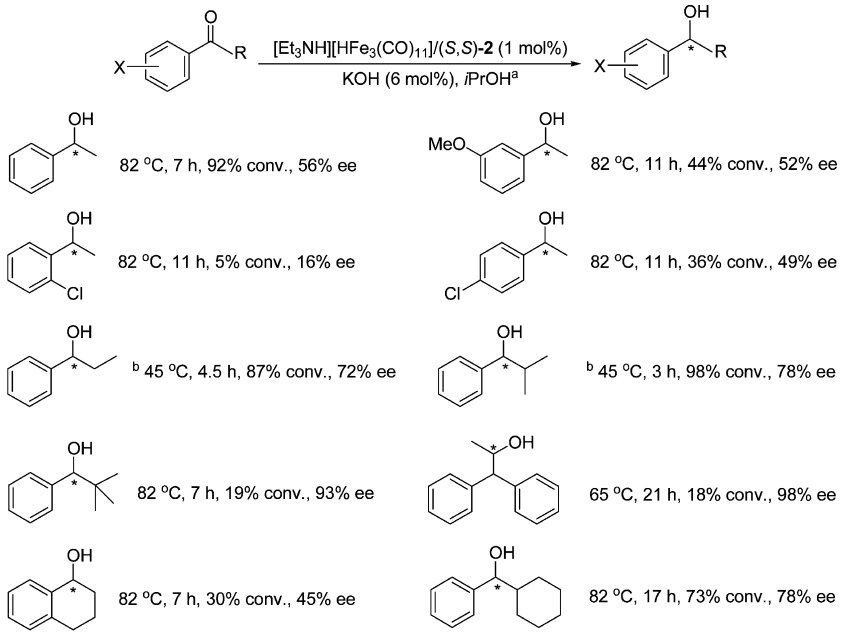




chiral iron catalyst	S/C/KOH	time(h)	conv. (%)	ee(%)
$CpFe(CO)_2I$/(*R*,*R*)-**2**	100:1:80	17	11	43
$CpFe(CO)_2I$/(*S*,*S*)-**4**	100:1:80	22	32	24
$[CpFe(CO)_2]_2$/(*R*,*R*)-**2**	100:1:80	45.5	15	37
$[CpFe(CO)_2]_2$/(*S*,*S*)-**4**	100:1:80	17	5	37
$Fe_2(CO)_9$/(*R*,*R*)-**2**	100:1:12	3	1	0
$Fe_2(CO)_9$/(*S*,*S*)-**4**	100:1:6	4.5	1	0
$Fe_3(CO)_{12}$/(*R*,*R*)-**2**	100:1:12	3	8	90
$Fe_3(CO)_{12}$/(*S*,*S*)-**4**	100:1:12	5	16	83
$[Et_3NH][HFe_3(CO)_{11}]$/(*R*,*R*)-**2**	100:1:6	4.5	87	72
$[Et_3NH][HFe_3(CO)_{11}]$/(*S*,*S*)-**4**	100:1:6	4.5	92	61

[a] Reaction was carried out by using 0.1 M solution of substrate in *i*PrOH.

Figure 3. Various iron catalysts containing chiral PNNP ligands for ATH of propiophenone.



[a] Reaction was carried out by using 0.1 M solution of substrate in *i*PrOH;
[b] (*R*,*R*)-**2** was used.

Figure 4. ATH of various ketones catalyzed by $[Et_3NH][HFe_3(CO)_{11}]$/(*S*,*S*)-**2**.

lectivities (up to 97% ee).[18] The ATH of acetophenone with a catalyst system generated in situ from $Ru_3(CO)_{12}$ and chiral PNNP ligand **3** proceeded smoothly to give the corresponding chiral alcohol in 91% yield and with 81% ee. More notably, the problematic substrate containing bulkier alkyl group, isobutyrophenone, was hydrogenated with excellent enantioselectivity (up to 99% ee).

An important long-standing goal in chemistry is the replacement of catalysts based on noble metals with those based on nonprecious metals.[26] While pursuing substitutes to these noble metal catalysts, we became interested in iron-catalyzed asymmetric reactions. Being abundant, inexpensive, environmentally benign, iron is an ideal alternative to precious metals for catalysis and sustainable chemical reaction. However, iron catalysts have been underdeveloped compared with other transition-metal catalysts.[33] In 2004, we reported the iron-catalyzed ATH of aromatic ketones.[7] Initially, we investigated the enantioselective reduction of propiophenone catalyzed by combining chiral PNNP ligand with various iron complexes (Figure 3). The results showed that the trinuclear iron clusters were superior to other iron compounds in terms of both activity and enantioselectivity. The catalyst system generated in situ from $[Et_3NH][HFe_3(CO)_{11}]$ and (*R*,*R*)-**2** gave 87% conversion with 72% ee, and the catalyst system formed in situ from $[Et_3NH][HFe_3(CO)_{11}]$ and (*S*,*S*)-**4** led to 92% conversion with 61% ee. To the best of our knowledge, this result represents the first example of the iron-catalyzed ATH of ketones.

Adding a base is crucial to the reaction of ATH in terms of both reactivity and enantioselectivity.[2] Therefore, we investigated the effect of base on the ATH of acetophenone catalyzed by $[Et_3NH][HFe_3(CO)_{11}]$/(*S*,*S*)-**2**.[7] Our results indicated that the reaction resulted in low conversion when the base was absent or present at low concentration. As the

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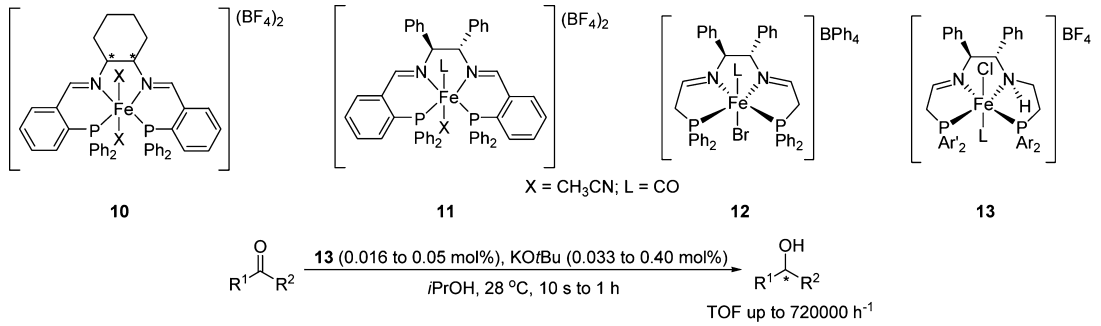


Figure 5. Representative chiral iron(II) catalysts used by Morris, and the ATH reaction of ketones.

base concentration was increased, the reaction rate increased greatly, whereas the ee decreased sharply. The base is thought to facilitate the formation of metal hydrides.

Next, we applied the catalyst system $[Et_3NH]$-$[HFe_3(CO)_{11}]$/(*S*,*S*)-**2** to the ATH of various ketones (Figure 4). For the ATH of acetophenone, the catalyst system exhibited high activity and moderate enantioselectivity (92% conversion, 56% ee). However, the substituted acetophenone, such as 2-chloroacetophenone, produced lower activities under the employed conditions. Notably, a more hindered aromatic ketone, 1,1′-diphenylpropan-2-one, yielded the corresponding chiral alcohol with low conversion but excellent enantioselectivity (18% conversion, 98% ee).

Although attempts to isolate the active catalysts failed, IR spectroscopy of the catalytic systems provided some information about the real catalyst. On the basis of spectra obtained while monitoring the reaction in situ using IR spectroscopy, we conjectured that the trinuclear skeleton of the iron cluster $[HFe_3(CO)_{11}]^-$ remained intact during the catalytic reaction. These results suggest that the trinuclear cluster combined with chiral ligand system likely exists as the catalytically active species under the investigated reaction conditions.

With these previous studies of chiral tetradentate PNNP ligands and iron-catalyzed ATH, Morris and co-workers improved the well-defined chiral PNNP iron(II) complexes and applied them to the ATH of a broad range of ketones with extraordinary catalytic activity.[8−12] Recently, they reported that partially saturated amine(imine)diphosphine ligands activate iron to catalyze the ATH of ketones and imines at turnover frequencies (TOFs) as high as 200 s^{-1} (Figure 5).[12] This excellent TOF even exceeds those observed for Ru- and Os-based catalysts.

2.3. Cobalt Carbonyl Cluster Catalysts Containing a Chiral PNNP Ligand for ATH of Ketones

In contrast to the encouraging results achieved for chiral iron catalysts, initial attempts at cobalt-catalyzed ATH of ketones were far from successful. Lemaire reported the ATH of acetophenone with moderate enantioselectivities (58% ee) but low conversion (Figure 6).[34] Generally, cobalt catalysts for enantioselective reduction contain chiral N,N or O,O ligands or their mixed moieties. Having synthesized a series of chiral PNNP ligands, we applied them to the cobalt-catalyzed ATH of ketones.[35]

We investigated the ATH of propiophenone with catalysts generated in situ from various cobalt complexes and chiral PNNP ligands **1** and **2** (Figure 7). The cobalt catalyst exhibited lower activity compared with the iron catalyst, which means that the reactions need to be carried out at higher temperatures,

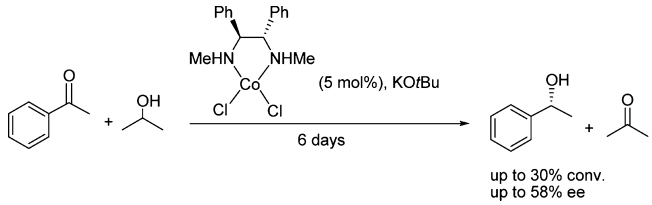
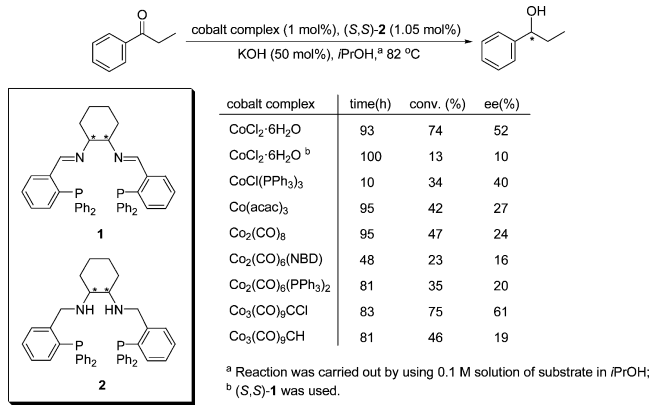


Figure 6. Cobalt-catalyzed ATH of acetophenone.



cobalt complex	time(h)	conv. (%)	ee(%)
$CoCl_2{\cdot}6H_2O$	93	74	52
$CoCl_2{\cdot}6H_2O$ [b]	100	13	10
$CoCl(PPh_3)_3$	10	34	40
$Co(acac)_3$	95	42	27
$Co_2(CO)_8$	95	47	24
$Co_2(CO)_6(NBD)$	48	23	16
$Co_2(CO)_6(PPh_3)_2$	81	35	20
$Co_3(CO)_9CCl$	83	75	61
$Co_3(CO)_9CH$	81	46	19

[a] Reaction was carried out by using 0.1 M solution of substrate in *i*PrOH; [b] (*S*,*S*)-**1** was used.

Figure 7. ATH of propiophenone catalyzed by cobalt complexes with (*S*,*S*)-**2**.

with a larger quantity of base, and at much longer reaction times to achieve satisfactory conversion. Among the cobalt complexes tested, the trinuclear cobalt carbonyl cluster $Co_3(CO)_9CCl$ was the optimum choice of catalyst, leading to 75% conversion in 83 h and 61% ee. Interestingly, the amino ligand **2** is superior to the imino ligand **1** in terms of both activity and enantioselectivity, although they have analogous structures. Conceivably, the NH moiety of ligand **2** accelerates the reaction by participating in the formation of a six-membered cyclic transition state through hydrogen bonding.[18]

When ligand **2**, which provided high enantioselectivity in the iron-catalyzed ATH of aromatic ketones, was used for the cobalt-catalyzed ATH of various ketones, the level of enantioselectivity was low to moderate (Figure 8). Isobutyrophenone was reduced to the corresponding chiral alcohol with 50% conversion and 63% ee. For acetophenone and its derivatives, the catalyst system gave lower enantioselectivities (6−30% ee). The chloro-substituent yielded chiral products at faster reaction rates, whereas 2-methyl-acetophenone only afforded 24% conversion even after 108 h.

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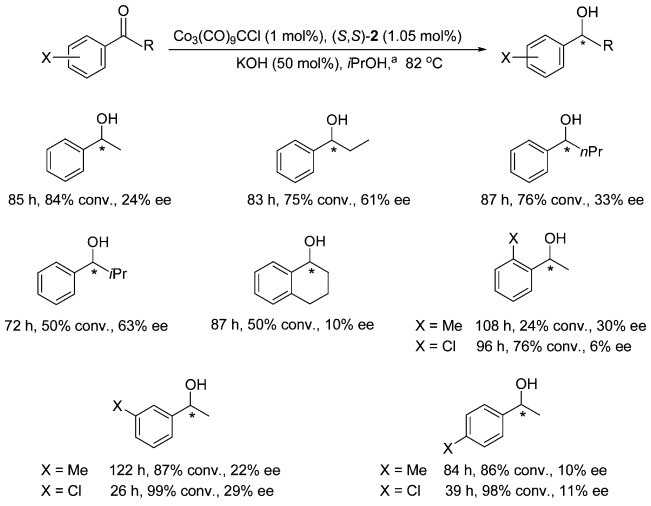

Figure 8. ATH of various aromatic ketones catalyzed by $Co_3(CO)_9CCl$/(*S*,*S*)-**2**.

3. IRON CATALYSTS CONTAINING CHIRAL MACROCYCLIC P_2N_4 LIGAND FOR ATH AND AH OF KETONES

3.1. Design and Synthesis of Chiral Macrocyclic P_2N_4 Ligands

As previously mentioned, chiral ligands are generally responsible for achieving high enantioselectivity in asymmetric catalysis. Therefore, the discovery of highly efficient and enantioselective chiral ligands, especially ligands with novel chiral backbones, constitutes a central challenge in asymmetric catalysis. Recently, chiral macrocycles containing O, N, S, or their mixed moieties have been successfully applied.[36−39] However, chiral macrocycles with P,N donors are very rare and have seldom been employed in asymmetric reactions.[40−44] In our development of chiral ligands, we designed and synthesized novel chiral 22-membered macrocycle ligands **14** and **15** (Figure 9), which contain four nitrogen atoms and two phosphorus atoms as potentially coordinating sites in the cyclic backbone.[41] The cyclization to obtain chiral macrocycle **14** was easily performed by cyclocondensation of bis(*o*-formylphenyl)-phenylphosphane and chiral diamine in a 1:1 molar ratio with one step. The ^{31}P NMR spectrum of the imine showed two singlets (δ −15.3 and −22.2 ppm), which may be due to the two isomers in the solution. Reduction of diimino **14** with $NaBH_4$ afforded the corresponding diamino **15** in 80% yield. The ^{31}P NMR spectrum of **15** showed a singlet at δ −27.1 ppm, suggesting that the two phosphorus atoms are equivalent. Further X-ray structure analysis also confirmed the elegant macrocyclic structure of ligand **14** and **15** (Figure 10).

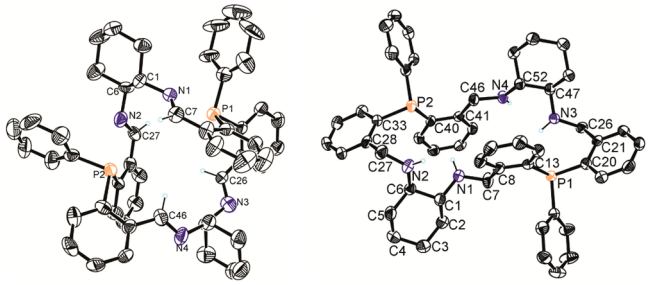

Figure 10. X-ray structure of chiral macrocycle **14** (left) and **15** (right).

3.2. Iron Carbonyl Cluster Catalyst Containing Chiral Macrocyclic P_2N_4 Ligands for ATH of Ketones

Although exciting progress has been achieved in the iron-catalyzed ATH of ketones, the development of new chiral iron catalysts with high efficiency as well as high enantioselectivity is highly desirable. During our continuing study of iron-catalyzed enantioselective reductions, we aimed to create catalysts that contain a novel chiral macrocyclic ligand.[41] Using the catalysts formed in situ from iron complexes and chiral P_2N_4-type macrocycles **14** and **15**, we investigated the ATH of propiophenone (Figure 11). Among the ligands used, macrocycle **15** was demonstrated to be very effective when combined with trinuclear iron carbonyl clusters. The best activity (93% conversion) and enantioselectivity (98% ee) was achieved with the catalytic system generated from $Fe_3(CO)_{12}$ and (*R*,*R*,*R*,*R*)-**15** in a 1:1 molar ratio. By contrast, the mononuclear and dinuclear iron(0) complexes and iron(II) and iron(III) salts gave poor activity in the reaction. Notably, the NH effect was again observed to improve the results. In contrast to the excellent results obtained with amino ligand **15**, the imino ligand **14** exhibited inferior activity and low enantioselectivity. Interestingly, the addition of an ammonium salt such as NH_4Cl promoted the reaction, although the role of ammonium remains unknown.

Next, a broad scope of aromatic ketones as well as heteroaromatic ketones was reduced using the catalytic system of a readily available iron carbonyl cluster $Fe_3(CO)_{12}$ in combination with macrocycle **15** (Figure 12). Under mild reaction conditions, the catalyst system exhibited outstanding enantioselectivities (90−99% ee) for the tested substrates. In most cases, highly catalytic activities were achieved with the exception of *ortho*-substituted ketones, which is presumably due to the steric hindrance of the substituents. Furthermore, the

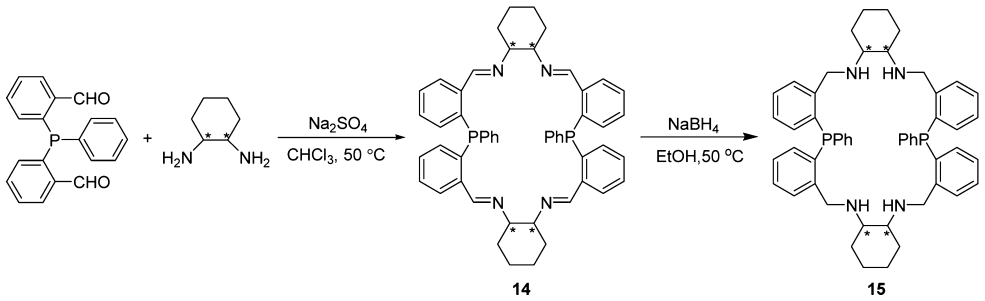

Figure 9. Synthesis of chiral macrocyclic P_2N_4 ligands.

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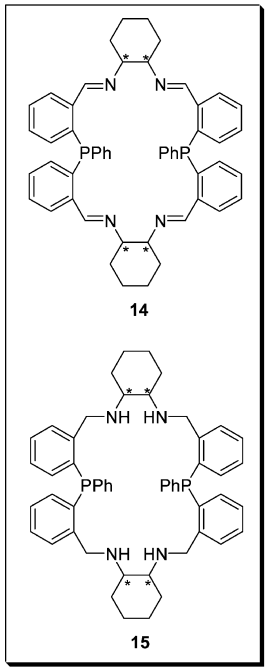
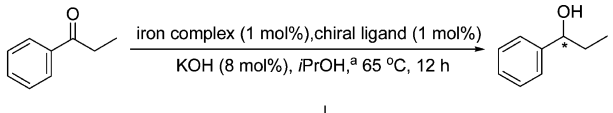
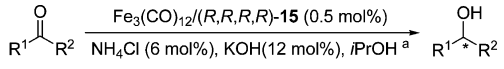


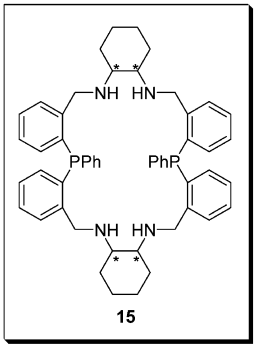


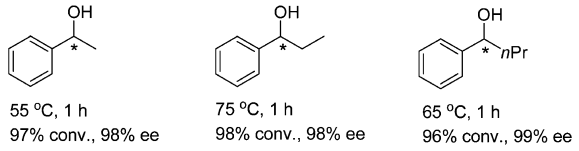
chiral iron catalyst	conv. (%)	ee(%)
$Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**14**	22	29
$Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15**	93	98
$Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15** [b]	98	98
$[Et_3NH][HFe_3(CO)_{11}]$/(*R*,*R*,*R*,*R*)-**15**	80	98
$[PPN][HFe_3(CO)_{11}]$/(*R*,*R*,*R*,*R*)-**15**	63	98
$[C_5H_5Fe(CO)_2]_2$/(*R*,*R*,*R*,*R*)-**15**	<1	0
$C_5H_5Fe(CO)_2I$/(*R*,*R*,*R*,*R*)-**15**	7	74
trans-$Fe(CO)_3(PPh_3)_2$/(*R*,*R*,*R*,*R*)-**15**	<1	0
$Fe(CO)_4(PPh_3)$/(*R*,*R*,*R*,*R*)-**15**	2	0
$FeH_2(CO)_2[P(OC_6H_5)_3]_2$/(*R*,*R*,*R*,*R*)-**15**	<1	0
$FeCl_2{\cdot}4H_2O$/(*R*,*R*,*R*,*R*)-**15**	2	0
$FeSO_4{\cdot}7H_2O$/(*R*,*R*,*R*,*R*)-**15**	<1	0
$FeCl_3$/(*R*,*R*,*R*,*R*)-**15**	<1	0
$Fe(acac)_3$/(*R*,*R*,*R*,*R*)-**15**	2	0

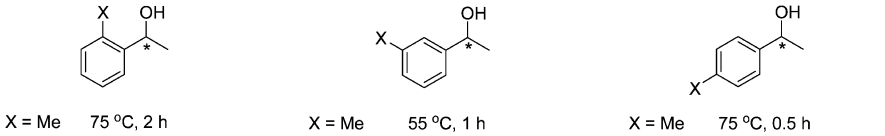
[a] Reaction was carried out by using 0.05 M solution of substrate in *i*PrOH;
[b] NH_4Cl (15 mol%) was added, KOH (23 mol%), 5 h.

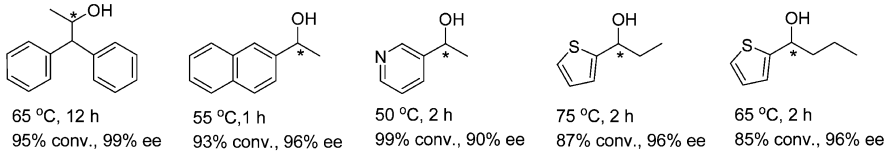
Figure 11. ATH of propiophenone catalyzed by iron complexes with chiral macrocycles.











[a] Reaction was carried out by using 0.1 M solution of substrate in *i*PrOH.

Figure 12. ATH of various ketones catalyzed by $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15**.

enantioselective reductions were carried out even at a low catalyst loading (0.1−0.02 mol %) with high yield and excellent enantioselectivity, indicating the remarkable efficiency of this iron-based catalyst. For instance, the ATH of 4-chloroaceto-

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phenone catalyzed by $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15** proceeded smoothly at S/C = 2000, yielding the chiral products with 97% conversion in 1 h and with 95% ee.

To the best of our knowledge, the catalytic system $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15** is the first example of chiral iron-based macrocycles successfully used for the enantioselective reduction of a broad scope of ketones with outstanding enantioselectivities. Compared to previous chiral open-chain tetradentate PNNP ligands, the chiral macrocyclic ligand exhibits greater catalytic activity and enantioselectivity. The novel cyclic structure may be responsible for the high ee, which would increase the rigidity of the ligand and restrict its configurational flexibility.

To better understand the mode of cooperation between the macrocycle and iron, we attempted to isolate the active catalysts from this reaction mixture but were unsuccessful. However, another chiral iron(0)-bearing macrocycle, **16**, was obtained as a yellow solid from the reaction of $Fe_3(CO)_{12}$ and (*R*,*R*,*R*,*R*)-**15** in a 1:1 molar ratio in acetonitrile (13% yield, Figure 13).[45] The ^{31}P NMR of complex **16** showed two singlets at δ 62.32 and 65.41 ppm because of the two coordinated phosphine atoms. Crystals of **16** suitable for X-ray diffraction were grown from $CHCl_3$/hexane (Figure 14). Complex **16** contains two iron atoms, each of which is coordinated to one phosphine atom.

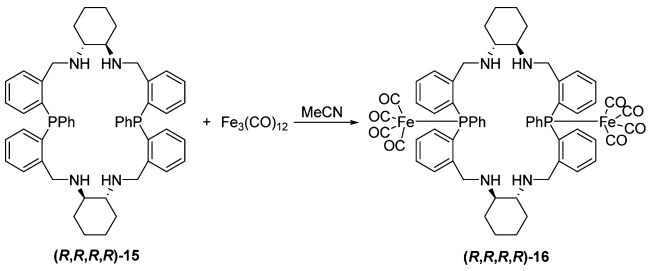

Figure 13. Synthesis of chiral P_2N_4–Fe(0) complex (*R*,*R*,*R*,*R*)-**16**.

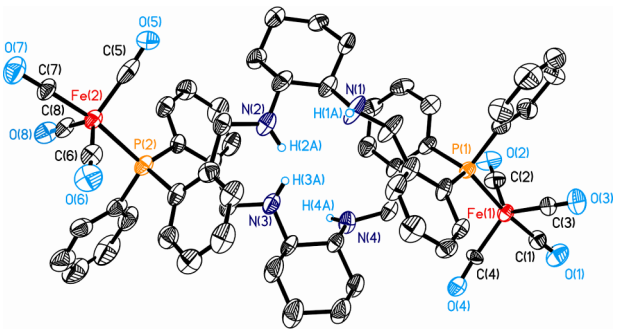

Figure 14. X-ray structure of chiral P_2N_4–Fe(0) complex (*R*,*R*,*R*,*R*)-**16**.

The catalytic performance of (*R*,*R*,*R*,*R*)-**16** was investigated for the ATH of various ketones. Because this complex is insoluble in *i*PrOH, the reaction was carried out in a mixture of toluene and *i*PrOH. Compared with the catalytic system formed in situ from $Fe_3(CO)_{12}$ and (*R*,*R*,*R*,*R*)-**15**, the complex exhibited lower activity and decreased enantioselectivity (Figure 15). Given these results, we speculate that complex (*R*,*R*,*R*,*R*)-**16** may not be the actual active catalyst.

Recently, Mezzetti and co-workers reported the first example of the synthesis of chiral C_2-symmetric N_2P_2 macrocycles and bis(isonitrile) iron(II) complexes bearing an N_2P_2 macrocyclic ligand (Figure 16).[42−44] These stable, fully characterized, diamagnetic iron(II) complexes could be successfully applied in the ATH of a broad range of substrates (ketones, enones, and imines) in high yield (up to 99.5%), with excellent enantioselectivity (up to 99% ee), and with low catalyst loading (typically 0.1 mol %).

3.3. Iron Carbonyl Cluster Catalyst Containing Chiral Macrocyclic P_2N_4 Ligands for AH of Ketones

AH with H_2 of unsaturated bonds is one of the most efficient and practical methods for obtaining various chiral compounds.[46−48] In contrast to precious metal-based catalysts used universally, highly active and enantioselective inexpensive metal catalysts for this reaction have been rare. Before we began our research on iron-catalyzed AH reactions, only two examples of chiral iron catalysts for AH of acetophenone had been reported—one by Morris et al. and the other by Neudörfl et al.—and these catalysts gave 31% ee or less.[8,49] A more recent successful example of iron-catalyzed AH of ketones was reported by Morris et al.[13] When iron precatalysts containing unsymmetrical P−N−P′ pincer ligands were used, the hydrogenation of ketones proceeded at TOF up to 2000 h^{-1} and with up to 85% ee. Notably, the catalyst system must be activated by treatment with $LiAlH_4$ and then with alcohol. Still, the structure of the real catalyst is not clear. To the best of our knowledge, the literature contains no previous reports of a successful chiral cobalt or nickel catalyst for the AH of ketones. Therefore, the development of efficient, inexpensive metal catalysts for AH reactions remains a grand challenge.

In our research on the enantioselective reduction of ketones, we were pleased to observe that the iron-based cluster catalyst $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15**, which provides excellent enantioselectivities in the ATH of ketones, also enables efficient asymmetric pressure hydrogenation of ketones (Figure 17).[15] Using H_2 as hydrogen source, the AH of acetophenone proceeded smoothly, leading to more than 99% conversion and 97% ee. Imino macrocycle **14** still gave low activity and enantioselectivity for this reaction.

After optimizing the reaction conditions, we applied the catalytic system $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15** to the AH of a wide range of aromatic ketones as well as heterocyclic ketones. The

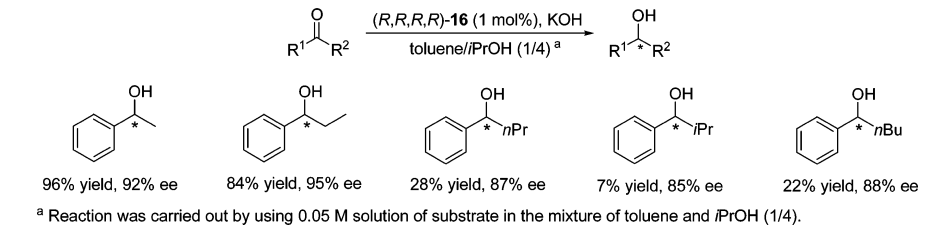

Figure 15. ATH of various ketones catalyzed by chiral P_2N_4–Fe(0) complex (*R*,*R*,*R*,*R*)-**16**.

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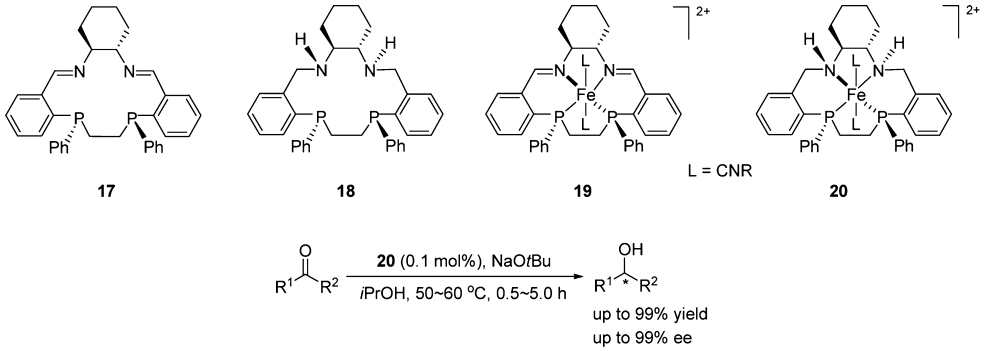
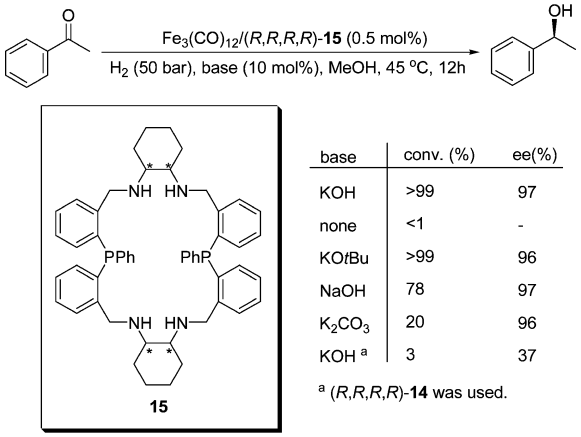


Figure 16. Mezzetti's chiral macrocyclic ligands, iron(II) complexes, and the ATH of ketones.



base	conv. (%)	ee(%)
KOH	>99	97
none	<1	-
KO*t*Bu	>99	96
NaOH	78	97
K_2CO_3	20	96
KOH [a]	3	37

[a] (*R*,*R*,*R*,*R*)-**14** was used.

Figure 17. AH of acetophenone catalyzed by $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15**.

reactions achieved high yields and excellent enantioselectivities, in most cases, approaching or surpassing those obtained using the precious metal catalysts (Figure 18). The electron property

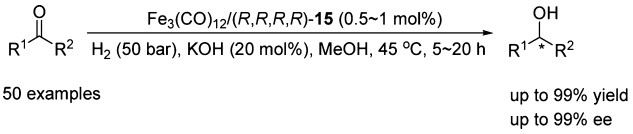
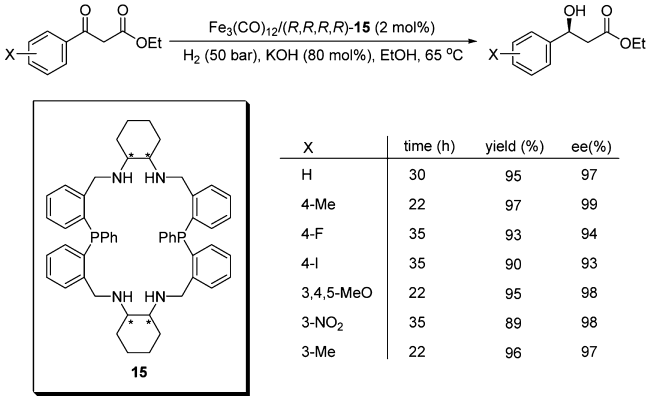


Figure 18. AH of various ketones catalyzed by $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15**.

of substituents on the aromatic ring had little influence on the catalytic activity while the substitution position took important effect on the enantioselectivities. For aryl methyl ketones, the highest enantioselectivity (97−99% ee) was obtained with *ortho*-substituted ketones, which is unusual for most of precious metal catalysts. Moreover, for the problematic α-substituted acetophenones, such as 4-methyl propiophenone, α-isopropyl-phenylmethanone, and α-cyclohexyl-phenylmethanone, the iron-based catalyst enantioselectively reduced them to corresponding chiral alcohols with 98−99% ee while typically used Ru-(diphosphine) (diamine) catalysts gave 38−98% ee.[48] The AH of a class of heterocyclic ketones with $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15** also proceeded smoothly with high yields and excellent ee's. It highlights again the extraordinary enantioselectivity of iron-macrocycle catalyst for a broad range of ketones. It is worth mentioning that the interactions of the substrates bearing functionalities with the NH proton of **15** must not be ignored. For example, lower ee obtained with *ortho*-methoxy acetophenone and 2-acetylpyridine.

The versatile macrocyclic iron-based catalyst was further proved by the enantioselective hydrogenation of functionalized ketones, β-ketoesters (Figure 19). The reactions afforded



X	time (h)	yield (%)	ee(%)
H	30	95	97
4-Me	22	97	99
4-F	35	93	94
4-I	35	90	93
3,4,5-MeO	22	95	98
3-NO_2	35	89	98
3-Me	22	96	97

Figure 19. AH of β-ketoesters catalyzed by $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15**.

excellent yields and ee's which are comparable with those observed using catalysts based on noble metals. In comparison with aforementioned aromatic ketones and heterocyclic ketones, the AH of β-ketoesters was carried our under a higher temperature and longer reaction time, probably owing to chelating interactions between the catalyst and the ketoester. Notably, electronic properties of the substituted groups onto the phenyl ring in substrates had an important effect on the catalytic activity as well as the enantioselectivity. That is electron-donating groups seem to accelerate the reaction and increase the ee, whereas electron-withdrawing groups take the negative effect. For example, the asymmetric reduction of methyl- and trimethoxy-substituted ketoesters proceeded smoothly in 22 h with 98−99% ee while the AH of the fluoro- and iodo-substituted ketoesters required 35 h to achieve high yield accompanying with slightly decreased enantioselectivity.

The chiral iron(0) cluster catalyst $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15** proved to be highly effective for both ATH and AH of a broad range of ketones, giving excellent enantioselectivities approaching or exceeding those achievable with noble-metal catalysts. Up to now, such "universal" catalysts are very rare.[46] When Morris' iron complex **13**, which catalyzed the ATH of ketones and imines with extraordinary activity and up to 99% ee, was applied to the AH of ketones, only 0−70% ee and a TOF of 80 h^{-1} were obtained.[14] Therefore, macrocycle **15** coupled with

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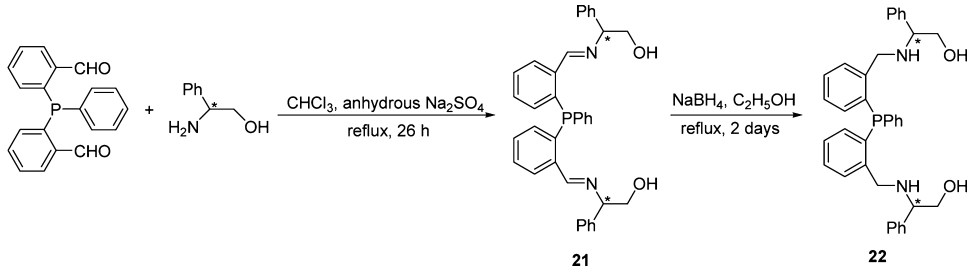

Figure 20. Synthesis of chiral PNO-type ligands.

$Fe_3(CO)_{12}$ fills, to a significant degree, a gap in the area of asymmetric ketone reduction.

To gain insight into the catalytic behavior of the iron(0) cluster catalyst, we conducted mechanistic studies of this reduction system. We tried our best to obtain the active catalysts from the mixture of AH reaction but failed. Another difficulty to carry out the mechanistic observations is that the catalytic system is paramagnetic under the employed reaction conditions. Therefore, NMR studies in situ would not give any valuable information. Interestingly, dynamic light scattering (DLS) experiments revealed the existence of iron particles during the reaction. Furthermore, when poisons of diverse nature, such as PPh_3, Hg(0), or 1,10-phenanthroline were added separately to the AH with $Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**15**, we observed a clear poisoning effect. These preliminary experimental results suggest that the AH of ketones catalyzed by iron(0) cluster most likely involved the formation of chiral macrocycle-modified iron nanoparticles as the active catalytic species to realize the excellent enantioinduction.[15] The unique feature distinguishes our catalyst from other reported chiral iron(II) complexes is the combination of chiral macrocycles with iron(0) cluster. It demonstrates that chiral metal cluster catalysts may offer new opportunities in asymmetric catalysis and will stimulate further studies on the development of efficient chiral cluster catalytic systems.

4. NICKEL CATALYSTS CONTAINING CHIRAL PNO-TYPE LIGAND FOR ATH OF KETONES

Compared with the relative prices of some transition metals in the form of their corresponding anhydrous chlorides, iridium and rhodium are extraordinarily expensive; palladium and ruthenium are somewhat cheaper, and nickel and iron are 100-fold and more than 1000-fold cheaper than ruthenium, respectively.[50] Although some successful examples of iron complexes as catalysts for the enantioselective reduction of ketones have been demonstrated, other inexpensive metals, such as Ni or Co complexes, have been elusive. On the basis of our study of chiral ligands and related catalysis, we synthesized novel chiral multidentate PNO-type ligands and observed that these chiral ligands, coupled with a simple Ni(II) complex, $[NiCl_2(PPh_3)_2]$, exhibited good catalytic activity and enantioselectivity toward the ATH of aromatic ketones.[51]

Using commercially available (*R*)-phenylglycinol as a starting material, we conveniently prepared novel chiral multidentate PNO-type ligands **21** and **22** (Figure 20).[51] The condensation of bis(*o*-formylphenyl)phenylphosphane with (*R*)-phenylglycinol afforded a light-yellow solid **21** in 80% yield (Figure 21). The ^{1}H NMR spectrum of **21** contained two doublets at δ 8.61 and δ 8.55 for the imino protons. The ^{31}P NMR spectrum exhibited a singlet at δ −10.83. Reduction of **21** with $NaBH_4$ in ethanol yielded the corresponding NPO-type ligand **22** as a white solid. The ^{31}P NMR spectrum of ligand **22** exhibited a singlet at δ −26.07.

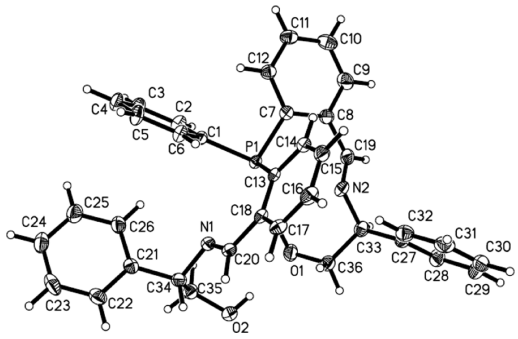

Figure 21. X-ray structure of chiral multidentate PNO-type ligand **21**.

The ATH of various ketones with the catalyst formed in situ from $[NiCl_2(PPh_3)_2]$ and ligand (*R*,*R*)-**22** proceeded with satisfactory yields and with up to 84% ee (Figure 22). Generally, the increasing bulkiness of the alkyl substituents on the α-position of the substrate results in an improved enantioselectivity. However, there is an exception in the case of *n*-butyrophenone, which afforded lower conversion with decreased ee (56 h, 51% conversion, 60% ee). Furthermore, the enantioselective reduction of methyl-substituted acetophenones reacted sluggishly under the employed conditions.

5. CONCLUSIONS

The replacement of noble-metal-based catalysts with those containing a nonprecious metal such as iron, cobalt, or nickel constitutes a challenging and highly attractive goal in asymmetric catalysis. Although some promising progress in the iron-catalyzed enantioselective reduction of ketones has been previously reported, it continues to be desirable to develop new chiral inexpensive metal catalysts that not only provide high enantioselectivity but also exhibit high efficiency (as reflected in the high TOF of the catalyst) and a high reaction rate under mild conditions and with a simple reaction procedure, and so forth. For the past decade, we have devoted ourselves to the development of ATH and AH of ketones with iron, cobalt, and nickel catalysts containing novel chiral aminophosphine ligands. In the present study, we observed that iron catalysts that contain chiral aminophosphine ligands, which are expected to control the stereochemistry at the metal atom, restrict the number of possible diastereomers and effectively transfer chiral information, making them successful catalysts for the enantioselective reduction of ketones. Among these novel chiral aminophosphine ligands, 22-membered macrocycle P_2N_4 exhibited extraordinary enantioselectivities when combined with iron(0)-cluster $Fe_3(CO)_{12}$. A broad range of ketones, including aromatic, heteroaromatic, and β-

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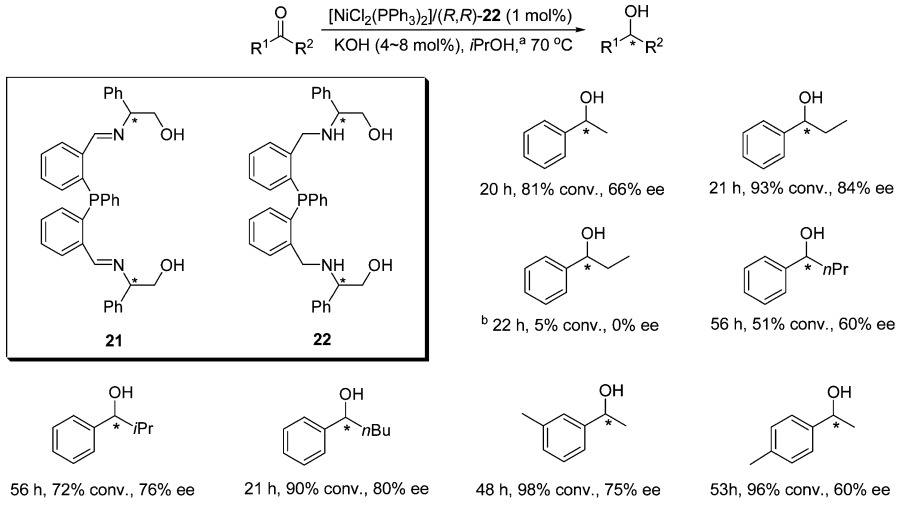

[a] Reaction was carried out by using 0.1 M solution of substrate in *i*PrOH;
[b] Ligand **21** was used.

Figure 22. ATH of various aromatic ketones catalyzed by $[NiCl_2(PPh_3)_2]/(R,R)$-**22**.

ketoesters, were reduced smoothly with excellent enantioselectivities (up to 99% ee) approaching or exceeding those achievable with noble-metal catalysts. Notably, the chiral iron-based catalyst proved to be highly efficient for both the ATH as well as the AH of various ketones. Our preliminary studies suggest that the AH reaction most likely involved iron particles as the active catalytic species. These research results point to a new direction for the development of viable and effective nonprecious-metal catalysts for asymmetric catalytic reactions. Continued study of the electronic and steric properties of these chiral catalysts as well as their catalytic mechanism will lead to the development of new inexpensive chiral metal catalysts that are highly effective and will further expand their use in asymmetric catalysis.

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