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Iron Catalyzed Asymmetric Hydrogenation of Ketones

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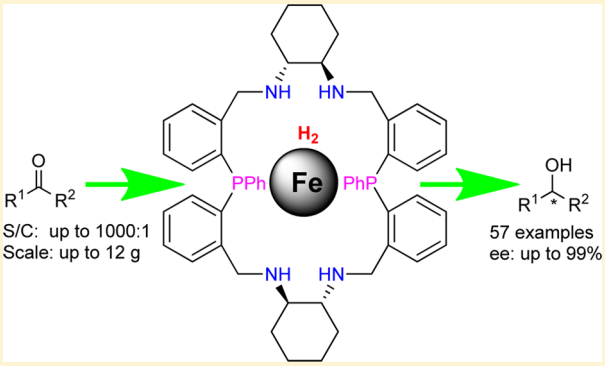
Supporting Information

ABSTRACT: Chiral molecules, such as alcohols, are vital for the manufacturing of fine chemicals, pharmaceuticals, agrochemicals, fragrances, and novel materials. These molecules need to be produced in high yield and high optical purity and preferentially catalytically. Among all the asymmetric catalytic reactions, asymmetric hydrogenation with H_2 (AH) is the most widely used in the industry. With few exceptions, these AH processes use catalysts based on the three critical metals, rhodium, ruthenium, and iridium. Herein we describe a simple, industrially viable iron catalyst that allows for the AH of ketones, a process currently dominated by ruthenium and rhodium catalysts. By combining a chiral, 22-membered macrocyclic ligand with the cheap, readily available $Fe_3(CO)_{12}$, a wide variety of ketones have been hydrogenated under 50 bar H_2 at 45−65 °C, affording highly valuable chiral alcohols with enantioselectivities approaching or surpassing those obtained with the noble metal catalysts. In contrast to AH by most noble metal catalysts, the iron-catalyzed hydrogenation appears to be heterogeneous.



INTRODUCTION

Asymmetric hydrogenation (AH) has come a long way over the last half century, culminating with the award of the Nobel Prize to Noyori and Knowles for their contribution to the field in 2001. Being totally atom-economical, scalable, and robust, AH is now universally used for the synthesis of various chiral compounds, ranging from alcohols through amines to acids, and accounts for more than half of all the industrial asymmetric catalytic processes.[1−4] In both academic laboratories and industrial operations, AH reactions are catalyzed principally by metal complexes based on rhodium, ruthenium, and iridium. A case in point is the AH of ketones, which has been used in a number of industrial processes ranging from kilogram to ton scales for the synthesis of pharmaceuticals, agrochemicals, and fragrances, where ruthenium- and rhodium-based catalysts currently dominate the scene.[1,3,4] However, the limited availability, risk in supply, high and volatile price, and toxicity of these critical metals call for their replacement with abundant, inexpensive, and biocommon metals, such as iron.[5,6]

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.[6,7] However, iron catalysts have been significantly undeveloped compared with other transition metals. Only in the past few years has significant progress been witnessed in iron catalysis,[7−10] including in particular transfer hydrogenation[9] and hydrosilylation.[10]

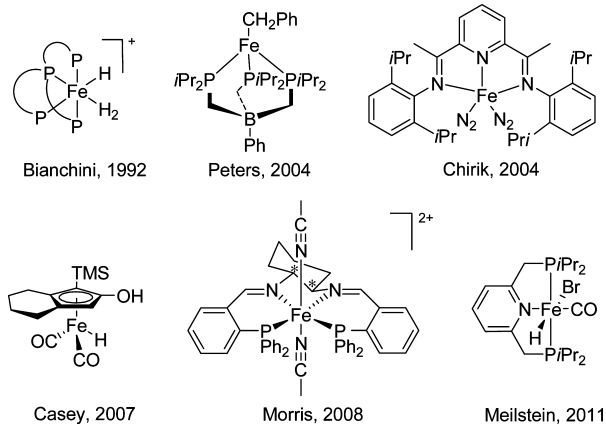


Figure 1. Representative iron catalysts used for hydrogenation.

Hydrogenation with H_2 catalyzed by achiral iron catalysts has also been demonstrated (Figure 1).[11] Notable examples include the hydrogenation of alkenes reported by the groups of Chirik[11n] and Peters,[11o] ketones by Casey,[11p] Morris,[11q,r] and Milstein,[11s] and CO_2 and nitroarenes by Beller[11t,u] and their co-workers. A recurring feature of the catalysts reported is the use of multidentate open-chain ligands, presumably echoing the

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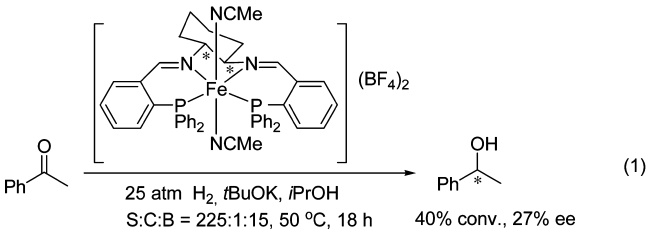
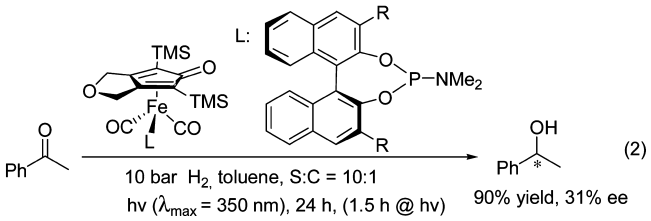
generally lower stability of iron complexes in comparison with those made of the noble metals. In contrast, in most AH reactions catalyzed by the noble metals, bidentate and to some degree monodentate chiral phosphorus compounds are the ligand of choice.[1]

Iron catalysts that are efficient for AH reactions have been elusive, however. No iron catalysts have been known capable of AH of olefins, and only recently has AH of imino bonds been reported by Beller et al. using the achiral Knölker complex in the presence of a chiral Bronsted acid.[12] Concerning the AH of ketones, there are only two iron catalysts so far, which show appreciable activities and enantioselectivities, and in both cases only the substrate acetophenone was examined.[11q,r,13,14] In one case, acetophenone was reduced with a chiral Fe−N_2P_2 complex in the presence of a base, affording 27% ee and 40% conversion in isopropanol (*i*PrOH) at 50 °C under 25 atm of H_2 at a substrate/catalyst (S/C) ratio of 225 (eq 1).[11q]



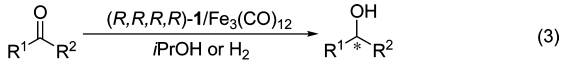
(1)



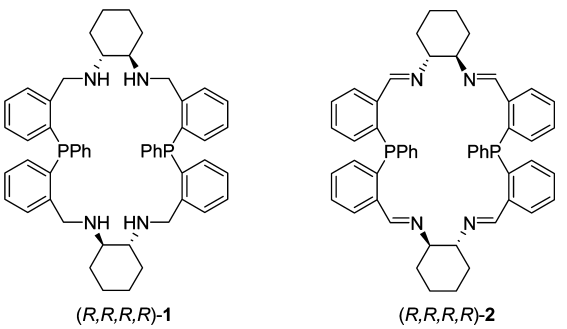
(2)

In the other, a Knölker type complex modified with a chiral phosphoramidite ligand catalyzed the AH under UV radiation, furnishing 1-phenylethanol in 31% ee and 90% yield under 10 bar of H_2 at an S/C ratio of 10 (eq 2).[13] Clearly, it remains a grand challenge to develop an iron catalyst that is capable of synthetically viable AH reactions.

One of our groups recently reported a novel chiral ligand (*R,R,R,R*)-**1**, which, when combined with a readily available iron carbonyl compound $Fe_3(CO)_{12}$, displays excellent enantioselectivities in the asymmetric transfer hydrogenation (ATH) of various ketones with *i*PrOH as the reductant (eq 3).[15] In contrast to almost all the chiral ligands found in the noble



(3)



(*R,R,R,R*)-**1** (*R,R,R,R*)-**2**

metal-catalyzed AH and ATH and to those attempted for AH with iron,[1−4,7−10] ligand **1** is macrocyclic, having 22 atoms including 6 potentially coordinating N and P atoms in the ring. In continued effort on asymmetric reduction in our laboratories,[15,16] we have found that the same combination also enables highly efficient AH of a broad range of ketones, with enantioselectivities approaching or exceeding those achievable with the noble metal catalysts. It is worth pointing out that over the past half century, only a few catalysts have been shown to be effective for both AH and ATH reactions,[1v,17] and developing a "universal" catalyst that allows the AH as well as ATH of a range of substrates remains challenging. Ligand **1** coupled with $Fe_3(CO)_{12}$ fills, to a significant degree, the gap in the area of asymmetric ketone reduction. Reported herein are our results on the AH of ketones with this catalyst.

METHODS

Ligand **1** can be readily accessed by condensing a phosphino-aldehyde with chiral cyclohexyl diamine followed by reduction of the resulting cyclic imino compound **2** with $NaBH_4$.[15]

Typical Procedure for AH. A dried glassliner (20 mL) was charged with $Fe_3(CO)_{12}$ (2.5 mg, 0.005 mmol) and **1** (4.0 mg, 0.005 mmol) under N_2 and then loaded into an dried autoclave. After the addition of freshly distilled MeOH (5 mL), the autoclave was purged with H_2 (1 bar) three times. The mixture was then stirred at 45 °C under 5 bar H_2 for 1 h. After releasing the H_2 gas in a fumehood, KOH in MeOH (0.5 M, 0.4 mL) and acetophenone (1 mmol) were sequentially introduced through an injection port. The autoclave was then pressurized to 50 bar H_2, and the reaction mixture stirred at 45 °C for 5 h. After cooling down to room temperature and subsequently releasing the H_2 pressure in a fumehood, the mixture was concentrated and purified by chromatograph on a silica-gel column with ethyl acetate/hexane (v/v = 5:95), affording 1-phenylethanol in 97% isolated yield. The enantioselectivity of the product was determined by GC equipped with a chiral Chrompack Chirasil-Dex CB column (25 m x 0.25 mm).

Procedure for Larger-Scale AH of Acetophenone. The procedure was similar to that above, using a 125 mL glassliner charged with $Fe_3(CO)_{12}$ (101.0 mg, 0.2 mmol), **1** (160.0 mg, 0.2 mmol), and MeOH (50 mL). Following stirring for 1 h at 45 °C under 5 bar H_2, a MeOH solution of KOH (0.5 M, 16 mL) and acetophenone (12.00 g, 100.0 mmol) were introduced. The mixture was then stirred for 12 h at 45 °C under 50 bar H_2 pressure. Purification by chromatograph on a silica-gel column with ethyl acetate/hexane (v/v = 5:95) afforded the corresponding chiral alcohol in 98% isolated yield (11.93 g) with 96% ee.

Procedure for AH of Acetophenone in the Presence of a Poison Additive. A dried glassliner (20 mL) was charged with $Fe_3(CO)_{12}$ (5 mg, 0.01 mmol) and **1** (8.0 mg, 0.01 mmol) under N_2 and then loaded into an dried autoclave. After the addition of freshly distilled MeOH (8 mL), the autoclave was purged with H_2 (1 bar) three times. The mixture was then stirred at 45 °C under 5 bar H_2 for 1 h. After releasing the H_2 gas in a fumehood, KOH in MeOH (0.5 M, 0.8 mL), acetophenone (1 mmol) and an additive (triphenylphosphine, 1,10-phenanthroline, or mercury, 0.001−0.03 mmol) (see Table 6) were sequentially introduced through an injection port. The autoclave was then pressurized to 50 bar H_2, and the reaction mixture stirred at 45 °C for a certain period of time (see Table 6). After cooling down to room temperature and subsequently releasing the H_2 pressure in a fume hood, the sample was analyzed as above. In the case of using mercury, the sample was carefully taken at the top of the reaction mixture, the rest of which was quenched with sulfur and collected in a special bottle for disposal.

RESULTS AND DISCUSSION

Optimization of AH Conditions. We first examined the AH of the benchmark substrate acetophenone by combining

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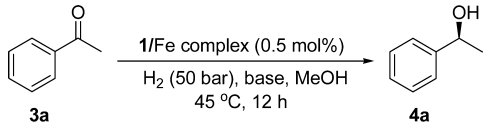
Table 1. Screening of Catalysts and Conditions for the AH of Acetophenone[a]



3a 4a

Entry	Iron source	Base	Conv (%)[b]	Ee (%)[b]
1	$[Et_3NH][HFe_3(CO)_{11}]$	KOH	<1	
2	$[PPN][HFe_3(CO)_{11}]$	KOH	<1	
3	$[CpFe(CO)_2]_2$	KOH	none	
4	$[CpFe(CO)_2I]$	KOH	<1	
5	$Fe(CO)_4(PPh_3)_2$	KOH	1	
6	*trans*-$Fe(CO)_3(PPh_3)_2$	KOH	<1	
7	$Fe(acac)_3$	KOH	none	
8	$FeCl_2{\cdot}4H_2O$	KOH	<1	
9	$Fe_3(CO)_{12}$	KOH	>99	97
10[c]	$Fe_3(CO)_{12}$	KOH	>99	97
11[d]	$Fe_3(CO)_{12}$	None	<1	
12[d]	$Fe_3(CO)_{12}$	KOH	82	97
13	$Fe_3(CO)_{12}$	*t*BuOK	>99	96
14	$Fe_3(CO)_{12}$	NaOH	78	97
15	$Fe_3(CO)_{12}$	K_2CO_3	20	96
16[e]	$Fe_3(CO)_{12}$	KOH	26	97
17[f]	$Fe_3(CO)_{12}$	KOH	3	37

[a]Reaction conditions: acetophenone (1 mmol) with ketone/Fe/(*R*,*R*,*R*,*R*)-**1**/base = 200:1:1:20 (molar ratio), MeOH (5 mL), initial H_2 pressure 50 bar, 45 °C and 12 h. [b]Conversion and ee were determined by GC analysis with a chiral CP-Chriasil-Dex CB column. [c]5 h reaction time with 20 mol % KOH. [d]5 h reaction time. [e]AH at 25 °C. [f](*R*,*R*,*R*,*R*)-**2** was used.

the macrocyclic ligand **1** with various iron compounds in addition to $Fe_3(CO)_{12}$. To facilitate the screening, the catalyst was generated in situ by reacting **1** with an iron species. As can be seen from Table 1, while all the other iron complexes, regardless of the oxidation state, failed to catalyze the AH in question, the carbonyl cluster $Fe_3(CO)_{12}$ led to almost full conversion in 12 h and a remarkable enantioselectivity of 97% ee (Table 1, entry 9), a value which is comparable to that obtained with some of the most successful catalysts based on the critical metals Ru, Os, Rh, and Ir.[1−4] To the best of our knowledge, this is the first example of highly efficient and enantioselective AH of a ketone catalyzed by iron. A slightly higher ee of 98% was obtained in the ATH of the same substrate, and the ATH appears to be faster.[15] The AH with the **1**/$Fe_3(CO)_{12}$ combination involved reacting **1** (0.005 mmol) with 1 equivalent of $Fe_3(CO)_{12}$ in methanol under 5 bar H_2 at 45 °C for 1 h, before introducing 20 equiv of KOH and 1 mmol of acetophenone; the resulting mixture was then stirred at 45 °C under 50 bar H_2 for 12 h. It must be noted that the AH becomes much slower and less enantioselective without the initial 1 h pretreatment (vide infra). In addition, without H_2, no AH took place, showing that methanol is not acting as the hydrogen source in the AH catalyzed by **1**/$Fe_3(CO)_{12}$. The base plays a critical role in the AH. In fact, when the concentration of KOH was doubled, the AH was complete in 5 h (Table 1, entry 10). In its absence, little AH took place, and lowering its concentration afforded a lower conversion. Similarly, when a weaker base was used, a slower reaction resulted. However, the enantioselectivity remained approximately the same in all the scenarios (Table 1, entries 11−15) (For more details, see the Supporting Information (SI)). These observations appear to indicate that the formation of active catalyst species, for example, iron hydrides, depends on the basicity of the reaction mixture. The accelerating effect of a base on the reaction rate of AH with precious metal catalysts has been noted in a number of cases;[18] however, base-free conditions have also been demonstrated.[11a,19] Further optimization revealed that lowering the reaction temperature did not improve the ee but significantly reduced the AH rate (Table 1, entry 16), and ligand **2** was ineffective in the AH (Table 1, entry 17), hinting that the NH group of **1** may play an important role in the reaction, as in the case of the Noyori metal−ligand bifunctional catalysts, for example, Ru(diphosphine)(diamine).[1v,3a]

AH of Aryl Ketones. With the optimized reaction conditions in hand, we then applied the catalytic system to the reduction of a wide range of ketones. As shown in Table 2, various aryl methyl ketones were reduced with **1**/$Fe_3(CO)_{12}$, affording high isolated yields and excellent ee's which are comparable with those obtained with the noble metal catalysts in most cases.[1−4] Under the conditions employed, there appears to be no unambiguous correlation between the electron property of substituents on the phenyl ring and the yield of products (Table 2, entries 1, 5, and 8 vs 2, 14, and 19). However, the enantioselectivities vary with the substitution position, with the highest ee value being associated with, surprisingly somehow, *ortho*-substituted ketones. For example, ee's ranging from 97% to 99% were obtained for *ortho*-substituted acetophenones (Table 2, entries 4, 7, 13, 16), which are 2−7% higher than their *meta*- and *para*-substituted analogues. In contrast, the precious metal catalysts usually show the opposite trend and more notably, none of them are known to afford ee's higher than **1**/$Fe_3(CO)_{12}$ for such *ortho*-substituted acetophenones. An exception is found in the methoxy substituent in the AH with **1**/$Fe_3(CO)_{12}$; the ketone gives decreasing ee values on going from the *para* to *meta* and *ortho* substitution, a result which could arise from hydrogen-bonding interactions between the methoxy group and ligand NH proton (Table 2, entries 8−10). Other acetophenones were also shown to be viable. For instance, naphthyl and anthraceneyl ethanones were hydrogenated in 96−98% ee, and the bulky 1,1′-diphenylpropan-2-one gave rise to 99% ee (Table 2, entry 26). There is no literature report on the AH of this latter ketone, although ATH with Ir-PNNP catalysts is known (94−99% ee).[16e,f] However, tetralone could not be reduced efficiently with **1**/$Fe_3(CO)_{12}$, affording only 25% yield and 70% ee under the current conditions.

Still interestingly, excellent ee's of 98−99% were observed with α-substituted acetophenones, including those bearing the ethyl, propyl, butyl, and sterically more demanding isopropyl and cyclcohexyl groups (Table 3, entries 1−7). These results highlight again the distinctive difference between **1**/$Fe_3(CO)_{12}$ and the noble metal catalysts in AH of such problematic ketones, with the iron catalyst displaying superior enantioselectivities in general. For instance, using the iron catalyst, 4-methyl propiophenone was reduced in 98% ee (Table 3, entry 2), and the AH of both α-isopropyl- and α-cyclohexylphenylmethanone gave 99% ee (Table 3, entries 5 and 7). In comparison, the most-often used Ru-(diphosphine)(diamine) catalysts are less enantioselective for these ketones (38−98% ee).[20,21] However, an iridium amido complex afforded >99% ee,[22] and in the case of 2,2,2-trifluoroacetophenone, the Noyori Ru-(BINAP)(diamine) catalyst shows better performance than **1**/$Fe_3(CO)_{12}$ (96% vs 92% ee).[23]

AH of Heterocyclic Ketones. The **1**/$Fe_3(CO)_{12}$ catalyst is effective for the AH of heterocyclic ketones as well, furnishing

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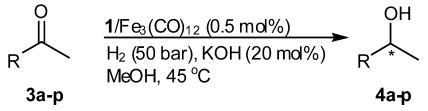
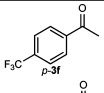
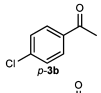
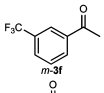
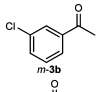
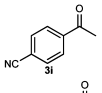
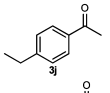
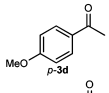
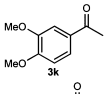
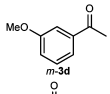
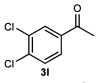
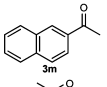
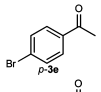
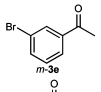
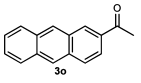
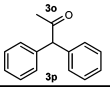
Table 2. AH of Aromatic Ketones with 1/$Fe_3(CO)_{12}$[a]



3a-p 4a-p

Entry	Ketone	Time (h)	Yield (%)[b]	Ee (%)[c]	Config.[c]	Entry	Ketone	Time (h)	Yield (%)[b]	Ee (%)[c]	Config.[c]
1	 3a	5	97	97	*S*	14	 *p*-3f	10	66	91	*S*
2	 *p*-3b	10	99	95	*S*	15	 *m*-3f	10	82	91	*S*
3	 *m*-3b	5	96	94	*S*	16	 *o*-3f	10	60	98	*S*
4	 *o*-3b	5	89	97	*S*	17	 3g	10	98	96	*S*
5	 *p*-3c	10	91	97	*S*	18	 3h	10	69	96	*S*
6	 *m*-3c	10	93	95	*S*	19	 3i	10	98	96	*S*
7	 *o*-3c	10	82	99	*S*	20	 3j	10	99	97	*S*
8	 *p*-3d	10	98	96	*S*	21	 3k	10	88	85	*S*
9	 *m*-3d	5	97	91	*S*	22	 3l	10	96	91	*S*
10	 *o*-3d	10	73	60	*S*	23	 3m	10	98	96	*S*
11	 *p*-3e	10	99	96	*S*	24	 3n	10	95	98	*S*
12	 *m*-3e	5	98	93	*S*	25	 3o	10	97	96	*S*
13	 *o*-3e	10	98	99	*S*	26[d]	 3p	10	68	99	*R*

[a]Reaction conditions: ketone (1 mmol) with ketone/$Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**1**/KOH = 200:1:1:40 (molar ratio), initial H_2 pressure 50 bar, 45 °C in MeOH (5 mL). [b]Isolated yield. [c]Determined by GC or HPLC analysis. The absolute configuration was determined by comparison of the retention times with the literature data (see the SI). [d](*S*,*S*,*S*,*S*)-**1** was used.

good to excellent yields and ee's (Table 4). Thus, 3- and 4-acetylpyridine were reduced to pyridinyl alcohols with 94% and 90% ee, respectively (Table 4, entries 1 and 2). The lower ee with 2-acetylpyridine may again be traced to possible interactions of the pyridine nitrogen with the ligand NH functionality. Acetylthiophenes are particularly suitable, as highlighted by 2,5-dimethyl-3-acetylthiophene which led to an ee of 99% (Table 4, entries 4–8). In a previous study using a Ru(BICP)(diamine) (BICP = (2*R*,2*R*′)-bis(diphenylphosphino)-(1*R*,1*R*′)-dicyclopentane) catalyst, the AH of 2-acetylthiophene and 5-Cl-2-acetylthiophene afforded 93% and 89% ee at −30 °C, respectively.[24] However, AH of acetylfurans and 2-acetylthiazole produced only moderate ee values under the current conditions (Table 4, entries 9, 10, and 13), reminiscent of the observations made with substrates bearing functionalities that could hydrogen-bond with the NH proton of **1**. In contrast, much higher enantioselectivities were obtained for 3-acetylfuran and 5-acetylthiazole (Table 4, entries 11 and 14). The significantly higher ee values observed for these two ketones indicate that the ring heteroatom is more likely to interact with the ligand or iron when it is next to the carbonyl group, possibly resulting in hindering the face discrimination of the carbonyl group by the catalyst at the step of hydride transfer.

AH of *β*-Ketoesters. To demonstrate further the utility of the catalyst, we studied the AH of a class of functionalized ketones, *β*-ketoesters. As shown in Table 5, excellent yields and ee's were again observed. In comparison with the ketones above, a higher temperature and longer reaction time were necessary, probably due to chelating interactions of the substrate with the iron. However, hydrogen bonding interactions with the ligand NH proton cannot be ruled out. Thus, the reduction of ethyl 3-oxo-3-phenylpropanoate afforded 95% yield with 97% ee in

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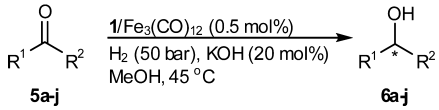
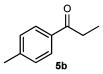
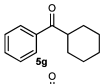
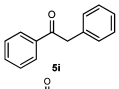
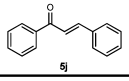
Table 3. AH of α-Substituted Aromatic Ketones with $1/Fe_3(CO)_{12}$[a]



Entry	Ketone	Time (h)	Yield (%)[b]	Ee (%)[c]	Config.[c]
1		5	80	98	*S*
2		10	99	98	*S*
3[d]		10	93	98	*R*
4[d]		10	97	99	*R*
5[e]		10	92	99	*S*
6		10	99	93	*S*
7[d]		10	63	99	*R*
8[e]		10	82	92	*R*
9[e]		20	95	98	*S*
10[e]		20	98	65	*S*

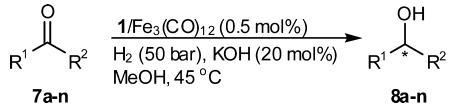
[a]For reaction conditions, see Table 2. [b]Isolated yield. [c]Determined by GC or HPLC analysis. The absolute configuration was determined by comparison of the retention times with the literature data or analogy (see the SI). [d](*S,S,S,S*)-**1** was used. [e]S/C ratio was 100/1.

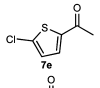
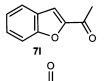
30 h at 65 °C in ethanol (Table 5, entry 1). This result is comparable with those from Ru-diphosphine catalysts (92–97% ee).[25] For these substrates, electron donating groups on the phenyl ring appear to benefit both the reaction rate and enantioselectivity, while electron withdrawing groups have the opposite effect. This is seen by comparing the AH of methyl and trimethoxy substituted keto esters (Table 5, entries 2, 5, and 7), which completed in 22 h, with that of the halo substituted ones, which necessitated more than 30 h for complete reduction and showed slightly lower ee's (Table 5, entries 3 and 4).

Larger Scale AH. While most of the reactions above were carried out at an S/C ratio of 200, lower catalyst loading is possible. For instance, the AH of acetophenone with $1/Fe_3(CO)_{12}$ proceeded smoothly at S/C = 500, being complete in 10 h and affording 96% ee. At still a higher S/C ratio of 1000, the ketone was hydrogenated in 84% conversion and 92% ee in 24 h. Larger scale AH was also shown to be feasible. Thus, AH of acetophenone (12.00 g) afforded the desired chiral alcohol in 98% isolated yield (11.93 g) with 96% ee in 12 h (catalyst/KOH = 1:40), demonstrating the commercial potential of this iron catalyst (eq 4).

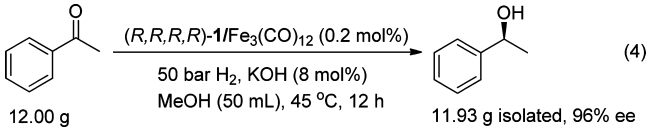
Mechanistic Observations. Preliminary studies suggest that in contrast to AH with vast majority of the noble metal catalysts, which is homogeneous in nature, the AH in question appear to be heterogeneous, most likely involving iron particles

Table 4. AH of Heterocyclic Ketones with $1/Fe_3(CO)_{12}$[a]



Entry	Ketone	Time (h)	Yield (%)[b]	Ee (%)[c]	Config.[c]
1		10	80	94	*S*
2		5	98	90	*S*
3		5	97	72	*S*
4		10	92	93	*S*
5		10	94	92	*S*
6		10	98	95	*S*
7[d]		10	96	93	*R*
8		10	88	99	*S*
9		10	90	79	*S*
10[e]		10	95	51	*S*
11		10	75	97	*S*
12		10	90	90	*S*
13		10	77	55	*S*
14		10	95	98	*S*

[a]For reaction conditions, see Table 2. [b]Isolated yield. [c]Determined by GC or HPLC analysis. The absolute configuration was determined by comparison of the retention times with the literature data or analogy (see the SI). [d](*S,S,S,S*)-**1** was used. [e]S/C ratio was 100/1.



as the active catalytic species. This assertion is supported by several observations.

First, the reaction mixture is cloudy throughout the entire AH process. Indeed, dynamic light scattering confirmed the existence of iron particles when $1/Fe_3(CO)_{12}$ in MeOH was treated with H_2 with or without KOH (For details, see the SI).

Second, as mentioned above, efficient AH necessitates reacting **1** with $Fe_3(CO)_{12}$ under 5 bar of H_2 for 1 h before the AH reaction (see Methods). Thus, when the AH of acetophenone

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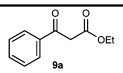
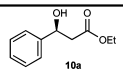
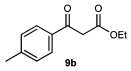
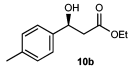
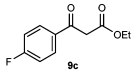
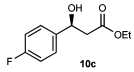
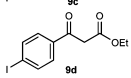
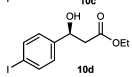
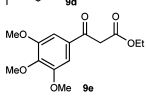
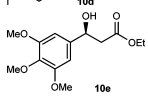
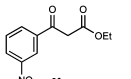
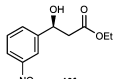
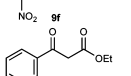
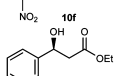
Table 5. AH of β-Ketoesters with $1/Fe_3(CO)_{12}$[a]

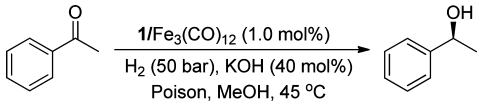
Entry	Ester	Product	Yield (%)[b]	Ee (%)[c]
1	 9a	 10a	95	97
2[d]	 9b	 10b	97	99
3[e]	 9c	 10c	93	94
4[e]	 9d	 10d	90	93
5[d]	 9e	 10e	95	98
6[e]	 9f	 10f	89	98
7[d]	 9g	 10g	96	97

[a]Reaction conditions: β-keto ester (1 mmol) with ester/$Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**1**/KOH = 50:1:1:40 (molar ratio), EtOH (5 mL), initial H_2 pressure 50 bar, 65 °C and 30 h. [b]Isolated yield. [c]Determined by GC or HPLC analysis. The absolute configuration was determined by comparison of the retention times with the literature data (see the SI). [d]22 h reaction time. [e]35 h reaction time.

was carried out under the conditions of Table 2 except without the initial 1 h pretreatment, a lower conversion of 72% and a lower ee of 83% were obtained in 15 h reaction time. This observation suggests that efficient AH with $1/Fe_3(CO)_{12}$ involves a period in which active and selective catalytically species is generated under H_2, a phenomenon bearing resemblance to hydrogenation by heterogeneous catalysts, where catalytically active metal particles are often formed through an induction period.[26,27]

Third, a significant poisoning effect was observed when poisons of diverse nature[26] were introduced separately to the AH by $1/Fe_3(CO)_{12}$ (Table 6). Thus, in the presence of substiochiometric PPh_3 (0.3 equivalent, relative to the iron carbonyl cluster $Fe_3(CO)_{12}$), the AH of acetophenone proceeded to a conversion of only 20% (S/C = 100). An even lower conversion of 11% was observed when 0.3 equivalent of 1,10-phenanthroline was added (Table 6, entry 6). A similar effect was observed with Hg(0), a poison commonly used to distinguish homogeneous catalysis from catalysis by metal particles.[26] Thus, 1 equiv of Hg was sufficient to almost fully stop the AH from occurring (Table 6, entry 9). Insightfully, a considerable decrease in enantioselectivity was recorded in all three cases, suggesting that the active catalytic species are changed by the introduction of the poison molecules. For comparison, the same AH reaction gave full conversion with 97% ee in 3 h in the absence of the poison (Table 6, entry 1). These results indicate that AH by $1/Fe_3(CO)_{12}$ is probably heterogeneous, with **1**-modified iron particles acting as the active catalyst. The significant decrease in the catalytic activity and enantioselectivity by a substiochiometric poison is consistent with adsorption of the poison molecules onto, or amalgamation in the case of Hg with,[26] the surface of the particles, reducing the number of active iron atoms that are expected to locate on the surface of the particles and altering their interactions with **1**. Although few effective AH catalysts are known to be based on metal nanoparticles,[28,29] Morris has recently shown that a $Fe-N_2P_2$ complex catalyzes transfer hydrogenation through the formation of iron nanoparticles.[27a]

Table 6. Effect of Poisoning Additives on the AH of Acetophenone with $1/Fe_3(CO)_{12}$[a]



Entry	Additives	Quantity[b]	Time [h]	Conv (%)[c]	Ee (%)[c]
1	none		3	>99	97
2	PPh_3	1	10	8	56
3	PPh_3	0.3	10	20	84
4	PPh_3	0.1	10	98	92
5	1,10-phenanthroline	1	10	<1	
6	1,10-phenanthroline	0.3	10	11	75
7	1,10-phenanthroline	0.1	10	92	83
8	mercury	3	10	<1	
9	mercury	1	10	4	45

[a]Reaction conditions: ketone (1 mmol), with ketone/$Fe_3(CO)_{12}$/(*R*,*R*,*R*,*R*)-**1**/KOH = 100:1:1:40 (molar ratio), 50 bar H_2, 45 °C in MeOH. [b]Equivalent, relative to $Fe_3(CO)_{12}$. [c]Conversion and ee were determined by GC analysis with a chiral CP-Chriasil-Dex CB column.

CONCLUSION

In summary, a remarkably effective iron catalyst has been identified for the AH of ketones, showing enantioselectivities approaching or even surpassing those achieved with the well-established precious metal catalysts. The value of the catalyst is further strengthened by its efficacy in related ATH reactions.[15] A key element of the catalyst is the 22-membered macrocyclic ligand **1**, a feature that distinguishes the catalyst from almost all known metal catalysts successful in AH and ATH reactions. While how the ligand induces asymmetry and what active iron species are involved in the AH concerned remain to be delineated in detail, the macrocyclic feature of the ligand points to a new direction in developing viable iron catalysts for asymmetric reduction and probably for other reaction as well.

ASSOCIATED CONTENT

Supporting Information

Further details of the AH reactions, including characterization data of products, GC/HPLC trace records, and technical details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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