Fe-Catalyzed Hydrogenation

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Highly Efficient Catalyst Systems Using Iron Complexes with a Tetradentate PNNP Ligand for the Asymmetric Hydrogenation of Polar Bonds**

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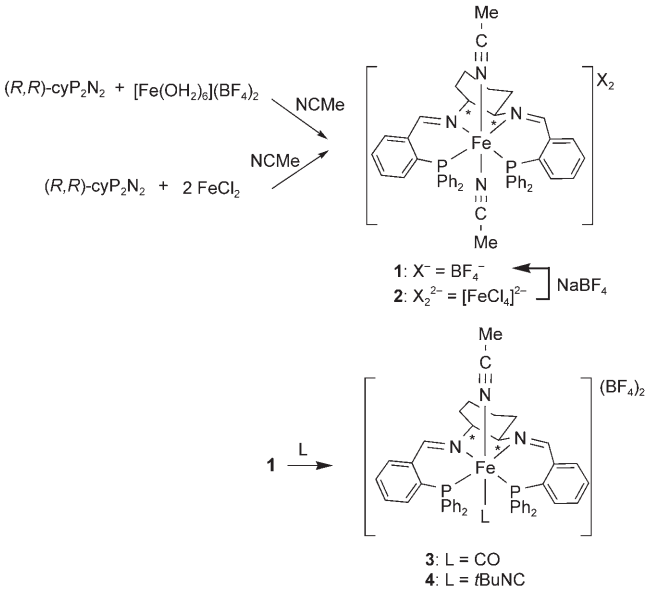
The transfer of hydrogen from 2-propanol to prochiral, unsaturated molecules catalyzed by certain transition-metal complexes is a powerful method for the synthesis of enantiopure alcohols and amines.[1] To date, the most efficient and enantioselective catalysts for this reaction are based on ruthenium and rhodium.[2,3] They catalyze the asymmetric hydrogenation of acetophenone near room temperature with the highest turnover frequencies (TOFs) in the range 100–4000 h^{-1}.[4] Iron-based catalysts of comparable activity would be desirable owing to their potentially lower cost, toxicity, and environmental impact. However, the reported iron hydrogenation catalysts have poor activities[5] apart from the iron catalysts for olefin hydrogenation reported by Chirik and co-workers[6,7] and the achiral iron catalyst recently reported by Casey and Guan for ketone and imine hydrogenation and acetophenone transfer hydrogenation.[8] Achiral transfer hydrogenation catalysts, specifically $[FeH(H_2)\{(PPh_2CH_2CH_2)_3P\}]BPh_4$,[9] $[Fe_3(CO)_{12}]$/porphyrin,[10] $[Fe_3(CO)_{12}]$/terpyridine/PPh_3, and $[NMe_4][Fe_3H(CO)_{11}]$,[11,12] which use alcohols as the reductant, provide complete conversion of ketones into alcohols at 80–100 °C within 1–24 h. Gao's group has mixed the cluster complex $[Et_3NH][Fe_3H(CO)_{11}]$ with chiral diaminodiphosphine P-NH-NH-P ligands to produce systems for the asymmetric transfer hydrogenation of ketones (TOF = 13 h^{-1} at 82 °C).[13] They postulated that the iron carbonyl cluster stays intact during catalysis, as proposed previously by Jothimony et al.[11,12] for a carbonyl cluster without phosphine present.

Given the high activity and enantioselectivity for acetophenone transfer hydrogenation[14,15] and H_2 hydrogenation[15] displayed by the ruthenium complexes $[RuCl_2\{(S,S)\text{-}cyP_2(NH)_2\}]$, in which (S,S)-$cyP_2(NH)_2$ is the tetradentate P-NH-NH-P ligand (S,S)-$\{PPh_2(o\text{-}C_6H_4)CH_2NHC_6H_{10}NHCH_2(o\text{-}C_6H_4)PPh_2\}$, we wondered whether similar iron catalysts could be developed. The ruthenium catalyst is thought to hydrogenate ketones by a transfer of hydride from ruthenium and proton from nitrogen to the C=O bond in an outer-sphere hydrogenation.[16] Therefore, the NH group is thought to be essential. Gao and co-workers reported the synthesis of the dicationic complexes $[Fe(NCMe)_2\{ethP_2N_2\}](ClO_4)_2$ ($ethP_2N_2 = \{PPh_2(o\text{-}C_6H_4)CH{=}NCH_2\}_2$) and $[Fe(NCMe)_2\{ethP_2(NH)_2\}](ClO_4)_2$ ($ethP_2(NH)_2 = \{PPh_2(o\text{-}C_6H_4)CH_2NHCH_2\}_2$) but did not report X-ray structures and catalytic activity of these complexes.[17]

Herein we report the discovery of the first catalyst systems using iron complexes for asymmetric H_2 hydrogenation at 50 °C and asymmetric transfer hydrogenation at room temperature. Surprisingly, the precatalysts have the tetradentate diiminodiphosphine ligand (R,R)-$\{PPh_2(o\text{-}C_6H_4)CH{=}NC_6H_{10}N{=}CH(o\text{-}C_6H_4)PPh_2\}$ ((R,R)-cyP_2N_2) with no NH functionality.

Our starting point was the synthesis of well-defined complexes containing the enantiopure tetradentate ligand (R,R)-cyP_2N_2. We prepared such complexes in excellent yield (60–90%) by two different routes (Scheme 1). In the first route, the hexaaquairon(II) complex is treated with the ligand in MeCN to produce the red-orange dicationic complexes $[Fe(NCMe)_2\{(R,R)\text{-}cyP_2N_2\}](BF_4)_2$ (**1**) in a fashion similar to that reported by Gao and co-workers.[17] A second route is the reaction of two equivalents of $FeCl_2$ with the ligand to give the complex $[Fe(NCMe)_2\{(R,R)\text{-}cyP_2N_2\}](FeCl_4)$ (**2**) in excellent



Scheme 1. Synthesis of the Fe^{II} complexes **1**–**4**.

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yield. Treatment of **2** with $NaBF_4$ produces the tetrafluoroborate complex **1**.

Complexes **1** and **2** are thermally stable and can be handled in air for a few hours (both in the solid state and in solution) without appreciable decomposition. They dissolve in CH_2Cl_2, $CHCl_3$, MeCN, and DMSO to give a red-orange solution, but they are poorly soluble in 2-propanol and insoluble in diethyl ether, THF, and hydrocarbons. They display a characteristic singlet in the $^{31}P\{^1H\}$ NMR spectrum and a singlet for the imine resonance at $\delta = 9.2$ ppm in the ^1H NMR spectrum. The structure of complex **1** as determined by single-crystal X-ray diffraction is shown in Figure 1.[18] The

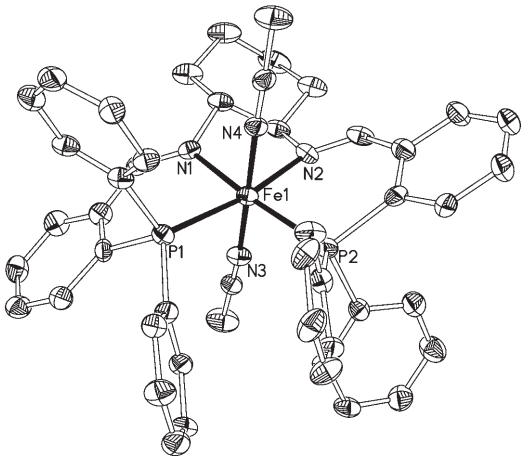
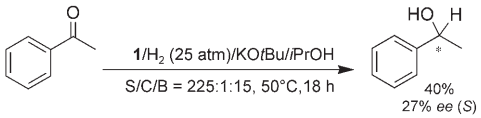


Figure 1. X-ray structure of **1** with thermal ellipsoids drawn at the 30% probability level. The BF_4 anions, the solvent, and the hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Fe1-N1 2.007(6), Fe1-N2 2.010(6), Fe1-N3 1.904(4), Fe1-N4 1.915(7), Fe1-P1 2.276(2), Fe1-P2 2.272(2); N4-Fe1-N3 175.9(3), N1-Fe1-N2 82.5(3), P2-Fe1-P1 100.24(8), N1-Fe1-P1 87.9(2).

complex is *trans* octahedral. The *R*,*R*-substituted cyclohexyl group causes an asymmetry in the placement of the two phenyl groups next to each acetonitrile binding site. The Fe–P bond lengths are between those observed for the low-spin iron(II) complex *cis*-$[Fe(CO)(NCMe)(PEt_2CH_2NMeCH_2PEt_2)(PMe_2CH_2PMe_2)](BF_4)_2$ (Fe–P 2.30–2.38 Å)[19] and those observed in the complexes *trans*-$[FeH(NCMe)(PEt_2CH_2NMeCH_2PEt_2)(PMe_2CH_2PMe_2)](BF_4)$ (Fe–P 2.20–2.22 Å)[19] and *trans*-$[Fe(H_2)H(dppe)_2](BPh_4)$ (Fe–P 2.23–2.25 Å)[20] while the Fe–N3 and Fe–N4 bond lengths are similar to that of the former (carbonyl) complex.

The carbonyl complex **3** and the isocyanide complex **4** (Scheme 1) were prepared in quantitative yield by reaction of complex **1** with carbon monoxide (1 atm) and 2 equivalent of *t*BuNC, respectively, in acetone at 22 °C or in refluxing chloroform (Scheme 1). Yellow solutions of complex **3** are stable to oxidation in air for at least one day. The ^1H NMR spectrum of **3** shows the presence of a singlet for the imine protons at $\delta = 9.11$ ppm while the $^{13}C\{^1H\}$ NMR spectrum displays a pseudotriplet for the carbonyl carbon atom. The ^1H NMR spectrum of complex **4** has two distinct resonances for the imine protons. The $^{31}P\{^1H\}$ NMR spectra consist of AB patterns at about $\delta = 51$ and 48 ppm ($^2J_{P\text{-}P} \approx 40$ Hz) for **3** and about 58 and 48 ppm ($^2J_{P\text{-}P} = 51$ Hz) for **4**. The IR spectra of **3** and **4** proved valuable. The carbonyl ligand of **3** absorbs at 2000 cm^{-1}, similar to the carbonyl ligand of *cis*-$[Fe(CO)(NCMe)(PEt_2CH_2NMeCH_2PEt_2)(PMe_2CH_2PMe_2)](BF_4)_2$ (1991 cm^{-1}).[19] Complex **4** exhibits absorptions at 2151 and 2173 cm^{-1} for the *t*BuNC and MeCN ligands.

The dicationic complex **1** was tested as a catalyst precursor for the H_2 hydrogenation of acetophenone to 1-phenylethanol. Under 25 atm of H_2 at 50 °C and in the presence of KO*t*Bu, it showed 40% conversion with an *ee* value of 27% (Scheme 2). This is the first report of a well-

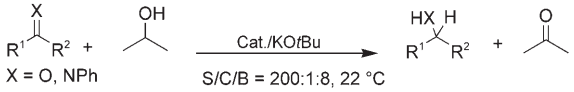


Scheme 2. Hydrogenation of acetophenone catalyzed by **1**.

defined iron precatalyst for the asymmetric hydrogenation of ketones. The current system has a TOF of about 5 h^{-1} at 50 °C, somewhat less active than Casey's iron catalyst (TOF 2 h^{-1} at 25 °C). No activity was found for transfer hydrogenation catalysis.

Complex **3** was found to be inactive for H_2 hydrogenation, but it is a surprisingly efficient catalyst for the solvent transfer hydrogenation of ketones, aldehydes, and imines (Table 1).

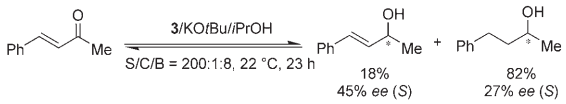
Table 1: Catalytic transfer hydrogenation from 2-propanol catalyzed by **3** and **4**.[a]



Entry	Substrate	*t* [h]	Conv. [%]	*ee* [%]	TOF [h^{-1}]
1[b]	Ph-CO-Me	0.4	95	29 (*S*)	907
2[c]	Ph-CO-Me	0.7	33	39 (*S*)	93
3	Ph-CO-Me	0.4	95	33 (*S*)	454
4	(2′-Cl-C_6H_4)-CO-Me	0.2	>99	18 (*S*)	995
5	(3′-Cl-C_6H_4)-CO-Me	0.4	99	24 (*S*)	495
6	(4′-Cl-C_6H_4)-CO-Me	0.2	94	26 (*S*)	938
7	(4′-Br-C_6H_4)-CO-Me	0.2	93	33 (*S*)	930
8	(4′-Me-C_6H_4)-CO-Me	0.6	86	33 (*S*)	279
9	(4′-OMe-C_6H_4)-CO-Me	0.5	69	23 (*S*)	260
10	Ph-CO-Et	3.6	95	61 (*S*)	26
11	$C_{10}H_7$-CO-Me[d]	0.3	94	25 (*S*)	564
12	Ph-CO-Ph	0.4	94	–	470
13	Ph-$(CH_2)_2$-CO-Me	0.6	100	29 (*S*)	315
14	Ph-CHO	2.4	94	–	77
15	Ph-CH=N-Ph	17	100	–	12
16	Ph-CMe=N-Ph	17	<5	–	–
17	cyclohexanone	17	0	–	–
18	Ph-CO-Me[e]	2.6	34	76 (*S*)	28

[a] The reactions were carried out in a glovebox under Ar at 22 °C. S/C/B = 200:1:8, [cat.] = 1.04 mM, 5 mL *i*PrOH. The catalyst is **3** unless otherwise noted. [b] S/C/B = 400:1:8, [cat.] = 0.1 mM, 10 mL *i*PrOH. [c] S/C/B = 200:1:2, [cat.] = 0.1 mM, 5 mL *i*PrOH. [d] $C_{10}H_7$-CO-Me = 2-acetonaphthone. [e] Reaction catalyzed by **4**. S/C/B = substrate/catalyst/base.

This system was also extensively investigated with a variety of substrates. The electronic properties of the substituents on the phenyl ring of the ketone changed the reduction rate but had less effect on the enantioselectivity (18–33% *ee*). An acetophenone substituted in the *para* position by an electron-releasing group, such as 4′-methyl and 4′-methoxy, is reduced more slowly than acetophenone (Table 1, entries 3, 8, and 9). The chloro-substituted acetophenones are all reduced faster, especially for the *ortho* position (Table 1, entries 3–7). This trend is opposite to the generally observed trend for the transfer hydrogenation catalysts reported by Noyori and coworkers in which an *ortho*-Cl substitution decreases the rate of the reduction.[21] The catalyst **3** with KO*t*Bu is also efficient for the transfer hydrogenation of propiophenone, 2-acetonaphthone, benzophenone, benzylacetone, benzaldehyde, and *N*-benzylideneaniline (Table 1, entries 10–15). The hydrogenation of propiophenone gave 1-phenylpropanol in 61% *ee* (*S*; Table 1, entry 10). The more difficult ketimine *N*-phenyl-(1-phenylethylidene)amine (Ph-CMe=N-Ph) was only partially reduced (<5%) after 17 h under the same conditions (Table 1, entry 16), while cyclohexanone was not hydrogenated (entry 17). Transfer hydrogenation of α,β-unsaturated ketones was complicated by some reduction of the C=C bond (Scheme 3). When the reduction of acetophenone was carried out in the presence of complex **4** (Table 1, entry 18), the *ee* value reached 76% with 34% maximal conversion after 2.6 h. Further work is required to determine the cause of this deactivation of catalysis.



Scheme 3. Transfer hydrogenation of *trans*-4-phenyl-3-buten-2-one catalyzed by **3**.

The mechanism of the catalysis is uncertain. We targeted this tetradentate ligand complex assuming that its imine linkage would be hydrogenated in the reaction medium to produce an amine intermediate such as $[FeH(CO)\{(R,R)\text{-}cyP_2(NH)_2\}]^+$. We have not yet been able to synthesize such an amine complex or observe it in the catalytic solution. Such a complex might be expected to transfer a hydride from iron and a proton from nitrogen to polar bonds in an outer-sphere hydrogenation, the mechanism postulated for the related complexes $[RuH_2\{(S,S)\text{-}cyP_2(NH)_2\}]$[15] and $[RuH_2\{PPh_2(o\text{-}C_6H_4)CH_2NHCMe_2CMe_2NHCH_2(o\text{-}C_6H_4)PPh_2\}]$.[22] Since there is poor chemoselectivity for the reduction of the C=O bond versus the C=C bond during the hydrogenation of *trans*-4-phenyl-3-buten-2-one, another mechanism might be involved.

During the transfer hydrogenation of acetophenone catalyzed by **3** (Table 1, entry 3), the $^{31}P\{^1H\}$ NMR shows an AB pattern at $\delta = 56$ and 74 ppm (d, $^2J_{P\text{-}P} = 28$ Hz) owing to an (as yet) unidentified intermediate. There is also a singlet for the free ligand $(R,R)\text{-}cyP_2N_2$ and some other minor, unassigned peaks at $\delta = 29$ and -12.3 ppm. For the reaction catalyzed by **4**, the AB pattern for the intermediate is observed at 54 and 58 ppm (d, $^2J_{P\text{-}P} = 31$ Hz). This intermediate decomposes upon attempts to isolate it from the catalytic mixture. It might be a complex such as $[Fe(CO)(X)\{(R,R)\text{-}cyP_2N_2\}](BF_4)$ (X = alkoxide or hydride), but further study is required.

The observation of free PNNP ligand in the catalytic solution might suggest the formation of colloidal iron. However, there is evidence that the active catalyst is homogeneous instead of heterogeneous. The reaction solutions are clear, the *ee* values of the product alcohols are reproducible, and there is no poisoning of the catalysis by mercury when it is added during the reaction.[23]

In summary, complex **1** constitutes the first well-defined iron catalyst for the asymmetric H_2 hydrogenation of acetophenone. Its modification by reaction with CO or *t*BuNC gives the precatalysts **3** and **4**, which promote the first asymmetric transfer hydrogenation of polar bonds, such as those of ketones, aldehydes and imines, at room temperature with an excellent TOF ($907\ h^{-1}$) for complex **3**, competitive with the best ruthenium catalysts.[4] Mechanistic studies and catalyst optimization are currently underway.

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