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Efficient Asymmetric Transfer Hydrogenation of Ketones Catalyzed by an Iron Complex Containing a P−N−N−P Tetradentate Ligand Formed by Template Synthesis

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Enantiopure alcohols have important uses in the pharmaceutical, fragrances, and flavors industries. A common method for their synthesis is via the catalytic asymmetric transfer hydrogenation of prochiral ketones. There are excellent platinum group metal catalysts used to produce the desired enantioenriched alcohols selectively and efficiently.[1] Iron catalysts with similar properties would be very desirable from both an economic and health viewpoint.[2] We report here a major step toward this goal.

Recently we reported that the new Fe complex *trans*-[Fe(CO)(NCMe)(cyP$_2$N$_2$)](BF$_4$)$_2$, with the P−N−N−P ligand derived from (*R*,*R*)-1,2-diaminocyclohexane (Figure 1), serves as a catalyst precursor for the asymmetric transfer hydrogenation of prochiral ketones under very mild conditions.[3] Significantly complex **1** is almost as active at room temperature (900 h^{-1} turnover frequency (TOF)) for acetophenone transfer hydrogenation to 1-phenylethanol in 29% ee) as the most active Ru catalysts (TOF up to 4000 h^{-1} at 25 °C) for the hydrogenation of aryl ketones using 2-propanol as the reductant. The substrate that gave the best results using **1** was 1-phenylpropanone which upon hydrogenation gave (*S*)-1-phenylpropanol in 61% ee with a TOF of greater than 29 h^{-1}. Gao's group reported the other asymmetric transfer hydrogenation system using Fe, where ligands of the type P−NH−NH−P are added to [HFe$_3$(CO)$_{11}$]$^-$ to generate *in situ* catalysts of lower activity (TOF 17 h^{-1} at 45 °C for 1-phenylpropanone reduction, 72% ee).[4] Beller and co-workers reported the asymmetric reduction of ketones by Fe-catalyzed hydrosilylation.[5] Clearly this is the beginning of effective Fe-based homogeneous asymmetric hydrogenation catalysis.

Here we disclose the efficient synthesis of the new catalyst precursor **2** (Figure 1) which compared to **1** has a significantly higher activity and selectivity. Complex **2** is prepared in a facile and economical two-step synthesis (Scheme 1). The first step utilizes a direct template synthesis method similar to one that we recently reported for other P−N−N−P diiminodiphosphine complexes.[6] The easily prepared, air-stable phosphonium salt **3** is reacted with Fe(II) and base, and then acetonitrile, the enantiopure diamine (*R*,*R*)-1,2-diphenyethylenediamine (dpen), and finally NaBPh$_4$ to produce the orange solid *trans*-(*R*,*R*)-[Fe(NCMe)$_2$(PPh$_2$CH$_2$CHNCHPhCHPh−NCHCH$_2$PPh$_2$)](BPh$_4$)$_2$ (**4**) in 76% yield. The dpen diamine is known to endow Ru catalysts with high enantioselectivity.[7]

Complex **4** was also prepared with BF$_4$ anions to obtain crystals suitable for X-ray diffraction (Figure 2). The complex is distorted octahedral with trans nitrile ligands. The most prominent feature is a very wide P−Fe−P angle of 108.77(7)°. This is a consequence of the small chelate ring sizes (5-,5-,5-membered rings) in **4** compared to the (6-,5-,6-membered rings in [Fe(NCMe)$_2$-(cyP$_2$N$_2$)](BF$_4$)$_2$ which has a corresponding angle of 100.24(8)°.[3] The phenyl groups are in equatorial positions on the carbons of the Fe−N−C−C−N− ring. The complex sits on a crystallographic

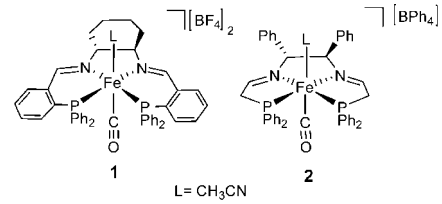

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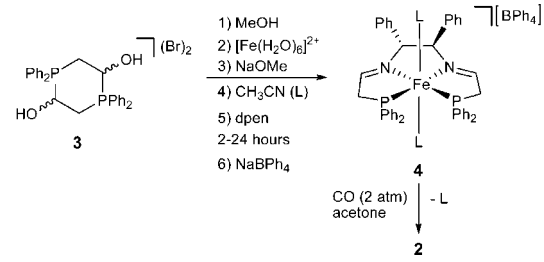
Figure 1. Active asymmetric transfer hydrogenation catalysts.

Scheme 1. Synthesis of Precatalyst **2**



3 4 2

2-fold axis and maintains this C_2-symmetry when it is dissolved in CD$_3$CN. This conclusion is based on the observation of a single resonance for the imine hydrogens in the ^{1}H NMR spectrum and a singlet in the ^{31}P{^{1}H} NMR spectrum. The axial MeCN ligands are rapidly substituted by CD$_3$CN when **4** is dissolved in this solvent.

The carbonyl complex precatalyst *trans*-[Fe(CO)(NCMe)-(PPh$_2$CH$_2$CHNCHPhCHPhNCHCH$_2$PPh$_2$)] (BPh$_4$)$_2$ (**2**) is prepared by treating **4** in acetone with carbon monoxide (2 atm) and is isolated as a yellow solid in 92% yield. It displays a carbonyl vibration in the IR spectrum at 2001 cm^{-1}. The asymmetry of the molecule is reflected in the observation of two doublets ($^2J_{PP}$ 30

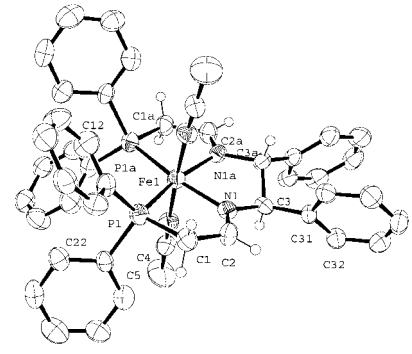
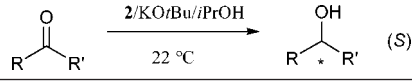


Figure 2. X-ray structure of **4** with thermal ellipsoids drawn at the 50% probability level. BF$_4$ anions and some hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): P1−Fe1 2.260(1), N1−Fe1 1.975(1), N2−Fe1 1.911(1), P1a−Fe1−P1 108.77(7).

10.1021/ja809493h CCC: $40.75

Table 1. Transfer Hydrogenation of Ketones Catalyzed by Complex **2**



	substrate	S/C/B	time (min)	conv (%)	ee (%)	TOF (h^{-1})[a]
1	Ph-CO-Me	600/1/8	8/30	75/90	83/12	3400
2	Ph-CO-Me	600/1/4	20	75	81	1350
3	Ph-CO-Me	2000/1/8	30	90	82	3600
4	Ph-CO-Me[b]	2000/1/8	30	75	84	3000
5	Ph-CO-Me[c]	2000/1/8	30	80	83	3200
6	Ph-CO-Et	1500/1/8	25	90	94	3375
7	Ph-CO-*t*Bu	500/1/8	200	35	99	53
8	Ph-CO-(*cyclo*-C_4H_7)	1000/1/8	40	95	94	1425
9	Ph-CO-(*cyclo*-C_6H_{11})	1000/1/8	85	76	26	536
10	$PhCH_2CH_2$-CO-Me	1000/1/8	30	98	14	1960
11	(4′-Cl-C_6H_4)-CO-Me	1500/1/8	18	96	80	4800
12	(3′-Cl-C_6H_4)-CO-Me	1000/1/8	13	98	80	4523
13	(4′-MeO-C_6H_4)-CO-Me	1000/1/8	40	65	54	930
14	(3′-MeO-C_6H_4)-CO-Me	1500/1/8	30	80	85	2400
15	*i*Pr-CO-Me	1500/1/8	60	86	50	1280
17	1-aceto-naphthone	1500/1/8	60	93	92	1380
18	2-aceto-naphthone	1000/1/8	11	90	84	4900
19	Ph-CH=N-Ph	1000/1/8	240	41	−	100

[a] TOF is calculated at the conversion and the first time noted. [b] NaO*t*Bu was used as a base. [c] KOH was used as a base.

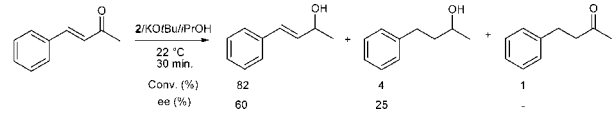
Hz) in the $^{31}P\{^1H\}$ NMR spectrum of its $(CD_3)_2CO$ solution. It reacts slowly with air as a solid and as a solution. It reacts with neat acetonitrile over 5 h and converts back to **4**.

Complex **2** in basic isopropanol was tested for the asymmetric transfer hydrogenation of ketones at room temperature (Table 1). It shows excellent activity for the hydrogenation of acetophenone to (*S*)-1-phenylethanol in 82% ee (entries 1−5). This is a great improvement in enantioselectivity and TOF compared to those displayed by the system with catalyst precursor **1**. The sense of asymmetric induction (*S*) is the same as that of Noyori and Noyori-like catalysts utilizing (*R*,*R*)-dpen.[8]

The addition of a strong base such as KO*t*Bu or NaO*t*Bu is essential for the catalysis, because no conversion is observed if the base is omitted. The optimal ratio of the catalyst to the base was found to be 1:8. From entry 1 it follows that as the reaction proceeds toward completion, racemization of product is observed. This limitation can be overcome by quenching the reaction at a specific time of the maximum conversion and highest ee by exposure to air. Increasing the ketone concentration increases the TOF to up to 3600 h^{-1} (entry 3) with the highest rate of conversion occurring during the first 30 min of the reaction. The loss of activity after 30 min may be due to the decomposition of the catalyst, a process that is not yet understood.

The reduction of the more hindered aromatic ketones (entries 6−8) proceeded with excellent enantioselectivity, although the expected trend of a decrease in conversion for the more bulky *t*Bu substituent was also observed. If the methyl group of the acetophenone is replaced with a bulkier cyclohexyl group (entry 9), then the ee of the reaction drops significantly. Hydrogenation of the ketone with the 2-phenylethyl group (entry 10) proceeds with reduced enantioselectivity. This result illustrates the importance of bulky groups next to the carbonyl for obtaining high enantioselectivity.

Scheme 2. Transfer Hydrogenation of *trans*-4-Phenyl-3-buten-2-one by **2**



The aromatic ketone (entry 11) with a strong σ-electron withdrawing and weak π-electron donating chloro group in the *para* position showed a higher TOF compared to that with acetophenone. Substrates with the π-electron donating methoxy group (entry 13), on the other hand, showed lower selectivity and activity. Aromatic ketones with methoxy and chloride substituents (entries 12, 14) in the *meta* position both showed comparable conversion and selectivity to acetophenone. These results indicate that *meta* substitution has a minor effect on the catalytic process.

Nonaromatic ketones are challenging substrates for enantioselective reduction. Catalyst **2** was found to be active for such a ketone (entry 15) and showed moderate enantioselectivity. The acetonaphthone isomers were also efficiently reduced (entries 17, 18). An aldimine (entry 19) was reduced with low activity.

The reduction of *trans*-4-phenyl-3-buten-2-one to *trans*-4-phenyl-3-buten-2-ol using precatalyst **2** shows a high chemoselectivity (Scheme 2). This supports the idea that an outer sphere attack by an H−Fe−N−H motif on the ketone group might be operational.[9]

In conclusion we have discovered the first Fe catalyst for the asymmetric transfer hydrogenation of ketones that has useful activity and enantioselectivity in the production of valuable enantioenriched alcohols.

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Supporting Information Available: Preparations (pdf), crystallographic data (cif) of **4**, and a detailed procedure for the catalytic reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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