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An Efficient and Chemoselective Iron Catalyst for the Hydrogenation of Ketones

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Ligand metal bifunctional catalysis has provided efficient new precious metal catalysts (Ru, Rh, Ir) for the hydrogenation of polar multiple bonds.[1] In contrast, nature often uses iron-based catalysts such as hydrogenase for reductions.[2−4] Here we report an effective iron-based catalyst **1** for the selective hydrogenation of aldehydes and ketones under mild conditions (Figure 1).Our extensive studies of a tolyl analogue **2**[1d,5] of the active reducing agent of the Shvo ruthenium catalyst led us to investigate the possible use of Knölker's iron complex **1**[6] as a hydrogenation catalyst. Complex **1**, like the diiron cofactor of Fe hydrogenase **3**,[2c] has an iron hydride and an acidic hydrogen available for transfer to polar multiple bonds.

Stoichiometric reduction of acetophenone by **1** was observed in toluene-d_8 at room temperature (Scheme 1). ^{1}H NMR spectroscopy showed the formation of 1-phenylethanol complex **4a**;[7] the methyl doublet at δ 1.37 and a CH_3CHOH quartet at δ 4.41 were shifted from resonances for the free alcohol. Two resonances at δ 0.36 and 0.40 were observed for the $SiMe_3$ groups of **4a**, rendered diastereotopic by complexation of the chiral alcohol. The symmetric alcohol complex **4b**, generated from the reaction between **1** and acetone, gave only one TMS resonance (δ 0.33). Unfortunately, because the reduction of acetophenone did not go to completion and because **4a** slowly decomposed (>12 h) to unidentified products, it was not possible to isolate and fully characterize **4a**.

To test the hypothesis that partial reduction might be due to the reversibility of hydrogen transfer, we studied the reaction of **1** with acetophenone in the presence of 2 equiv of PPh_3 as a trapping agent for reactive intermediate **A** and found complete hydrogen transfer reaction within 4 h, with clean formation of iron triphenylphosphine complex **5**[8] and free 1-phenylethanol. Kinetic studies showed first-order dependence on both **1** and acetophenone and no dependence on PPh_3. When the reduction was carried out in the presence of 10 equiv of 1-phenylethanol (0.08 M) in addition to PPh_3, the disappearance of **1** was 15% slower and up to 20% of alcohol complex **4a** was detected, but **4a** was then converted to **5**. These data are consistent with more rapid trapping of intermediate **A** by PPh_3 than either dehydrogenation of alcohol by **A** or formation of alcohol complex **4a** from **A** (i.e., $k_3[PPh_3] \gg (k_{-1} + k_2)$[alcohol]). The second-order rate constant k_1 at 25 °C was 9.8(2) × 10^{-3} M^{-1} s^{-1}. Rate measurements between 10 and 25 °C gave $\Delta H^{\ddagger} = 9.0 \pm 0.6$ kcal mol^{-1} and $\Delta S^{\ddagger} = -37.5 \pm 2.1$ eu. The large negative entropy of activation is consistent with a highly ordered transition state bringing **1** and acetophenone together for hydrogen transfer.[1d,9]

If H_2 efficiently traps intermediate **A** to regenerate iron hydride **1**, then a catalytic hydrogenation cycle would be completed (Scheme 2). Indeed, **1** (2 mol %) catalyzed the hydrogenation of acetophenone under 3 atm H_2 at room temperature (eq 1). In situ monitoring with a ReactIR apparatus allowed quantitative measurement of the rate of hydrogenation and also established that **1** (2001 and 1941 cm^{-1})[10] was the only iron complex present during catalysis. This implies that hydrogen transfer from **1** is the rate-limiting step in the catalytic cycle. The rate of hydrogenation was first order in **1**

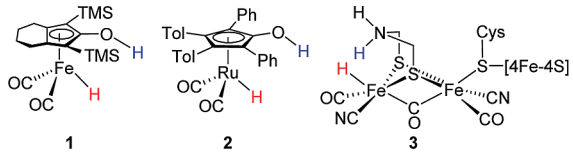
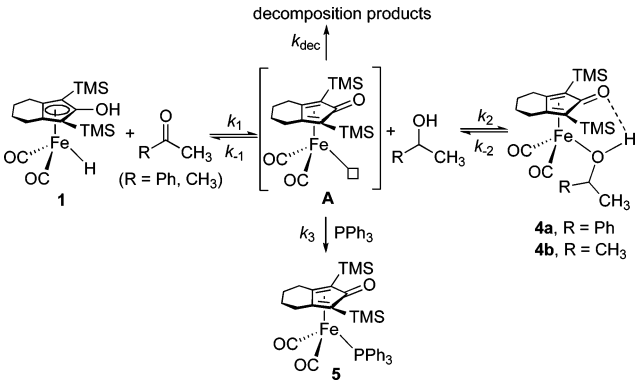
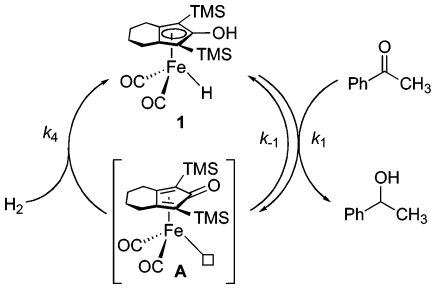


Figure 1. Catalysts with acidic (in blue) and hydridic (in red) hydrogens.

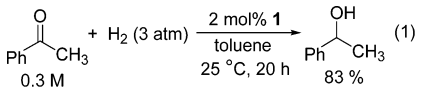
Scheme 1



Scheme 2. Catalytic Cycle for the Hydrogenation of Acetophenone



and in acetophenone and was independent of hydrogen pressure between 4.4 and 35 atm ($k_4[H_2] \gg k_{-1}$[alcohol]).[11] The second-order rate constant for the catalytic process (1.1(1) × 10^{-2} M^{-1} s^{-1}) at room temperature was similar to that for the stoichiometric reaction of **1** with acetophenone at 25 °C.



Iron complex **1** is an efficient and selective catalyst for hydrogenation of the polar multiple bonds of aldehydes, ketones, and imines (Table 1). Benzaldehyde was hydrogenated much more rapidly than ketones. Ketones with electron-withdrawing groups (entries 9 and 10) reacted unusually fast. High diastereoselectivity (*meso*/*dl* = 25) was seen in the hydrogenation of benzoin (entry 10). High chemoselectivity was also observed: epoxides, esters,

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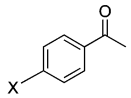
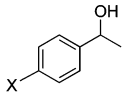
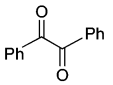
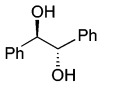
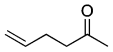
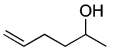
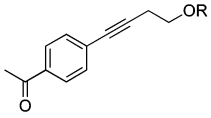
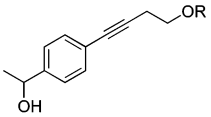
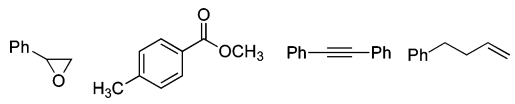
Table 1. Hydrogenation of Ketones and Related Substrates Catalyzed by Iron Hydride **1**[a]

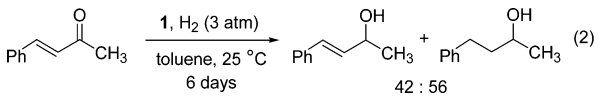
entry	substrate	product	time	yield [d]
1	PhCHO	$PhCH_2OH$	1 h	90% (100%)
2	$PhCH_2CH_2COCH_3$	$PhCH_2CH_2CH(OH)CH_3$	24 h	88% (98%)
				
3	X = H		20 h	83% (99%)
4	X = Br		24 h	91% (99%)
5	X = I		20 h	84% (99%)
6	$X = NO_2$		6 h	89% (99%)
7	X = CN		19 h	(< 1%)
8	PhCOPh	PhCH(OH)Ph	72 h	55% (69%)
9	$PhCOCF_3$	$PhCH(OH)CF_3$	10 min	91% (100%)
10			2 h	86% (100%) (*meso*/*dl* = 25)
11 [b]			36 h	87% (100%)
				
12	R = H		24 h	57% (71%)
13	$R = CH_2Ph$		20 h	84% (87%)
14			68 h	46% (50%)
15			8 h	87% (100%)
16 [c]			40 h	50% (54%)

[a] Conditions: substrate (1.5 mmol), iron hydride **1** (30 μmol, 2.0 mol % catalyst), toluene (5 mL), 3 atm H_2 at 25 °C. [b] Hydrogenation was performed in diethyl ether for ease of product isolation. Hydrogenation is slower in ether than in toluene. [c] Reaction run at 65 °C. [d] Isolated yield (NMR conversion in parentheses).

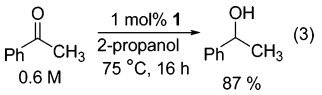
Chart 1. Substrates Which Are Not Hydrogenated



and isolated alkenes and alkynes are not hydrogenated (Chart 1).[12,13] For ketones with isolated C═C or C≡C, only the ketone is hydrogenated (entries 11−13). Iron catalyst **1** shows great functional group tolerance. For example, carbon halogen bonds (entries 4, 5, and 9),[14] nitro groups (entry 6),[15] benzyl ethers (entry 13), and cyclopropyl rings (entry 14) survive the hydrogenation conditions. A pyridine moiety can potentially bind iron and inhibit the catalytic reaction; however, 2-acetyl pyridine (entry 15) was rapidly hydrogenated. 4-Acetylbenzonitrile (entry 7) was not hydrogenated, possibly due to the nitrile trapping of unsaturated intermediate **A**. Hydrogenation of α,β-unsaturated ketones was complicated by some reduction of the C═C double bond (eq 2).[16]



Based on the reversibility of hydrogen transfer, we expected that **1** might catalyze the transfer hydrogenation of ketones.[17] Indeed, iron hydride **1** catalyzes the transfer hydrogenation of acetophenone using 2-propanol as the hydrogen donor (eq 3).



In summary, we have described the first well-defined iron catalyst for the hydrogenation of ketones. The hydrogenations can take place at room temperature under low hydrogen pressure with high chemoselectivity. Efforts to develop asymmetric hydrogenation of ketones catalyzed by related chiral iron complexes are currently in progress.

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Supporting Information Available: Experimental details, summary of kinetic runs, and Eyring plot. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) No **4a** (1985 and 1924 cm^{-1} in toluene) was observed.

(11) High concentrations of added alcohol decreased the rate of catalytic hydrogenation under low H_2 pressure (see Supporting Information).

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