An Efficient and Chemoselective Iron Catalyst for the Hydrogenation of Ketones

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Supporting Information

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General Procedures. All air-sensitive compounds were prepared and handled under a nitrogen atmosphere using standard Schlenk and inert-atmosphere box techniques. Toluene was deoxygenated and dried in a solvent purification system by passing through an activated alumina column and an oxygen scavenging column under argon.[1] Toluene-d_8 was distilled from Na and benzophenone under a nitrogen atmosphere. Hydride **1**,[2] 1-[4-(4-hydroxy-1-butynyl)phenyl]ethanone (entry 12, Table 1),[3] 1-[4-[4-(phenylmethoxy)-1-butynyl]phenyl]ethanone (entry 13, Table 1),[4] and *N*-benzylideneaniline (entry 16, Table 1)[5] were prepared as described in the literature.

Stoichiometric Reduction of Ketones by 1. A resealable NMR tube containing a solution of **1** (11.8 mg, 30 μmol) and acetophenone (3.5 μL, 30 μmol) in toluene-d_8 (500 μL) was monitored by ^{1}H NMR spectroscopy over days. Alcohol complex **4a** grew in at the expense of **1**. After 12 h, about 28 % of **1** was converted to **4a**. Extended reaction times resulted in unidentified decomposition products and free 1-phenylethanol. ^{1}H NMR spectrum of **4a** (toluene-d_8, 300 MHz) δ 0.36 (s, Si(CH_3)$_3$, 9H), 0.40 (s, Si(CH_3)$_3$, 9H), 0.92-1.15 (m, CH_2, 4H), 1.37 (d, J = 6.3 Hz, CH_3, 3H), 1.80-1.95 (m, CH_2, 4H), 4.41 (q, J = 6.3 Hz, C*H*OH, 1H), aromatic and OH resonances were not located. IR of **4a** (in toluene): 1985 and 1924 cm^{-1}. For comparison, the spectrum of free 1-phenylethanol was recorded: ^{1}H NMR (toluene-d_8, 300 MHz) δ 1.31 (d, J = 6.3 Hz, CH_3, 3H), 1.80 (br s, O*H*, 1H), 4.58 (q, J= 6.3 Hz, C*H*OH, 1H).

A similar reaction with acetone generated the mixture of **1** and **4b**. ^{1}H NMR spectrum of **4b** (toluene-d_8, 300 MHz) δ 0.33 (s, Si(CH_3)$_3$, 18H), 0.82 (s, O*H*, 1H), 0.98 (d, J = 6.0 Hz, CH_3, 6H), 1.11-1.14 (m, CH_2, 4H), 1.87-1.95 (m, CH_2, 2H), 1.98-2.04 (m, CH_2, 2H), 4.41 (septet, J = 6.0 Hz, C*H*OH, 1H).

NMR Measurements of Rate Constants for the Reduction of Acetophenone by 1. Under a nitrogen atmosphere a solution of acetophenone (1.0 M) in toluene-d_8 was mixed with a solution of **1**, mesitylene (internal standard) and PPh_3 in a resealable NMR tube at –78 ºC. The first ^{1}H NMR spectrum was recorded within 5 min of mixing, and the reaction was monitored for three to five half-lives. The height of the $Si(CH_3)_3$ resonance of the hydride **1** (δ 0.33) was compared to that of mesitylene (δ 2.15). Zero-filling was used to ensure adequate digital resolution. The NMR probe temperature was calibrated using a 100 % methanol standard.[6] The results are summarized in Tables S1-S4 and Figures S1-S3.

Table S1. Rate of reduction of acetophenone by iron hydride **1** in toluene-d_8 at 25 °C.

$[\mathbf{1}]_0$ (M)	$[PhCOCH_3]_0$ (M)	$[PPh_3]_0$ (M)	k_{obsd} (s^{-1})
0.0090	0.10	0.018	1.1×10^{-3}
0.0084	0.16	0.017	1.5×10^{-3}
0.0080	0.20	0.016	2.0×10^{-3}
0.0076	0.24	0.015	2.3×10^{-3}

Figure S1. Plot of observed rate versus concentration of acetophenone for its reduction by iron hydride **1** in toluene-d_8 at 25 °C.

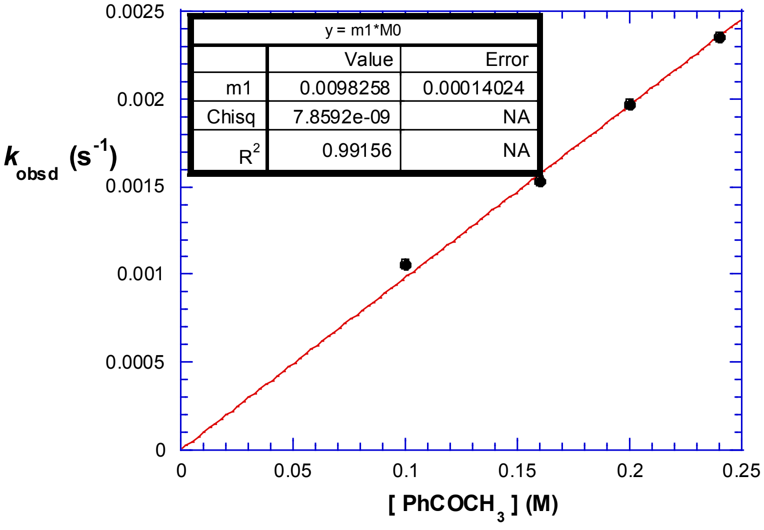


Table S2. Rate of reduction of acetophenone by iron hydride **1** in toluene-d_8 at 10 °C.

$[\mathbf{1}]_0$ (M)	$[PhCOCH_3]_0$ (M)	$[PPh_3]_0$ (M)	k_{obsd} (s^{-1})
0.0084	0.16	0.017	6.4×10^{-4}
0.0080	0.20	0.016	8.5×10^{-4}
0.0076	0.24	0.015	9.9×10^{-4}
0.0070	0.30	0.014	1.2×10^{-3}

Figure S2. Plot of observed rate versus concentration of acetophenone for its reduction by iron hydride **1** in toluene-d_8 at 10 °C.

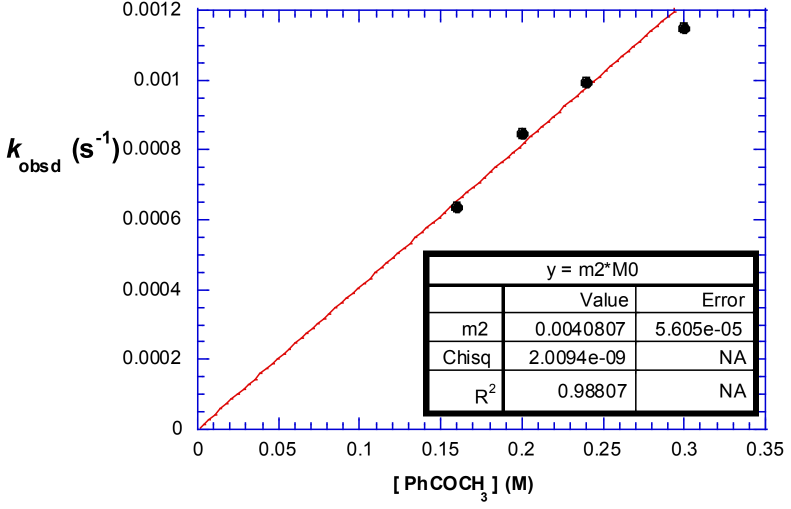
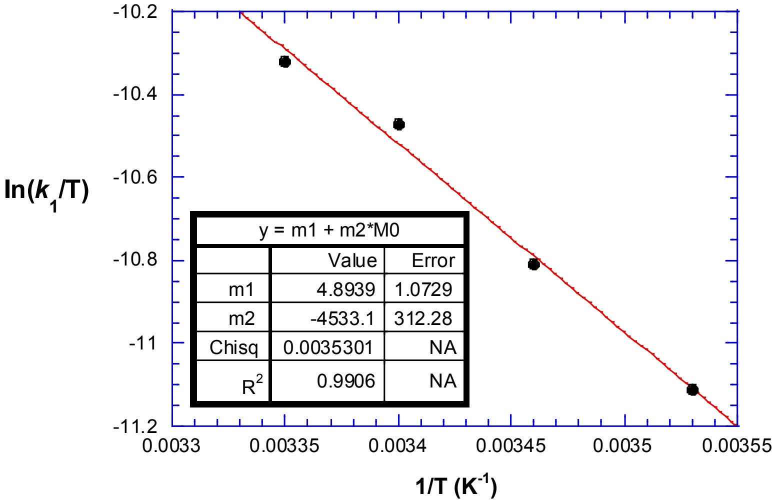


Table S3. Rate of reduction of acetophenone by iron hydride **1** in toluene-d_8 at various temperatures.[a]

T (K)	k_{obs} (s^{-1})	$k_1 = k_{obs}/[PhCOCH_3]_0$ ($s^{-1}M^{-1}$)	1/T	$\ln(k_1/T)$
298.1	2.0×10^{-3}	1.0×10^{-2}	0.00335	-10.32
293.8	1.7×10^{-3}	8.5×10^{-3}	0.00340	-10.47
289.3	1.2×10^{-3}	6.0×10^{-3}	0.00346	-10.81
283.5	8.5×10^{-4}	4.2×10^{-3}	0.00353	-11.11

[a] Conditions: $[\mathbf{1}]_0 = 0.0080$ M, $[PhCOCH_3]_0 = 0.20$ M, $[PPh_3]_0 = 0.016$ M.

Figure S3. Eyring Plot for the reduction of acetophenone by iron hydride **1** in toluene-d_8 between 25 °C and 10 °C.



$\Delta H^{\ddagger} = 9.0 \pm 0.6$ kcal mol^{-1} $\Delta S^{\ddagger} = -37.5 \pm 2.1$ eu

Table S4. Effect of added PPh_3 and alcohol on the rate of reduction of acetophenone by iron hydride **1** in toluene-d_8 at 25 °C. [a]

$[PhCH(OH)CH_3]_0$ (M)	$[PPh_3]_0$ (M)	k_{obs} (s^{-1})
0.00	0.016	2.0×10^{-3}
0.00	0.080	2.0×10^{-3}
0.016	0.016	1.8×10^{-3}
0.080	0.016	1.7×10^{-3}

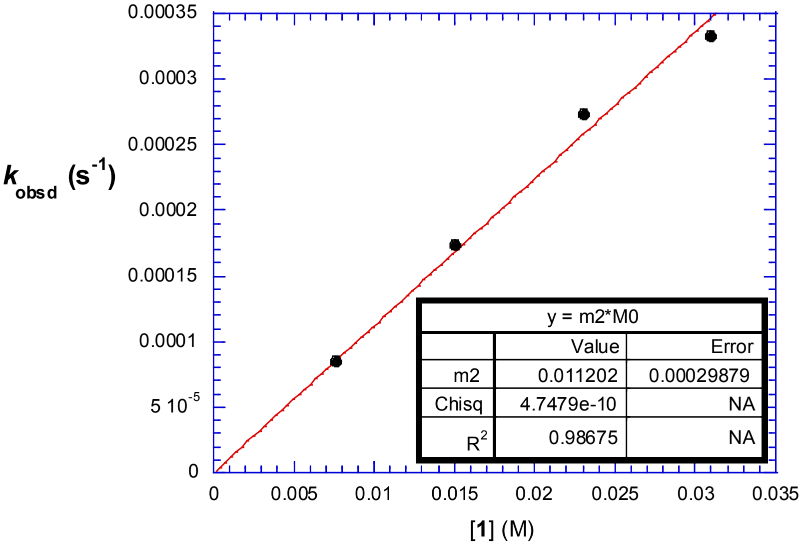
[a] Conditions: $[\mathbf{1}]_0 = 0.0080$ M, $[PhCOCH_3]_0 = 0.20$ M.

Kinetics of the Hydrogenation of Acetophenone Catalyzed by 1. In a high-pressure vessel equipped with an attenuated total reflection IR detector, a solution of **1** in toluene was mixed with a solution of acetophenone in toluene at 25 °C under H_2 atmosphere. The IR spectra of the resulting reaction mixture were collected using an ASI Applied Systems ReactIR 1000 FTIR. The only iron species observed during catalysis was **1** (2001 and 1941 cm^{-1}); no **4a** (1985 cm^{-1} and 1924 cm^{-1}) was observed. The disappearance of acetophenone (at 1690 or 1266 cm^{-1}) was monitored as a function of time. Reaction data were imported into Excel and processed in KaleidaGraph. The results are summarized in Tables S5-S6 and Figure S4.

Table S5. Rate of hydrogenation of acetophenone catalyzed by **1** in toluene at 25 °C.

[**1**]$_0$ (M)	[$PhCOCH_3$]$_0$ (M)	$p(H_2)$ (atm)	k_{obsd} (s^{-1})
0.0076	0.15	4.4	0.85×10^{-4}
0.015	0.15	4.4	1.7×10^{-4}
0.023	0.15	4.4	2.7×10^{-4}
0.031	0.15	4.4	3.3×10^{-4}

Figure S4. Plot of observed rate versus concentration of **1** for the hydrogenation of acetophenone in toluene at 25 °C.

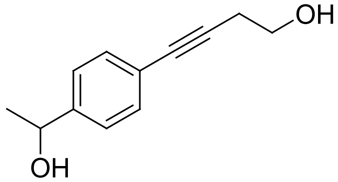


$k_1 = 1.1\ (1) \times 10^{-2}\ M^{-1}s^{-1}$

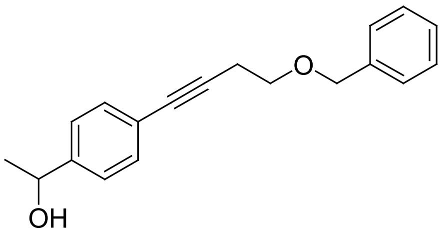
Table S6. Effect of hydrogen pressure and added alcohol on the rate of hydrogenation of acetophenone catalyzed by **1** (0.023 M) in toluene at 25 °C.^{a}

[$PhCH(OH)CH_3$]$_0$ (M)	[$PhCOCH_3$]$_0$ (M)	$p(H_2)$ (atm)	k_{obsd} (s^{-1})
0.00	0.15	4.4	$2.7\ (2) \times 10^{-4}$
0.00	0.15	14.6	$2.6\ (2) \times 10^{-4}$
0.00	0.15	35.0	$2.5\ (4) \times 10^{-4}$
0.00	0.30	4.4	$2.7\ (1) \times 10^{-4}$
0.00	0.30	14.6	$2.8\ (2) \times 10^{-4}$
0.00	0.30	35.0	$2.8\ (1) \times 10^{-4}$
0.60	0.30	35.0	$2.3\ (2) \times 10^{-4}$
0.30	0.15	4.4	$1.3\ (1) \times 10^{-4}$

Catalysis of the Hydrogenation of Various Ketones (or Imines) by 1. In a typical experiment, a ketone substrate (1.5 mmol) was added to a Fischer-Porter bottle under a nitrogen atmosphere. The bottle was flushed several times with hydrogen gas. Then 5 mL of a solution of **1** in toluene (0.0060 M) was added by syringe under a flow of hydrogen and the resulting solution stirred under 3 atm of hydrogen at 25 °C. When the hydrogenation was complete, solvent was evaporated and the residue was dissolved in $CDCl_3$ and its ^1H NMR spectrum recorded. Hydrogenation products were purified by column chromatography and their ^1H NMR spectra matched those reported in the literature. For the hydrogenation of benzoin (entry 10, Table 1), the *meso*/*dl* ratio of product was determined by examining the ^1H NMR spectra of crude materials.[7] The pure *meso* product was obtained after recrystallization from pentane. The characterization of new compounds are summarized below.



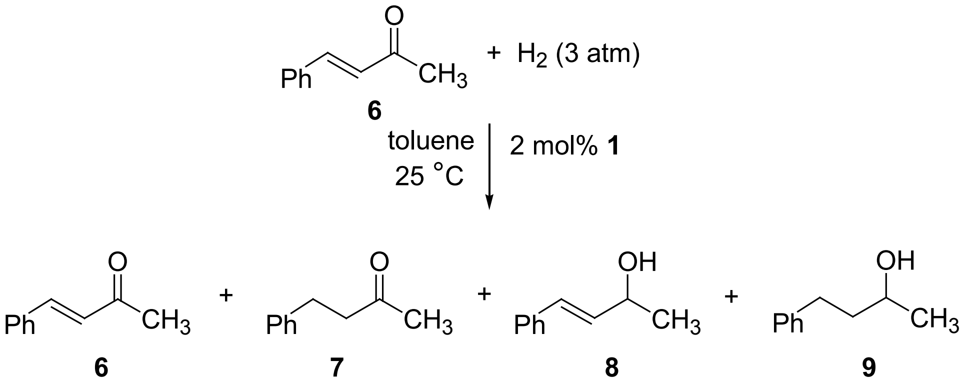
1-[4-(4-Hydroxy-1-butynyl)phenyl]ethanol (entry 12, Table 1) was isolated as a white solid (mp 84-85 °C). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (d, J = 6.3 Hz, CH_3, 3H), 2.10-2.14 (m, OH, 2H), 2.67 (t, J = 6.3 Hz, $C{\equiv}CCH_2$, 2H), 3.79 (q, J = 6.3 Hz, $C{\equiv}CCH_2CH_2$, 2H), 4.86 (q, J = 6.3 Hz, CH_3CHOH, 1H), 7.26-7.39 (m, Ar H, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 90 MHz) δ 24.03, 25.30, 61.34, 70.25, 82.49, 86.48, 122.58, 125.51, 131.99, 145.83. IR (dry film, cm^{-1}) 3294 (OH), 2969, 2936, 2879, 1506, 1469, 1372, 1301, 1089, 1069, 1044, 1008, 932, 904, 838, 783. HRMS (ESI) calcd (found) for $[C_{12}H_{14}O_2+Na]^{+\bullet}$ 213.0891 (213.0887).



1-[4-[4-(Phenylmethoxy)-1-butynyl]phenyl]ethanol (entry 13, Table 1) was isolated as a light yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.45 (d, *J* = 6.3 Hz, C*H*$_3$, 3H), 1.99 (br s, O*H*, 1H), 2.72 (t, *J* = 6.9 Hz, C≡CC*H*$_2$, 2H), 3.67 (t, *J* = 6.9 Hz, C≡CCH$_2$C*H*$_2$, 2H), 4.58 (s, PhC*H*$_2$O, 2H), 4.84 (q, *J* = 6.3 Hz, CH$_3$C*H*OH, 1H), 7.26-7.40 (m, Ar H, 8H). ^{13}C{^{1}H} NMR (CDCl$_3$, 90 MHz) δ 20.92, 25.15, 68.50, 69.91, 73.00, 81.55, 86.73, 122.64, 125.35, 127.76, 128.49, 131.75, 138.16, 145.65. IR (liquid film, cm^{-1}) 3402 (OH), 3062, 3030, 2970, 2926, 2865, 2234, 1723, 1605, 1453, 1364, 1293, 1204, 1090, 1009, 899, 838, 738, 699, 562. HRMS (ESI) calcd (found) for $[C_{19}H_{20}O_2+Na]^{+\bullet}$ 303.1361 (303.1360).

Hydrogenation of *trans*-4-Phenyl-3-buten-2-one (6) by 1. Hydrogenation was performed with similar procedures as those for other ketones. After 1 day, an aliquot of the reaction was removed by syringe under a flow of hydrogen. Solvent was evaporated and the residue was dissolved in CDCl$_3$ and its ^{1}H NMR spectrum recorded. The reaction was monitored over 6 days. The results are summarized in Scheme S1.

Scheme S1. Hydrogenation of an α,β-unsaturated ketone



6 : **7** : **8** : **9** = 22 : 13 : 45 : 20 (1 day)
1 : 1 : 42 : 56 (6 days)

Both C=C and C=O bonds of **6** are hydrogenated. Interestingly, the double hydrogenation is incomplete even after 6 days. The prolonged reaction time is probably due to the facile dehydrogenation of the allylic alcohol **8** by unsaturated intermediate **A**. In accordance with this explanation, we found 1 mol% **6** along with 2 mol% of **9** (by ^{1}H NMR spectroscopy) when pure **8** was placed under similar hydrogenation conditions for 1 h. Extended reaction time (29 h) afforded a mixture of **6** : **7** : **8** : **9** = 5 : 6 : 67 : 22. Even though C=C bonds have been shown to resist hydrogenation (entry 11, Table 1), the hydroxyl group in allylic alcohol **8** somehow directs the hydrogenation of C=C bond. Compound **7** can be potentially generated by 1,4-reduction of **6** or isomerization of allylic alcohol **8**. However, the mixture of **8** and catalytic amount of **1** in acetone at 60 °C gave the dehydrogenation product **6** exclusively, suggesting that isomerization of **8** to **7** was unlikely under these conditions.

Transfer Hydrogenation of Acetophenone Catalyzed by 1. Under a nitrogen atmosphere, acetophenone (350 μL, 3.0 mmol) was added to a solution of 1 (11.8 mg, 30 μmol, 1 mol% catalyst) in 5 mL of 2-propanol. The resulting orange solution was stirred at 75 °C for 16 h. After cooling, the solvent was evaporated and the residue was purified by column chromatography (hexanes : ethyl acetate = 4 : 1) to give pure 1-phenylethanol.

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