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Reduction of ketones to corresponding alcohols with magnesium metal in absolute alcohols

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Abstract—Various aliphatic and aromatic ketones are treated with 10 equiv of magnesium metal in absolute methanol or ethanol to afford corresponding alcohols in very high yields at room temperature within 12 h.
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For the reduction of ketones (or aldehydes) to the corresponding alcohols, all the Group I metals (Li, Na, K, Rb, and Cs) and Group II metals (Ca, Sr, and Ba),[1] Al(Hg),[2] Yb,[3] and low-valent transition metal compounds (Ti, V, Ce, and Sm)[4] have been used but the alkali metals (Li, Na, and K) are employed most frequently. Zn[5] or Fe[6] have been also used for aldehydes and aromatic ketones. The common reaction solvents were liquid NH_3 (or low-molecular weight aliphatic amines), NH_3/alcohol, alcohol, aqueous alcohol, and water. NaOH[5b] and acetic acid[6] were used for Zn[5] and Fe[6] as a proton source, respectively. Ether (THF, DMF, and diethyl ether) are often used as co-solvent to increase the solubility of the organic substrates in the reaction mixture.

The reduction potentials of alkali metals are not sufficiently high enough to add two electrons to aliphatic carbonyl group.[7a] Thus, an alternative mechanism[7] was suggested, which is now generally accepted to account for the reaction in the absence or the presence of added proton sources as shown in Scheme 1.

The reaction depends upon the reaction media and metals used. While the radical anion dimerized to give the pinacol adduct without an added proton source, the reaction in the presence of an added proton source proceeded by the protonation of radical anion to give carbon-centered radical followed by another one-electron transfer to give anion from which alcohol was obtained after abstracting proton from the proton
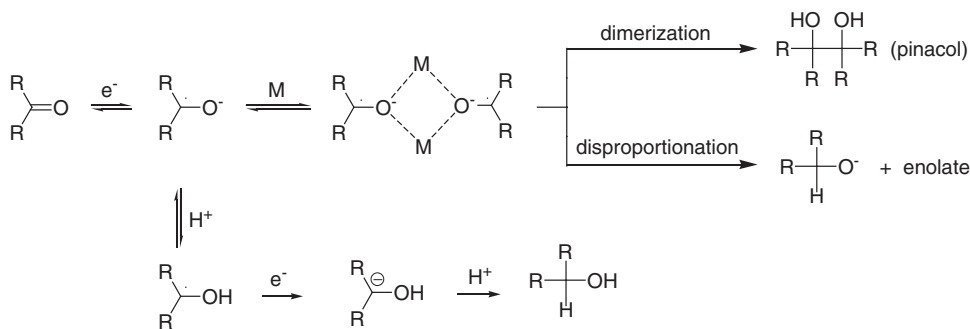
Scheme 1. Proposed mechanism for the electron transfer to carbonyl group.

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Table 1. Reduction of ketones to corresponding alcohols with magnesium metal in absolute EtOH in the presence of a catalytic amount of $HgCl_2$

Entry	Substrates **1**	Reaction condition[a]	Reaction time (h)	Products **2**	Isolated yield (%)	Cis/trans[b]
1	**1a**	A	12	**2a**	99	
2	**1b**	A	12	**2b**	97	
3	**1c**	B A	5 8	**2c**[12]	91	1/2.7 1/2.3
4	**1d**[10]	A	12	**2d**[13]	94	1/3.5
5	**1e**[10]	A	12	**2e**[14]	88	1/2.6
6	**1f**[11]	A	12	**2f**[15]	80	1/9.3
7	**1g**[11]	A	12	**2g**[15]	74	1/4.7
8	**1h**	A	12	**2h**[16]	97	1/3.3
9	**1i**	A	12	**2i**[17]	92	1/4.9
10	**1j**	A	12	**2j**[18]	93	1/10[c]
11	**1k**	A	12	**2k**[19]	92	1/11.3[c]

[a] A: EtOH/cat. $HgCl_2$, rt; B: MeOH/cat. $HgCl_2$, −23 °C.
[b] Ratios were determined by ^{1}H NMR.
[c] exo/endo ratio.

donor. The stereochemical results of the reaction are rel-
atively insensitive to the nature of the metals used for

reduction.[8] With less acidic proton donors, there is com-
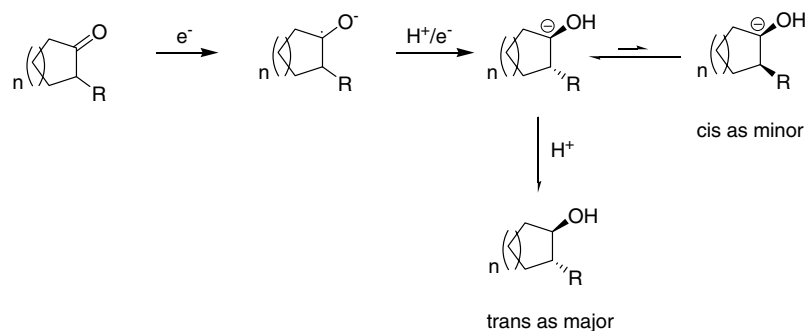petition between the reduction and the disproportion-

Figure 1. Proposed reduction mechanism for ketones.

ation. When K[1a] is used, the yield of pinacol adduct is lower than those from Li and Na regardless of the conditions employed.

In our continuing efforts to expand the synthetic utility and reaction mechanism of magnesium metal in protic solvents such as absolute methanol and ethanol as a convenient electron transfer agent,[9b–e] we have recently reported that magnesium metal in absolute methanol facilitates various reductive reactions.[9a] Here, we report the results of reduction of various aliphatic and aromatic ketones to corresponding alcohols with magnesium metal under mild reaction conditions in high yields (74–97%). Comparing to Na and K metals, handling of magnesium metal is very safe and easy.

Various substrates (**1a–k**) were treated with 10 equiv of magnesium metal in absolute EtOH at room temperature and results are shown in Table 1. In all cases, trans isomers were obtained as major products. These indicate that electron transfer from magnesium give ketyl radicals and additional electron transfer generate ketyl anions to afford more sterically and electronically favorable trans isomers after protonation by protic solvent such as MeOH and EtOH as shown in Figure 1.

Except for cyclobutanone (**1c**), when magnesium metal was used in absolute MeOH, reaction was not complete because reaction of magnesium with MeOH solvent to evolve hydrogen gas is faster than electron transfer to carbonyl groups. Also, reaction did not proceed with Mg/EtOH at room temperature after 12 h in the absence of HgCl$_2$. In the presence of the catalytic amount of HgCl$_2$, however, reduction products were obtained in high yields within 12 h. The stereochemistry of alcohols was determined with comparing to the reported proton NMR data. Noncyclic aliphatic ketone (**1a**) was smoothly reduced to afford corresponding alcohol quantitatively. In aromatic ketone (**1b**), however, reaction did not proceed in absolute EtOH solvent. Alcohol was obtained in high yield in absolute MeOH at 0 °C without catalyst. It seems that more basic Mg(OEt)$_2$ deprotonate acetophenone to give inert enolate. 2-Substituted cycloketones (**1c–g**)[1] were smoothly reduced to give corresponding trans alcohols as major adducts. Cyclobutanone (**1c**) was reduced in absolute MeOH at −23 °C but cyclopentanone (**1d**) and cyclohexanone (**1e**) were not

reduced at this reaction condition because carbonyl group of cyclobutanone is more strained comparing to five- and six-membered rings. Nonetheless, stereoselectivity was not improved comparing to EtOH/cat. HgCl$_2$/rt condition. The relative stereochemistry of **2c** was determined unequivocally by 2-D COSY experiments and 1-D NOE difference spectroscopy. Upon irradiation of the C$_1$–H resonance at 3.88 ppm, a 0.3% NOE at benzylic CH$_2$ was observed in trans isomer. In case of 2-hydroxymethyl cycloketones (**1f–g**), electronic repulsion between two oxygen atoms reinforces trans stereoselectivity similar to intramolecular ketyl-olefin cyclization. Substituted cyclohexanones (**1h–i**) gave the expected trans alcohols as major products. Bicyclic ketones (**1j–k**) were reduced to afford thermodynamically more stable *endo*-products as major. Interestingly, benzaldehyde was not reduced under above reaction conditions. In basic alcohols, aldehydes are transformed into hemiacetals which are inert intermediates against reduction.

In summary, magnesium metal can be used for the reduction of ketones more safely, easily, and economically and complementary to Na- and K-mediated reduction of ketones.

A typical procedure is as follows. A mixture of substrate (2.0 mmol), Mg (486 mg, 20.0 mmol, −50 mesh), and a few crystals of HgCl$_2$ in dry EtOH (50 mL) was stirred for 12 h at room temperature. The reaction mixture was poured into cold 0.5 N HCl solution and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaHCO$_3$ solution, dried (MgSO$_4$), filtered, and then concentrated in vacuo to give crude product which was purified by flash column chromatography (SiO$_2$).

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