# Catalytic Reduction of Carbonyl Functional Groups in 2-Propanol by Molybdocene Hydrides

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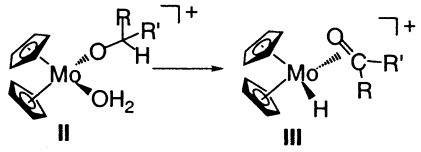
The catalytic reduction of acetophenone in 2-propanol by the organometallic complex $[Cp_2Mo(\mu\text{-}OH)_2\ MoCp_2](OTs)_2$ (**I**) proceeds through a molybdocene hydride intermediate. Activation parameters for the reduction of acetophenone to 1-phenylethyl alcohol in 2-propanol-$d_8$ are 19 kcal mol$^{-1}$ and −26 cal mol$^{-1}$ K$^{-1}$ for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively. These parameters suggest 2-propanol and **I** are involved in a C−H activation step to form a molybdocene monohydride that may be the active species in the hydrogenation catalysis. When the catalysis reaction was performed with $(CH_3)_2CHOD$ as the solvent, 1-deuterio-1-phenylethyl alcohol was almost quantitatively formed. This is consistent with a mechanism where a $Cp_2Mo$ hydride, formed in the C−H activation of $(CH_3)_2CHOD$, is converted to the deuteride by the solvent's alcoholic deuteron. The labeling experiment further supports the a molybdocene hydride as the catalytic species.



## Introduction

Metallocene hydrides are key intermediates and catalysts in olefin hydrogenation and polymerization reactions as well as useful reagents in organic synthesis.[1] It has been shown that a molybdocene hydride is the primary intermediate in the H/D exchange chemistry of alcohols by various molybdocene complexes in $D_2O$.[2] The key step (Scheme 1) involves a C−H activation[3] transformation that takes a molybdocene alkoxide complex (**II**) to a molybdocene hydride (**III**).[2] We have also shown that this molybdocene hydride is soluble in water and readily undergoes hydride−deuteride exchange in $D_2O$.[4] This aqueous chemistry prompted us to investigate the use of molybdocene complexes as possible hydrogenation catalysts in environmentally friendly solvents.[5] A key step in the hydrogenation chemistry would involve regenerating the molybdocene hydride after it has been used to reduce a carbonyl functionality. We report here that the molybdocene complex $[Cp_2Mo(\mu\text{-}OH)_2MoCp_2](OTs)_2$ (Cp = $\eta^5$-$C_5H_5$, OTs = tosylate) (**I**) and its corresponding $[Cp_2Mo(OH_2)_2](OTs)_2$ monomer[6] are effective catalysts in the reduction of acetophenone in the presence of 2-propanol. The

**Scheme 1**




alcohol 2-propanol serves as both a hydrogen source and a convenient solvent, since it is easy to handle and nontoxic and the acetone product is easily removed.[7] This is the first case of a molybdocene complex that serves as a catalyst in this hydrogenation transformation in an alcoholic solvent and contributes to the growing list of "green" transformations that organometallic complexes are capable of performing.[8]

The two halves of the catalytic cycle reported herein are based on the aforementioned molybdocene chemistries, where the key intermediate is the molybdocene hydride. This builds upon prior work on the aqueous chemistry of the monohydride $Cp_2Mo(H)(OTf)$ (OTf = triflate). In addition to the acid-promoted hydrogenation chemistry of molybdenum and tungsten metallocenes,[9−11] we showed that the molybdocene monohydride is an effective reducing agent under mild aqueous conditions (pH 7, 40 °C).[4] The monohydride **IV** reduces ketones and aldehydes to the corresponding alcohol via hydride attack on the coordinated carbonyl (Scheme 2). The

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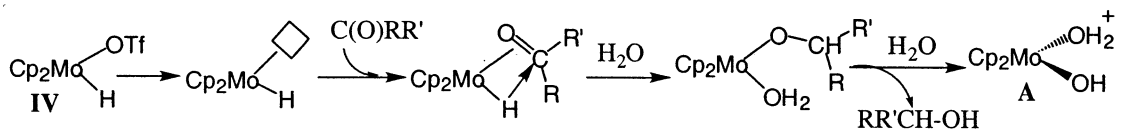
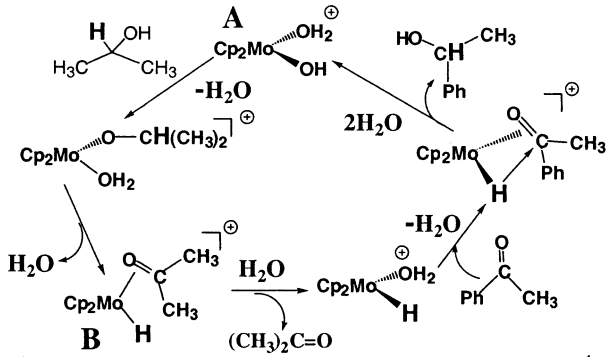
**Scheme 2**




**Scheme 3**




product of this reduction in water is the aquated $Cp_2Mo(OH)(OH_2)^+$ complex (**A**), which is the active species used in the C−H activation chemistry of alcohols.

When the two aforementioned processes (Schemes 1 and 2) are combined with 2-propanol serving as a solvent, we develop a catalytic cycle that capitalizes on molybdocene hydride chemistry (Scheme 3). First the monomeric molybdocene complex is converted to the corresponding hydride (**A** → **B**) via the C−H activation chemistry of 2-propanol[2] shown in Scheme 1. The molybdocene hydride (**B**) then binds to a carbonyl functionality such as acetophenone and reduces it to the corresponding 1-phenylethyl alcohol (**B** → **A**). The molybdocene, **A**, is then set up to regenerate the hydride in the presence of excess 2-propanol. The overall transformation where 2-propanol is the hydrogen source resembles the Meerwein−Pondorf−Verley (MPV) reaction.[12] However, there are mechanistic differences. In this report, we present kinetic and labeling studies consistent with a mechanism that uses the molybdocene hydride as the key reducing agent, as opposed to the MPV pathway, which uses the methine proton of 2-propanol as the hydrogenation source.

## Results and Discussion

In an anaerobic reaction of **I** (7.5 $\mu$mol) with acetophenone (0.103 mmol) in 2-propanol-$d_8$ (0.75 mL), we see a clean conversion to 1-phenylethyl alcohol that follows first-order kinetics in the decrease of acetophenone and increase in 1-phenylethyl alcohol (Figure 1). Although at room temperature **I** is sparingly soluble in 2-propanol-$d_8$, at higher temperatures the molybdocene dimer dissolves. Presumably when **I** dissolves in 2-propanol a dimer−monomer equilibrium is established, as is the case in $D_2O$[6] (see Supporting Information). The absence of a clean methyl doublet and methine quartet at 1.42 and 4.75 ppm for the 1-phenylethyl alcohol is attributable to the incorporation of the deuterium at the methine carbon. When a similar reaction is done in proteo-2-propanol, we clearly see 1-phenylethyl alcohol produced, as determined through authentic addition (Supporting Information). From the integration of the cyclopentadienyl and the acetophenone methyl peaks, it is clear that the ketone is in at least 10-fold excess of the molybdocene, which makes this hydrogenation process catalytic in **I**.

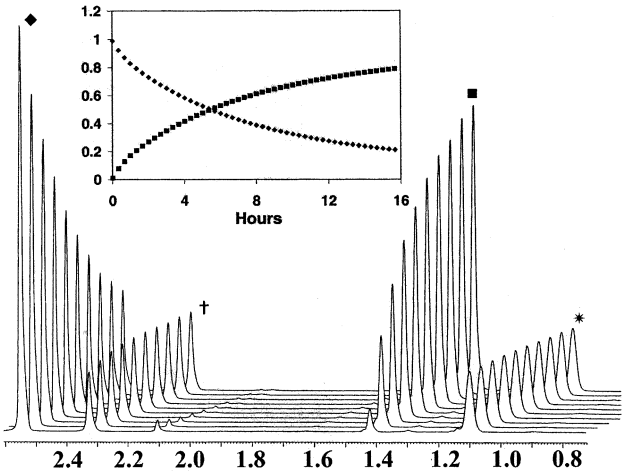



**Figure 1.** Acetophenone (0.103 mmol) reduction by **I** (7.5 $\mu$mol) as followed by $^1$H NMR in 2-propanol-$d_8$. A 20 min interval separates each spectrum, and the hydrogenation took place in 0.75 mL of 2-propanol-$d_8$ at 75 °C. The peaks at 2.55 (◆) and 1.42 ppm (■) represent methyl resonances for acetophenone and 1-phenylethyl alcohol, respectively. The peaks at 2.32 (†) and 1.10 (*) are due to the methyl signals of the tosylate anion for **I** and of 2-propanol-$d_8$, respectively. The inset graph shows the relative integrals for the methyl groups of acetophenone (◆) and 1-phenylethyl alcohol (■). Both the product increase and starting material decay follow exponential functions with equal rates ($k_{obs} = 3.4 \times 10^{-2}$ h$^{-1}$).

One of the difficulties with hydrogenating ketones with this metallocene catalyst is that the reverse reaction does occur, which can complicate mechanistic studies. In such a process the 1-phenylethyl alcohol coordinates to the molybdocene and undergoes C−H activation to form acetophenone (Scheme 1), which in turn can be hydrogenated. In this connection we compared the first-order rate constants for the hydrogenation reaction ($k_{obs} = 2.25 \times 10^{-3}$ h$^{-1}$) with the reverse oxidation process of 1-phenylethyl alcohol ($k_{obs} < 8.0 \times 10^{-5}$ h$^{-1}$) under the same conditions (45 °C in 2-propanol-$d_8$). We found that the hydrogenation process occurs ~$10^2$ times faster than the reverse reaction, which allows us, to a first approximation, to use the kinetics data to make mechanistic interpretations for the hydrogenation transformation.

An Arrhenius plot (35−75 °C) of this reduction process gives $\Delta H^‡$ and $\Delta S^‡$ values of 19.4 ± 1.0 kcal mol$^{-1}$ and −26 ± 2.0 cal mol$^{-1}$ K$^{-1}$, respectively (Figure 2). These parameters should be compared to similar studies on the H/D exchange of benzyl alcohol in $D_2O$ by $[(MeCp)_2Mo(\mu\text{-}OH)_2Mo(CpMe)_2]OTs_2$, where $\Delta H^‡$ and $\Delta S^‡$ values

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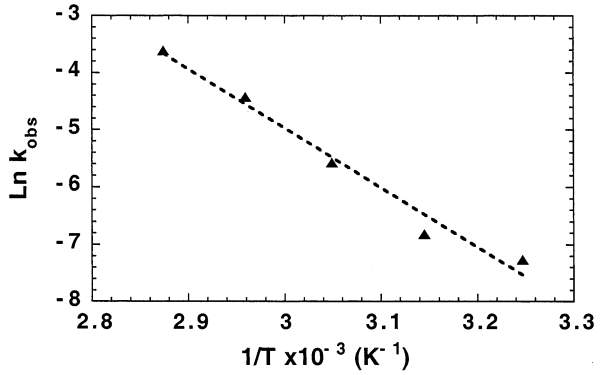


**Figure 2.** Arrhenius plot of acetophenone (0.103 mmol) reduction by **I** (7.5 $\mu$mol). Rate constants were taken from initial (first 10%) rates. The measured activation parameters from this plot were 19 kcal mol$^{-1}$ and −26 cal mol$^{-1}$ K$^{-1}$ for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively.

are 19.4 ± 0.2 kcal mol$^{-1}$ and −22.7 ± 0.7 cal mol$^{-1}$ K$^{-1}$, respectively.[2] It is remarkable that the $\Delta H^{\ddagger}$ value for the hydrogenation is identical, and the $\Delta S^{\ddagger}$ value is only 14% more negative than those of the former H/D exchange studies. In these exchange studies in $D_2O$, the rate-determining step was postulated to involve a C−H activation process that generates a molybdocene monohydride.[2,3c] Therefore, the measured activation parameters for our hydrogenation study suggest a pathway that involves a rate-determining C−H activation process on the 2-propanol solvent.

The hydrogenation of acetophenone (13 equiv) in 2-propanol with **I** is slow, with a $k_{obs}$ value of $3.4 \times 10^{-2}$ h$^{-1}$ and turnover of 0.1 h$^{-1}$ (75 °C); it would take 63 h to hydrogenate 90% of the ketone. However, this process can be greatly accelerated in the presence of KOH, which by itself does not reduce acetophenone in 2-propanol. The addition of ∼25 equiv of the base allows only 1.0% of catalyst to completely hydrogenate all the acetophenone overnight in refluxing 2-propanol (82 °C). Incomplete hydrogenation reactions (0.2% catalyst, 25 equiv of KOH) were used to calculate a turnover factor of 6.4 h$^{-1}$ in the presence of base. Rate accelerations by KOH have been reported for the activation of rhodium and ruthenium hydrogenation catalysts, wherein the base serves to deprotonate the coordinated 2-propanol.[13] Alternatively, the KOH could be used to make the isopropoxide that binds the molybdocene for the subsequent C−H activation step. Even in the Pd−sparteine-catalyzed asymmetric oxidation of 1-phenylethyl alcohol, it was found that one of the purposes of the exogenous sparteine was to deprotonate the coordinated alcohol.[14] At this point we cannot differentiate the two possibilities for the role of KOH in rate acceleration.

Balzarek and Tyler[2] have reported a similar hydrogenation reaction in the reduction of 2-butanone with **I**(aq) in the presence of 2-propanol. They alluded that the hydrogenation resembles the Meerwein−Ponndorf−Verley (MPV) reduction.[12] The role of the molybdenum center is to simultaneously coordinate the ketone and 2-propanol for the hydride transfer (Chart 1). In such a concerted reaction, there would be no molybdocene hydride intermediate.

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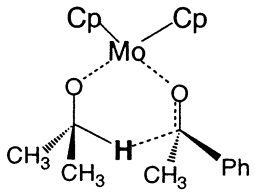
**Chart 1**




To discern whether this hydrogenation process goes through a hydride intermediate or through a MPV pathway, we ran the reaction in 2-propanol-$d_1$ ($(CH_3)_2$CHOD), where the alcoholic position is deuterated. If a Mo−H hydride intermediate is responsible for the reduction process, then it should undergo hydride−deuteride exchange with the alcoholic deuteron of the solvent. In such a case, the Mo−H → Mo−D transformation would lead to deuteration of the methine carbon of the 1-phenylethyl alcohol product that can be readily observed with $^1$H NMR. If on the other hand the hydrogenation proceeded through the MPV pathway, then the hydride source comes directly from the 2-propanol. The absence of a molybdocene hydride intermediate means the methine carbon of the 1-phenylethyl alcohol product should be protonated. In order for this isotopic labeling study to work, two critical controls must be in place, the Mo−H → Mo−D exchange must be faster than the hydrogenation process, and the backward oxidation reaction of 1-phenylethyl alcohol must be slow. We have shown that the molybdocene hydride, $Cp_2Mo(H)OTf$, readily undergoes hydride−deuteride exchange in $D_2O$ (complete reaction in 8 h at 100 °C).[4] When the same monohydride is incubated in 2-propanol-$d_8$ (75 °C), we also see a rapid hydride−deuteride exchange with the alcoholic deuteron where $k_{obs} = 0.30$ h$^{-1}$; complete deuteration took place in only 6.5 h. The rate of hydride−deuteride exchange is then 10 times faster than the hydrogenation of acetophenone at 75 °C. In addition, we have demonstrated that the reverse reaction, where the 1-phenylethyl alcohol is oxidized by molybdocene, is 2 orders of magnitude slower than the hydrogenation process. This indicates the methine proton of the 1-phenylethyl alcohol originates primarily from the hydrogenation (or deuteration) of acetophenone rather than from an alcohol oxidation−reduction sequence.

We prepared 2-propanol-$d_1$ through successive distillation of 2-propanol in $D_2O$, and the final deuterium incorporation (as determined from $^1$H NMR) was 88%. A hydrogenation reaction (0.075 mmol of **I** and 1.03 mmol of acetophenone) was run in this $(CH_3)_2$CHOD solvent. This was followed by evaporation of 2-propanol-$d_1$ (bp 82 °C) and a $^1$H NMR measurement (in $CDCl_3$) of the remaining 1-phenylethyl alcohol (bp 204 °C). The quartet at 4.45 ppm for the methine proton of 1-phenylethyl alcohol did not have the 1:5 integration with the phenyl protons (Figure 3). Instead the ratio was 1:29, which indicates that there was ∼83% deuterium incorporation. In addition, the methyl protons at 1.45 ppm were not split into a doublet; rather, they had a multiplet pattern evident of a neighboring methine carbon that had a deuterium−proton mixture. The ∼5% discrepancy between deuterium incorporation into 1-phenylethyl alcohol and the percent deuterium in the 2-propanol-$d_1$ solvent may be due to a small fraction of molybdocene hydride that did not undergo deuteride

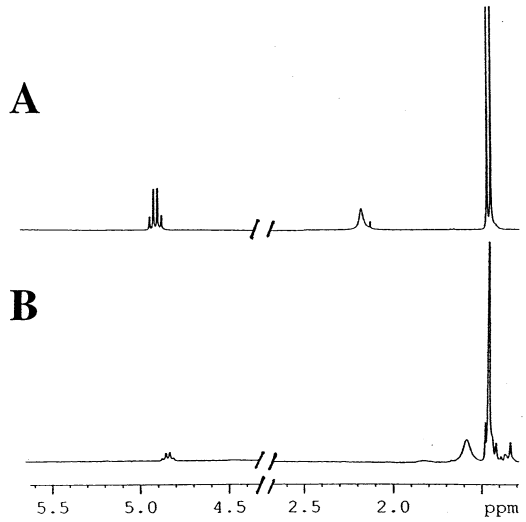



**Figure 3.** (A) $^1$H NMR spectrum ($CDCl_3$) of 1-phenylethyl alcohol alone. (B) $^1$H NMR spectrum of 1-phenylethyl alcohol showing deuterium incorporation into the methine position (4.85 ppm) when acetophenone is hydrogenated by **I** in 2-propanol-*d*. The broad peak at 1.60 ppm is due to the alcoholic proton. Spectrum A clearly shows the lack of a 1:3 ratio of the methine to methyl protons and the loss of the methyl doublet (1.45 ppm). Both spectral features are consistent with deuterium incorporation at the C-1 carbon of 1-phenylethyl alcohol.

exchange with the solvent and subsequently hydrogenated the acetophenone. This is not an unreasonable assumption, since the hydride/deuteride exchange is only 10 times faster than the hydrogenation reaction. These results suggest that the primary pathway for the hydrogenation of acetophenone by the molybdocene compound is via a hydride intermediate and that the Meerwein−Ponndorf−Verley route is almost nonexistent.

## Conclusion

In this report we present evidence that the molybdocene metallocene carries out catalytic hydrogenation of ketones via a monohydride intermediate. Regeneration of the monohydride comes from C−H activation of the 2-propanol solvent, which serves as a sacrificial oxidant. We are currently examining ways to augment the catalytic properties of this metallocene in terms of catalytic rates and enantioselectivity.

## Experimental Methods

Proton (300 MHz) NMR spectra were recorded with a Bruker Avance-300 spectrometer, and proton chemical shifts were referenced to $(CH_3)_4Si$ (TMS). The precursor compound $Cp_2MoH_2$ was made according to the procedure of Luo and coworkers, except NaCp was used instead of LiCp,[15] and all chemical reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used as received. The title compound **I** was made according to the procedure of Balzarek and coworkers.[2] All manipulations were done under a nitrogen atmosphere using standard Schlenk line or glovebox techniques. All liquid solvents and substrates were degassed by freeze−pump−thaw methods prior to use and stored over molecular sieves.

In a typical experiment, 5 mg of the title compound (**I** = $[Cp_2Mo(OH)]_2$) was added to a 10-fold excess (11 $\mu$L) of acetophenone in deuterated 2-propanol-$d_8$ in the glovebox. The reactions were monitored at various temperatures with a pulse delay of >10 s to ensure proper $^1$H NMR integration.

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**Supporting Information Available:** Text giving experimental methods and figures giving supporting $^1$H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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