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Kinetic Isotope Effect Evidence for a Concerted Hydrogen Transfer Mechanism in Transfer Hydrogenations Catalyzed by [*p*-(Me_2CH)C_6H_4Me]Ru-($NHCHPhCHPhNSO_2C_6H_4$-*p*-CH_3)

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Abstract: The isotope effects in the reaction of [*p*-(Me_2CH)-C_6H_4Me]Ru($NHCHPhCHPhNSO_2C_6H_4$-*p*-CH_3) (**1**) with isopropyl alcohol were 1.79 for transfer of hydrogen from OH to N and 2.86 for transfer from CH to Ru. The isotope effect for transfer of deuterium from doubly labeled material ($k_{CHOH}/k_{CDOD} = 4.88$) was within experimental error of the product of the two individual isotope effects. These isotope effects provide convincing evidence for a mechanism involving concurrent transfer of hydrogen from oxygen to nitrogen and from carbon to ruthenium.

The development of several new transition metal transfer hydrogenation catalysts is revolutionizing reduction chemistry. Noyori's chiral [*p*-(Me_2CH)C_6H_4Me)]Ru($NHCHPhCHPhNSO_2C_6H_4$-*p*-CH_3) (**1**) shows high activity and excellent enantioselectivity for the conversion of ketones to alcohols with isopropyl alcohol as the ultimate reductant (Scheme 1).[1] Reaction of **1** with isopropyl alcohol produces the ruthenium hydride [*p*-(Me_2CH)C_6H_4Me]RuH-($NH_2CHPhCHPhNSO_2C_6H_4$-*p*-CH_3) (**2**), which then transfers hydrogen to a ketone. The success of Noyori's catalyst has triggered extensive studies of isoelectronic Cp*Rh-(III)($NHCHPhCHPhNSO_2C_6H_4$-*p*-CH_3) and Cp*Ir(III)($NHCHPhCHPhNSO_2C_6H_4$-*p*-CH_3) catalysts by Mashima and Ikariya.[2,3] These new transfer hydrogenation catalysts provide an alternative to traditional stoichiometric $NaBH_4$ and $LiAlH_4$ reductions, and utilize environmentally friendly isopropyl alcohol as the terminal reductant, forming acetone as the byproduct.[4] The reduction of carbonyl groups by **2** and related complexes, which have an electronically coupled metal hydride and acidic NH proton, are proposed to transfer a hydride from ruthenium to carbon and a proton from nitrogen to the carbonyl oxygen; these transfers are suggested to occur without prior coordination of the alcohol to the metal center. This mechanism is distinctly different from that of the Meerwein−Ponndorf−Verley reaction in which an aluminum alkoxide catalyzes transfer hydrogenations. It is unusual for a transition metal complex to react with a substrate outside the coordination sphere of the metal. Noyori has reported extensive calculations that provide theoretical support for the concerted six-center transition state for transfer hydrogenation.[5] Noyori also reported an isotope effect of 1.5 for the reduction of acetophenone by $(CH_3)_2$-C***D***OH catalyzed by **1**; it is not clear whether this isotope effect is for the transfer of hydrogen from isopropyl alcohol to **1** or from **2** to acetophenone or some combination of the two processes. While this isotope effect is consistent with the proposed mechanism, we decided that further mechanistic investigation of this important system was warranted.

We are interested in catalysts that can simultaneously transfer hydride and proton to polar substrates. We have carried out mechanistic studies of Shvo's catalyst,[6] which can reduce ketones and aldehydes by either a transfer hydrogenation process with isopropyl alcohol as the reductant or by a direct hydrogenation with H_2 as the reductant. On the basis of detailed studies on the related active reducing agent [2,5-Ph_2-3,4-Tol_2(η^5-C_4COH)]Ru-$(CO)_2H$ (**3**), including observation of primary deuterium isotope effects for transfer of both OH and RuH hydrogens, we proposed a mechanism involving concerted transfer of proton and hydride to aldehyde outside the coordination sphere of the metal (Scheme 2).[7,8]

Here we report the application of the same mechanistic tools and isotope effect measurements to the mechanism of transfer hydrogenation catalyzed by Noyori's catalyst **1**. Our kinetic isotope effect measurements on the stoichiometric oxidation of isopropyl alcohol by **1** provide direct experimental support for a simultaneous hydrogen transfer mechanism.

Rate Law for Reaction of 1 with Isopropyl Alcohol. We experienced difficulty in measuring the rate of the reaction of **1** with isopropyl alcohol by ^1H NMR spectroscopy because the spectra were dominated by the methyl resonances of excess isopropyl alcohol, which limited the dynamic range of the spectrometer and our ability to accurately integrate the resonances of **1** and **2**. This problem was circumvented by using the deuterated substrate $(CD_3)_2CHOH$ and following the conversion of **1** [δ 5.7 (aryl), and δ 2.1 (Me)] to **2** [δ 4.8 and 4.7 (aryl), and δ −5.8 (RuH)] by NMR integration. Reaction of **1** (0.02 M) with a large excess of $(CD_3)_2CHOH$ (0.7 M, 35-fold excess) at −20 °C went to form an equilibrium ratio of **1**:**2** of about 10:90 (Scheme 3).

The rate of approach to equilibrium followed pseudo-first-order kinetics to over 3 half-lives, indicating a first-order dependence on ruthenium complex **1** with $k_{obs} = (9.80 \pm 0.30) \times 10^{-4}\ s^{-1}$ for the disappearance of **1**. A linear dependence of k_{obs} on the concentration of $(CD_3)_2$-CHOH between 0.35 and 0.90 M established a first-order dependence on alcohol concentration (Table 1). These data established the second-order rate law for disappearance of **1** (eq 1), with $k_{obs}/[\text{alcohol}] = (1.39 \pm 0.42) \times 10^{-3}$

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[1] (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

[2] (a) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199. (b) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1201.

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[7] The small square attached to ruthenium in Scheme 2 indicates an open coordination site.

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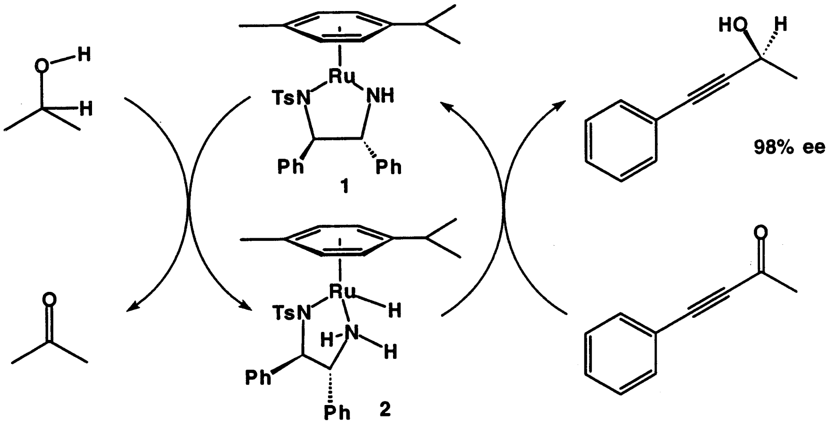
10.1021/jo0205457 CCC: $25.00

SCHEME 1



SCHEME 2

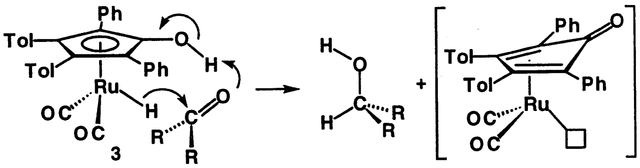


TABLE 1. Rates of Approach to Equilibrium for Reaction of Isopropyl Alcohol Isotopomers with 1 at −20 °C in CD_2Cl_2

	[alcohol] (M)	k_{obs} (s^{-1}) × 10^4	k_{obs}/[alcohol] (M^{-1} s^{-1}) × 10^4	K_{eq}
CHOH	0.363	5.0 ± 0.1	13.0 ± 0.3	0.181
	0.537	7.2 ± 0.2	14.2 ± 0.4	0.184
	0.707	9.8 ± 0.3	13.9 ± 0.4	0.179
	0.872	11.3 ± 0.4	13.8 ± 0.4	0.178
CHOD	0.706	5.4 ± 0.2	7.7 ± 0.3	0.170
CDOH	0.702	4.2 ± 0.1	5.9 ± 0.2	0.155
CDOD	0.706	2.3 ± 0.1	3.2 ± 0.2	0.148

TABLE 2. Second-Order Rate Constants for the Reaction of Isopropyl Alcohol Isotopomers with 1 at −20 °C and for Reaction of Acetone with 2[a]

	k (M^{-1} s^{-1}) × 10^4		k (M^{-1} s^{-1}) × 10^4
k_{CHOH}	11.8 ± 0.5	k_{RuHNH}	66 ± 5
k_{CHOD}	6.9 ± 0.1	k_{RuHND}	41 ± 3
k_{CDOH}	4.1 ± 0.2	k_{RuDNH}	27 ± 2
k_{CDOD}	2.4 ± 0.2	k_{RuDND}	16 ± 1

[a] Rate constants for reaction of acetone with **2** determined by dividing k_{CHOH} by K_{CHOH}.

M^{-1} s^{-1} for $(CD_3)_2CHOH$. The equilibrium constants are also presented in Table 1.

$$\frac{d[\mathbf{1}_{excess}]}{dt} \approx k_{obs}[\text{alcohol}][\mathbf{1}_{excess}] \tag{1}$$

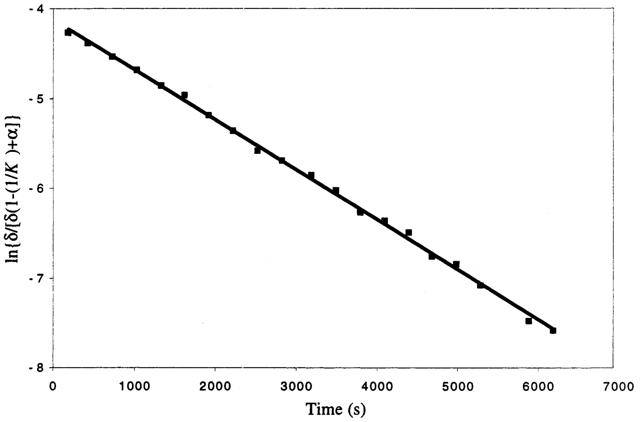


FIGURE 1. Plot of ln $\{\delta_t/[\delta_t(1 - K^{-1}) + \alpha]\}$ versus time used to determine the second-order rate constant for the reaction of **1** with isopropyl alcohol.

We have employed the methods outlined by Espenson[9] and King[10] for obtaining the second-order rate constant for a forward reaction when a significant amount of starting material remains at equilibrium (eq 2). Plots of ln $\{\delta_t/[\delta_t(1 - K^{-1}) + \alpha]\}$ versus time were linear (Figure 1) and rate constants are presented in Table 2.

$$\ln \{\delta_t/[\delta_t(1 - K^{-1}) + \alpha]\} = -k\alpha t + C \tag{2}$$

where

$$\alpha = [\mathbf{1}]_{eq} + [\text{alcohol}]_{eq} + K^{-1}([\mathbf{2}]_{eq} + [\text{acetone}]_{eq})$$

and

$$\delta_t = [\mathbf{1}]_t - [\mathbf{1}]_{eq}$$

Kinetic measurements were performed between −10 and −35 °C to allow determination of activation parameters. The second-order rate constants were the following: 19.7 × 10^{-4} M^{-1} s^{-1} at −11.3 °C; 18.1 × 10^{-4} M^{-1}

SCHEME 3

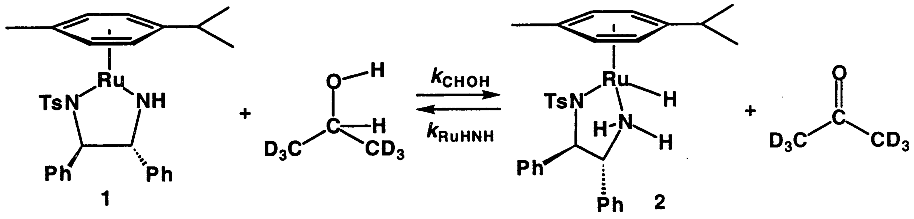


TABLE 3. Kinetic and Equilibrium Isotope Effects for the Reaction of Isopropyl Alcohol with 1 and for the Reaction of Acetone with 2

k_{CHOH}/k_{CHOD}	1.79 ± 0.07	K_{CHOH}/K_{CHOD}	1.05 ± 0.10	k_{RuHNH}/k_{RuHND}	1.69 ± 0.18
k_{CDOH}/k_{CDOD}	1.71 ± 0.16	K_{CDOH}/K_{CDOD}	1.05 ± 0.10	k_{RuDNH}/k_{RuDND}	1.64 ± 0.22
k_{CHOH}/k_{CDOH}	2.86 ± 0.20	K_{CHOH}/K_{CDOH}	1.16 ± 0.11	k_{RuHNH}/k_{RuDNH}	2.46 ± 0.30
k_{CHOD}/k_{CDOD}	2.73 ± 0.15	K_{CHOD}/K_{CDOD}	1.15 ± 0.11	k_{RuHND}/k_{RuDND}	2.38 ± 0.27
k_{CHOH}/k_{CDOD}	4.88 ± 0.41	K_{CHOH}/K_{CDOD}	1.21 ± 0.12	k_{RuHNH}/k_{RuDND}	4.03 ± 0.52

s^{-1} at −14.2 °C; 11.9×10^{-4} M^{-1} s^{-1} at −21.4 °C; 9.7×10^{-4} M^{-1} s^{-1} at −26.4 °C; and 6.4×10^{-4} M^{-1} s^{-1} at −34.1 °C. An Eyring plot provided the values $\Delta H^{\ddagger} = 5.8 \pm 1.5$ kcal mol^{-1} and $\Delta S^{\ddagger} = -48.4 \pm 4.6$ eu. The large negative entropy is indicative of a highly ordered transition state in which **1** and isopropyl alcohol associate prior to transfer of hydrogen.

Kinetic Isotope Effect Measurements. The rates of reaction of **1** with an excess of $(CD_3)_2CHO\boldsymbol{D}$, $(CD_3)_2C\boldsymbol{D}OH$, and $(CD_3)_2C\boldsymbol{D}O\boldsymbol{D}$ were measured at −20 °C at several different ruthenium concentrations while holding the isopropyl alcohol concentration constant. The second-order rate constants for the forward reaction are presented in Table 2.

We found primary deuterium isotope effects of 2.7−2.8 for breaking the CH bond of isopropyl alcohol and of 1.7−1.8 for breaking the OH bond of isopropyl alcohol (Table 3). These isotope effects are consistent with a mechanism involving concerted transfer of hydrogen from carbon to ruthenium and from oxygen to nitrogen.

Equilibrium Isotope Effect Measurements. The equilibrium constants for the reaction of each isopropyl alcohol isotopomer with ruthenium species **1** were determined by measuring the ratio of species after >20 half-lives (eq 3).[11] The amount of acetone was assumed to be the same as ruthenium hydride **2** because of stoichiometry. At −20 °C the equilibrium constant was $K_{eq} = 0.179 \pm 0.013$ for $(CD_3)_2CHOH$, which corresponds to about 90% conversion to **2** under typical reaction conditions. Equilibrium constants for all the isotopomers are given in Table 1.

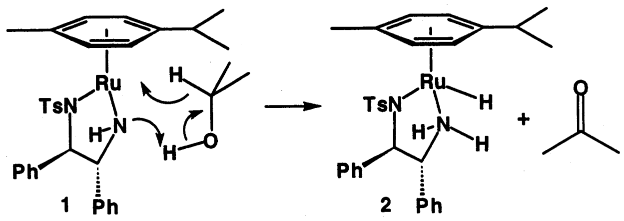
$$K_{eq} = \frac{[\mathbf{2}][\text{acetone}]}{[\mathbf{1}][\text{isopropyl alcohol}]} \qquad (3)$$

The equilibrium isotope effects determined from the individual equilibrium constants were small (eq 4). The equilibrium isotope effect for CD substitution ($K_{CHOH}/K_{CDOH} = 1.16 \pm 0.11$) is consistent with the expectation that deuterium will be concentrated in the stronger bond (CD favored over RuD). The equilibrium isotope effect for OD substitution was $K_{CHOH}/K_{CHOD} = 1.05 \pm 0.10$. (Table 3).

$$\text{equilibrium isotope effect}\left(\frac{\text{CHOH}}{\text{CHO}\boldsymbol{D}}\right) = \frac{K_{CHOH}}{K_{CHOD}} = \frac{[\mathbf{2}_{RuHNH}][(CD_3)_2CHO\boldsymbol{D}]}{[\mathbf{2}_{RuHND}][(CD_3)_2CHOH]} \qquad (4)$$

Kinetic Isotope Effects for Reverse Reactions. Since we know both the second-order rate constants for reactions of isopropyl alcohol isotopomers with ruthenium complex **1** and the equilibrium constants for the reactions, the second-order rate constants for the reverse reaction of acetone with ruthenium hydride **2** were readily determined by dividing the second-order rate constants for the forward reactions by the equilibrium constants (eq 5). The ratios of the rate constants gave isotope effects for the reverse reactions (Table 3).

SCHEME 4



$$k_{RuHNH} = \frac{k_{CHOH}}{K_{CHOH}} \qquad (5)$$

The observation of isotope effects for transfer of hydrogen both from carbon to ruthenium ($k_{CHOH}/k_{CDOH} = 2.86 \pm 0.20$) and from oxygen to nitrogen ($k_{CHOH}/k_{CHOD} = 1.79 \pm 0.07$) in the reaction of isopropyl alcohol with **1** provides strong evidence for a concerted mechanism. For a concerted mechanism, the isotope effect for transfer of deuterium from doubly labeled material should be the product of the two individual isotope effects. The observation that the combined isotope effect for transfer of deuterium from carbon and oxygen ($k_{CHOH}/k_{CDOD} = 4.88 \pm 0.41$) is within experimental error of the product of the two individual isotope effects ($2.86 \times 1.79 = 5.11 \pm 0.41$) provides convincing evidence that both transfers occur in the same step. These results provide strong support for the mechanism proposed by Noyori that involves simultaneous transfer of hydrogen from carbon to ruthenium and from oxygen to nitrogen outside the coordination sphere of ruthenium (Scheme 4). These isotope effects provide evidence only for the movement of the hydrogen atoms during this reaction and provide no information on the polarity of the hydrogens. However, we suggest that the hydrogen transferred from carbon to ruthenium behaves as a hydride, while the hydrogen transferred from oxygen to nitrogen behaves as a proton, and that both are transferred in a concerted process through a single transition state.

Stepwise alternatives to the concerted mechanism in which the hydride and proton are transferred to the unsaturated ruthenium species **1** in separate steps can be excluded based on the results reported here. In a two-step reaction (Scheme 5) in which k_{-1} and k_2 differ by an order of magnitude or more, a primary kinetic isotope effect would be seen for only the slower of the two reactions and an equilibrium isotope effect would be seen for the reversible step. The magnitude of the equilibrium isotope effect on the first step in the mechanism should

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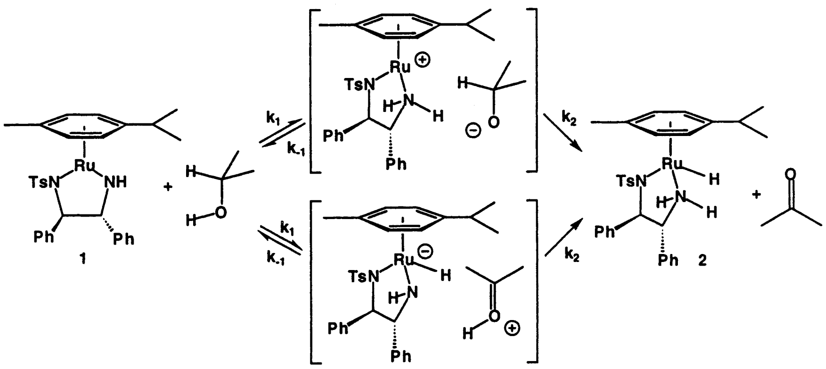
(9) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*, 2nd ed.; McGraw-Hill: St. Louis, 1995.

(10) (a) King, E. L. *Int. J. Chem. Kinet.* **1982**, *14*, 1285. (b) King, E. L. *J. Chem. Educ.* **1979**, *56*, 580.

(11) Even at long reaction times, no exchange into the ruthenium hydride position from excess alcohol was seen.

SCHEME 5



be similar to the equilibrium isotope effect for the overall reaction. In the present case, the equilibrium isotope effects for the overall reaction are small ($K_{\mathrm{CHOH}}/K_{\mathrm{CHOD}} =$ 1.05 and $K_{\mathrm{CHOH}}/K_{\mathrm{CDOH}} = 1.16$). Both the observed isotope effect of 1.79 for transfer of OH to nitrogen and of 2.86 for transfer of CH to ruthenium are much too large to be equilibrium isotope effects. Stepwise mechanisms of this type are therefore excluded.

A stepwise mechanism in which the barriers for proton transfer followed by hydride transfer are approximately equal ($k_{-1} \approx k_2$ in Scheme 5) would give rise to isotope effects for transfer of both O−H and C−H hydrogens. For this two-step mechanism, the isotope effect observed for doubly labeled material should be smaller than the product of the individual isotope effects. For example, assuming no equilibrium isotope effect for protonation of the amino group and equal barriers for OH and CH transfer, one must employ isotope effects of 2.62 on OH transfer and 3.76 on CH transfer to obtain the observed isotope effects of $k_{\mathrm{CHOH}}/k_{\mathrm{CHOD}} = 1.79 \pm 0.07$ and $k_{\mathrm{CHOH}}/k_{\mathrm{CDOH}} = 2.86 \pm 0.20$ (see Supporting Information). The combination of the two isotope effects predicts an isotope effect for doubly labeled material of $k_{\mathrm{CHOH}}/k_{\mathrm{CDOD}} = 3.17$, which is significantly smaller than the observed value of 4.88 ± 0.41. Therefore, a two-step mechanism with equal barriers can be excluded.

In the paper by Ryberg,[12] isotope effects for the catalytic reduction of acetophenone by deuterated isopropyl alcohol using a related Ru(cymene)(amino alcohol) catalyst were measured and evidence was presented that the rate determining step was hydrogen transfer from isopropyl alcohol to the ruthenium complex. They found isotope effects of 2.51 ± 0.22 for OH transfer and 2.69 ± 0.30 for CH transfer. The combination of our isotope effect measurements in stoichiometric reactions with Ryberg's isotope effect measurements in catalytic reactions make a convincing case for concerted transfer of hydrogen from OH to N and from CH to Ru in **1**, which occurs outside the coordination sphere of ruthenium. In addition, the activation parameters and equilibrium data presented here increase the overall understanding of this reaction, and in turn, the catalytic cycle as a whole.

Experimental Section

General. All syntheses and sample preparations were prepared following Schlenk techniques or in a nitrogen atmosphere glovebox. CD_2Cl_2 was dried over CaH_2 and distilled prior to use. Solvents were dried with activated alumina purification columns.[13] Commercially available starting materials were used without further purification. NMR spectra were recorded on a 360-MHz spectrometer. NMR spectra are referenced to residual protons in deuterated solvent. Ruthenium catalyst **1** was prepared according to a literature procedure.[1a] Deuterated isopropyl alcohol was prepared by reduction of acetone-d_6 (see Supporting Information).

General Kinetic Procedure. The general kinetic procedure will be illustrated with a specific example. A standard CD_2Cl_2 solution of **1** containing ferrocene as an internal NMR integration standard (0.70 mL, 0.031 M, prepared in a nitrogen glovebox from 44.1 mg of **1**, ∼10 mg of ferrocene, and 2.40 mL of CD_2Cl_2) in a resealable NMR tube was degassed with 3 freeze−pump−thaw cycles. The NMR tube was filled with N_2 at −78 °C and isopropyl alcohol (40.0 μL, 0.523 mmol, 25 equiv) was added from a 50-μL gastight syringe. The NMR tube was resealed, inserted into an NMR spin collar, shaken for 3 s, and then inserted into the NMR spectrometer precooled to −20 °C. After locking and shimming (∼3 min), data acquisition was begun. The disappearance of the ruthenium complex **1** and the appearance of the ruthenium hydride **2** were both followed by ^{1}H NMR spectroscopy for over 2.5 half-lives (∼100 min). The concentration of **1** was followed by measuring the integrations between δ 5.70−5.79 and δ 2.08−2.14 (cymene aromatic and methyl protons, respectively) compared to the integration of the ferrocene internal standard. The concentration of **2** was followed by measuring the integrations from δ 4.82 to 4.88, δ 4.75 to 4.82, and δ −5.73 to −5.90 (two cymene aromatic and hydride protons, respectively) compared to the integration of the ferrocene internal standard. The final equilibrium concentrations were determined from samples held at −20 °C in a slush bath for at least 8 h.

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Supporting Information Available: Preparation of deuterated alcohols, summary of kinetic runs, calculations of isotope effects assuming a two-step mechanism with equal barriers, and an Eyring plot. This material is available free of charge via the Internet at http://pubs.acs.org.

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