Ruthenium-Catalyzed Regioselective Deuteration of Alcohols at the β-Carbon Position with Deuterium Oxide

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Abstract: A convenient method for regioselective H/D exchange between D_2O and alcohols at the β -carbon position using the catalytic system [(*p*-cymene)RuCl₂]/ethanolamine/KOH is described. This method is applicable for deuteration of both primary and secondary alcohols. The H/D exchange reactions proceed through an oxidation/ modification/reduction reaction sequence. Alcohols are first temporarily oxidized to carbonyl compounds by the hydrogen transfer catalyst. The carbonyl compounds then undergo deuteration at the carbon adjacent to the carbonyl group by keto–enol tautomeriza-

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tion in the presence of D_2O and a catalytic amount of base. The deuterated carbonyl compounds are then reduced to produce deuterated alcohols. In support of the reaction mechanism, a well-defined bimetallic ruthenium complex was isolated from the reaction of [{(p-cymene)RuCl_2]2] with ethanolamine. The activity of this complex is similar to that of [{(p-cymene)RuCl_2]2]/ethanolamine.

Introduction

Deuterium-labeled compounds are useful for a wide range of applications. For example, they can be used as solvents in NMR spectroscopy, labeled drugs, probes in mass spectrometry, probes for mechanistic studies in chemical and biochemical processes, and raw materials for other labeled compounds and polymers. As a result, intense research has focused on the development of methodologies for the preparation of selectively deuterium labeled compounds.^[1,2]

This work concerns the regioselective deuteration of alcohols. Convenient preparations of deuterated alcohols are desirable because alcohols are readily available both synthetically and naturally and can be used as starting materials for a variety of organic syntheses. In addition, many drugs contain hydroxyl functional groups and can therefore be grossly considered as alcohols. Several approaches have previously been reported for the preparation of deuterium-labeled alcohols. α -Deuterated alcohols can be obtained through the reduction of the corresponding aldehydes or ketones by reagents such as NaBD₄,^[3] LiAlD₄,^[4] SiDMe₂Ph/F^{-,[5]} and D₂/ Raney Al.^[6] Deuterated chiral primary alcohols can be prepared from enantioselective reduction of carbonyl com-

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pounds using NaBD₄ catalyzed by optically active metal complexes.^[7] Alcohols labeled with deuterium at other positions can be obtained by multi-step organic synthesis from synthons.[8-14] deuterium-labeled For example. PhCH(OH)CD₃ can be prepared from the reaction of PhCHO with CD₃MgI (prepared from CD₃I and Mg)^[8] or the reaction of $LiAlH_4$ with $PhC(O)CD_3$ (prepared from PhCO₂H and CD₃Li);^[9] CH₃(CH₂)₅CH(OH)CDH₂ can be prepared from the reaction of CH₃(CH₂)₅CH=CH₂ with BD₃THF followed by treatment with H₂O₂/NaOH.^[11] A more cost-effective and time-efficient approach to deuterium-labeled alcohols involves metal-catalyzed direct H/D exchange between alcohols and an appropriate deuterium source. For example, alcohols with deuterium labeled at the α - and β -carbon positions could be obtained from H/D exchange reactions between alcohols and C₆D₆ at 135 °C catalyzed by [Cp*Ir(H)₃(PMe₃)][OTf] (5 mol %).^[15]

Because deuterium oxide (D₂O) is safe and is the cheapest source of deuterium, transition-metal-catalyzed H/D exchange reactions between D₂O and alcohols provide an attractive synthetic strategy for the preparation of deuteriumlabeled alcohols. Several systems have been reported to catalyze such transformations. Matsubara et al. reported that $[RuCl_2(PPh_3)_3]$ (5 mol%) can catalyze regioselective H/D exchange reactions between primary alcohols and D₂O at the α -carbon position under microwave irradiation (150 °C, 10 atm). $^{\rm [16]}$ Sajiki et al. showed that Ru/C-H $_2$ (20 wt %) can catalyze H/D exchange between D2O and both primary and secondary alcohols at the α -carbon position at 50–80 °C.^[17] Nishioka et al. observed that isopropanol and cyclohexanol undergo H/D exchange reactions with D₂O preferentially at the α -carbon position in the presence of a β -D-glucopyranoside-incorporated, N-heterocyclic carbene iridium com-

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plex.^[18] Tyler et al. found that $[Cp'_2Mo(OH)(OH_2)]^+$ (Cp' =C₅H₄Me) (5 mol%) can also catalyze regioselective H/D exchange reactions of primary alcohols with D_2O at the α carbon position at 80-102 °C.^[19] When secondary alcohols were used in [Cp'₂Mo(OH)(OH₂)]⁺-promoted reactions, H/ D exchange at both α - and β -carbon positions was observed.^[19] Sajiki et al. showed that Pd/C-H₂ (10 wt%) can catalyze H/D exchange between aryl-substituted alkyl alcohols and D₂O at the aliphatic carbon positions (except for the α-carbon position) at 110°C in a sealed tube (e.g., Ph-(CH₂)₄OH is converted into Ph(CD₂)₃CH₂OH).^[20] Under similar conditions, deuteration of secondary alcohols gives a mixture of labeled alcohols and ketones.^[21] Utilizing the same system, primary aromatic alcohols with deuterium at the benzylic site can be prepared at room temperature (e.g., $Ph(CH_2)_3OH$ is converted into $PhCD_2(CH_2)_2OH$.^[22] Tilley, Bergman, and co-workers observed that [Cp*Ir(PMe₃)Cl₂] (5 mol%) is catalytically active for deuteration of the alkyl chains of both propanol and isopropanol with D₂O at 135 °C.^[23]

Despite the impressive progress, catalytic systems that can efficiently catalyze regioselective H/D exchange reactions of alcohols at the β -position are still lacking. In this work, we report regioselective H/D exchange reactions at the β -carbon position of primary and secondary alcohols with D₂O catalyzed by ruthenium complexes.

Results and Discussion

Selection of catalysts: Previous studies on the chemistry of carbonyl compounds have shown that aldehydes and ketones can undergo H/D exchange reactions at the carbon adjacent to the carbonyl group in the presence of a base and a suitable deuterium source.^[24] The transformation involves reversible deprotonation/protonation, and takes advantage of the high acidity of the α -protons.

On the other hand, it is known that alcohols can be used as hydrogen donors in the catalytic transfer hydrogenation of ketones and aldehydes.^[25] It has also been demonstrated that transition-metal complexes can catalyze C-C^[26] and C-N^[27] bond-formation reactions of alcohols through an oxidation/modification/reduction sequence. This redox reaction sequence allows the modification of alcohols using carbonyl chemistry. Thus, we envisioned that H/D exchange between D_2O and alcohols at the β -carbon position could be achieved through reversible dehydrogenation of alcohols and hydrogenation of carbonyl compounds, and H/D exchange reactions between D₂O and carbonyl compounds generated in situ in an alkaline medium, as illustrated in Scheme 1. Metal complexes that catalyze hydrogen transfer reactions were thus considered to be good candidates for the intended H/D exchange reactions.

To test the hypothesis, we began our investigation by evaluating the catalytic activities of $[(p\text{-cymene})\text{RuCl-}(\text{NH}_2\text{CH}_2\text{CH}_2\text{NTs})]\text{Cl}$ (1),^[28] $[\text{RuCl}_2(\text{PPh}_3)_2(\text{ampy})]$ (2; ampy=2-(aminomethylene)pyridine),^[29] and $[[(\eta^6\text{-arene})\text{-}$



Scheme 1. Working hypothesis for H/D exchange between alcohols and D_2O at the β -carbon position.

 $RuCl_2$]/ligand^[25a,30] for H/D exchange reactions of alcohols with D₂O. These systems have proved to be efficient catalysts for transfer hydrogenation reactions.

To evaluate the catalytic property of complexes 1 and 2, the reaction of PhCH₂CH₂OH with D₂O was used as a model. The H/D exchange reaction was performed at 80°C in the presence of $3 \mod \%$ of complexes 1 or 2 and 15 mol% of KOH. The performance of complexes 1 and 2 in the catalytic reaction is shown in Scheme 2.



Scheme 2. H/D exchange reaction of $PhCH_2CH_2OH$ with D_2O catalyzed by complexes 1 and 2.

Complex 1 was found to mediate the deuteration of 2phenylethanol selectively at the β -carbon position. When a mixture of 2-phenylethanol and D₂O (in a molar ratio of 1:14.6) was heated at 80 °C in the presence of 3 mol% 1 and KOH (5 equiv vs. Ru) for 2 h, approximately 69% D was found at the β -carbon of 2-phenylethanol (theoretically 90% D can be achieved at this position when the hydrogen atoms associated with H₂O, KOH, and alcohols are considered). Complex 2 was found to mediate the deuteration of 2-phenylethanol at both the α - and β -carbon positions. When a mixture of 2-phenylethanol and D₂O was heated at 80°C in the presence of 3 mol% 2 and KOH (5 equiv vs. Ru) for 2 h, approximately 83 and 82% D were found at the α - and β -positions of 2-phenylethanol, respectively (theoretically 83.2% D can be achieved at these positions).

The catalytic properties of $[{(p-cymene)RuCl_2}_2]$ in combination with fourteen ligands (see Scheme 3 for their structures) in the catalytic H/D exchange reaction of 2-phenylethanol with D₂O was then examined. In these screening experiments, a mixture of D₂O, 2-phenylethanol,

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.OH [{(p-cymene)RuCl₂}₂]/L; KOH; Amines CD_2 .OD D₂O; dioxane; 80 °C; 2 h D_{theo}= 90% H/D Exchange is OBSERVED NH₂ HO `NH/ H₂N ΩН ОН L1 L3 L4 L2 NH_2 NH_2 NH₂ ∕NH₂ H₂N L5 L8 L7 L6 H/D Exchange is NOT OBSERVED ^NC₆H₁₃ NH₂ C₆H₁₃ L11 L9 1 10 H_2N NH₂ *⊳*Ń NH- $\dot{N}H_2$

L13 Scheme 3. Structures of ligands used in the screening experiments.

[{(p-cymene)RuCl₂]₂], KOH, and a ligand (molar ratio of substrate/ $D_2O/[{(p-cymene)RuCl_2}]/KOH/ligand =$

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1:11.74:0.015:0.15:0.03) was heated at 80°C for 2 h in an NMR tube. The deuterium content of the products were then determined by using ¹H NMR spectroscopic analysis. The results are summarized in Scheme 3 and Table 1.

As in the case of transfer hydrogenation, the ligand was found to play an important role in determining the activity and selectivity of the H/D exchange reaction. As shown in Table 1, many of the tested ligands (L9-L14) were ineffec-

Table 1. Effect of the ligand on the H/D exchange reaction of 1-phenylethanol with D₂O mediated by [{(p-cymene)RuCl₂]₂]/ligand.^[a]

	Ligand	D _{inc} [%] ^[b]		
		α -position	β-position	
1	ethanolamine (L1)	0	55	
2	(S)-(+)-2-amino-3-methyl-1-butanol (L2)	0	60	
3	(1 <i>R</i> ,2 <i>S</i>)-(+)- <i>cis</i> -1-amino-2-indanol (L3)	0	44	
4	N-methylethylenediamine (L4)	0	17	
5	benzylamine (L5)	0	5	
6	aniline (L6)	0	2	
7	2-(aminomethyl)pyridine (L7)	0	2	
8	ethylenediamine (L8)	0	1	
9	butylamine (L9)	0	0	
10	dihexylamine (L10)	0	0	
11	N,N'-diisopropylethylenediamine (L11)	0	0	
12	2-pyridinyl-propanol (L12)	0	0	
13	L-threonine (L13)	0	0	
14	2,4,6-triaminopyrimidine (L14)	0	0	
15	none	0	0	

[a] Reagents and conditions (reaction performed in an NMR tube): [{(pcymene)RuCl₂]₂] (1.5 mol%), ligand (3 mol%), KOH (15 mol%), N₂, 80°C, 2 h. D_{theo} (the statistical percentage of D considering the hydrogen atoms associated with H₂O, KOH and alcohols) was set to be approximately 90%. [b] Dinc is the percentage of deuterium incorporation determined experimentally by ¹H NMR spectroscopic analysis.

tive in promoting the H/D exchange reaction (Table 1, entries 9-14). The amino ligands L5-L8 were only marginally active and the reaction produced partially deuterated 2-phenylethanol with 5% or less deuterium incorporation at the β -carbon position (Table 1, entries 5–8). The diamine ligand L4 was more effective and promoted the reaction to give partially deuterated 2-phenylethanol with 17% D at the β carbon position (Table 1, entry 4). The most effective ligands were found to be the amino alcohol ligands L1-L3, which promoted the reaction to give partially deuterated 2-phenylethanol with respectively 55, 60, and 44 % D at the β -carbon position (Table 1, entries 1–3).

Because ethanolamine is inexpensive and more readily available, we further investigated the reactions catalyzed by $[{(p-cymene)RuCl_2}]/ethanolamine to establish the opti$ mum reaction conditions. We were pleased to find out that the combination of $[{(p-cymene)RuCl_2}_2]$ with ethanolamine can effectively promote the regioselective H/D exchange reaction of 2-phenylethanol with D₂O to give partially deuterated 2-phenylethanol with a deuterium content at the β carbon position close to the theoretical maximum. For example, deuterated 2-phenylethanol with 84% D at the β carbon was obtained when a mixture of 2-phenylethanol, D₂O, [{(p-cymene)RuCl₂]₂], KOH, and ethanolamine (in a molar ratio of 1:14.6:0.015:0.15:0.03) was heated at 80 °C for 5.5 h (Scheme 4). The deuterium content of 84% at the β carbon of 2-phenylethanol is very close to the theoretical value of 89.3%.

$$\begin{array}{c} \begin{array}{c} OH \\ + & D_2O \\ 1 & : & 14.6 \end{array} & \begin{array}{c} 3 \text{ mol } \% \ [[(\rho\text{-cymene})\text{RuCl}_2]_2] \\ 3 \text{ mol } \% \ \text{NH}_2\text{CH}_2\text{CH}_2\text{OH} \\ 15 \text{ mol } \% \ \text{KOH}, \ 80 \ ^\circ\text{C}, \ 5.5 \ \text{h} \end{array} & \begin{array}{c} \begin{array}{c} 84\% \\ CD_2 \\ CD_2 \\ 0\% \\ 0\% \end{array} + \ \text{HDO} \\ 0\% \end{array} \\ \begin{array}{c} 0 \\ D_{\text{theo}} = 89.3\% \end{array} \end{array}$$

Scheme 4. Deuteration [{(p-cymene)RuCl₂]₂]/ethanolamine with the system in D₂O.

Scope of substrates: We explored the scope of substrates in the H/D exchange reactions between D₂O and alcohols catalyzed by the [{(p-cymene)RuCl₂]₂]/ethanolamine/KOH system. In most cases, the H/D exchange reactions were performed in the presence of 1.5 mol % [{(p-cymene)RuCl₂]₂], 3 mol% ethanolamine, and 15 mol% KOH. The molar ratio of substrate and D₂O was chosen such that the theoretical percentage of deuterium incorporation at the β-carbon was approximately 90%. The results of the catalytic reactions are shown in Table 2.

As shown in Table 2, a variety of primary and secondary alcohols that were deuterated at the β -position were readily prepared by the present ruthenium-catalyzed H/D exchange reactions. For example, the reaction of 1-phenylethanol under the standard conditions for 5.5 h gave deuterated 1phenylethanol with 84% deuterium at the β -carbon position (theoretically ca. 90% deuteration can be achieved). The potentially coordinating alcohols 1-(2-pyridinyl)ethanol (S10) and 1-(4-pyridinyl)ethanol (S9) also underwent H/D

Table 2. H/D exchange reactions of alcohols with D_2O catalyzed by the [{(p-cymene)RuCl₂}]/ethanolamine/KOH system.^[a]

	Substrate	D _{theo}	t	Products
		[%] ^[b]	[h]	D _{inc} [%] ^[c]
1	2-phenylethanol (S1)	90.0	5.5	CD ₂ OD 84%
2	N-(2-hydroxyethyl)morpholine (S2)	90.0	9.25	OCD2OD
3	1-phenylethanol (S3)	89.9	5.5	CD ₃ 87%
4	1,1'-(1,4-phenylene)diethanol (S4)	90.0	9.25	DO D3C D0 CD ₃ 81% OD
5	1-phenylpropanol (S5)	90.0	6	OD CD ₂ 76%
6	1,2,3,4-tetrahydronaphthalen-1-ol (S6)	90.0	6	OD CD2 80%
7	2-buthanol (S7)	89.9	5.5	OD H ₃ C _{CD2} 69 % 73 %
8	cyclohexanol (S8)	90.0	8	OD H D 63% D 66%
9	1-(pyridin-4-yl)ethanol (89)	90.0	9.25	OD CD ₃ N 71%
10	1-(pyridin-2-yl)ethanol (S10)	89.9	9.25	OD N CD ₃ 52%

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methane at room temperature for 27 h afforded [${(p-cymene)}$ -RuCl $_2(\mu$ -NH $_2$ CH $_2$ CH $_2$ O·H·O-CH $_2$ CH $_2$ NH $_2$)]Cl (**3**), which was isolated as a yellow solid in 83 % yield (Scheme 6).

The structure of 3 was confirmed by X-ray diffraction analysis. As shown in Figure 1, complex 3 is a bimetallic complex with an O-H-O linkage in the solid state. The short O1A…O1B distance (2.397 Å) indicates a strong hydrogen bond between the two oxygen atoms. Each ruthenium center is ligated with an N,O-ligand. The complex has a +1 overall charge with a chloride ion as the counter anion. The ruthenium center adopts a piano-stool geometry with chloride and ethanolamine serving as the legs. The Ru-N (2.111(6) Å for Ru1A–N1A and 2.120(7) Å for Ru1B-N1B), Ru-Cl (2.422(2) Å for Ru1A–Cl1A and 2.418(2) Å for Ru1B-Cl1B), and Ru-O (2.079(6) Å for Ru1A-O1A and 2.094(5) Å for Ru1B-O1B) bond lengths, as well as the Ru-C(p-cymene)

[a] Reagents and conditions: [{(p-cymene)RuCl₂]₂] (1.5 mol%), ethanolamine (3 mol%), KOH (15 mol%), N₂, 80 °C in a Schlenk tube. [b] D_{theo} is the statistical percentage of D considering the hydrogen atoms associated with water, KOH, ethanolamine, and substrates. [c] D_{inc} is the percentage of deuterium incorporated, determined experimentally by ¹H and ²D NMR spectroscopic analyses.

exchange smoothly to give the corresponding deuterated pyridinylethanols.

Alcohols with more than 90% deuterium at the β -carbon position can be obtained by repeating the H/D exchange reaction. For example, PhCD₂CH₂OH with 91%D was obtained in the following way. A mixture of [{(*p*-cymene)-RuCl₂}] (36.8 mg, 0.06 mmol), 2-phenylethanol (480 µL, 4.0 mmol), ethanolamine (72 µL, 1.66 M in D₂O, 120 µmol), D₂O (716 µL), and KOH in D₂O (178 µL, 3.38 M, 0.6 mmol) was heated at 80°C for 4 h. The product was isolated and the reaction was repeated one more time. With a similar procedure, other alcohols with more than 90% deuterium at the β -carbon position can be obtained, as exemplified in Scheme 5.

Preparation and characterization of a bimetallic ruthenium complex from the reaction of $[{(p-cymene)RuCl_2}_2]$ with ethanolamine: To gain a better understanding of the nature of the active species in the catalytic reactions, we attempted to prepare well-defined metal complexes from the reaction of $[{(p-cymene)RuCl_2}_2]$ with ethanolamine.

Reaction of $[{(p-cymene)RuCl_2}_2]$ with two equivalents of ethanolamine in the presence of triethylamine in dichloro-



Scheme 5. Deuterated alcohols obtained by carrying out the H/D exchange reaction twice.



Scheme 6. Synthesis of complex 3.

distances (2.15–2.42 Å) are comparable to those found in related complexes such as $[(p\text{-cymene})\text{RuCl}\{\eta^2-N,O-(1S,2R)$ amino-1,2-diphenylethanolato}],^[31] $[(p\text{-cymene})\text{RuCl}\{\eta^2-N,N-(1S,2S)-\text{TsDPEN}\}]$ (N,N-(1S,2S)-TsDPEN=(1S,2S)-Np-toluenesulfonyl-1,2-diphenylethylenediamine),^[32] and [(p-

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Figure 1. ORTEP drawing of **3**. Thermal ellipsoids are shown at the 40% probability level. The chloride anion and acetonitrile are not shown. Selected bond lengths [Å] and angles [°]: average Ru1A–C (p-cymene) 2.165, average Ru1B–C (p-cymene) 2.172, Ru1A–Cl1A 2.422(2), Ru1B–Cl1B 2.418(2), Ru1A–N1A 2.111(6), Ru1B–N1B 2.120(7), Ru1A–O1A 2.079(6), Ru1B–O1B 2.094(5), O1A–Ru1A–N1A 79.1(2), O1B-Ru1B-N1B 78.6(2), C11A-N1A-Ru1A 109.5(5), C11B-N1B-Ru1B 109.5(5), C12A-O1A-Ru1A 114.5(5), C12B-O1B-Ru1B 113.6(5), O1A···O1B 2.397.

cymene)RuCl{ η^2 -*N*,*O*-(1*S*,2*R*)-*N*-(4-biphenylmethyl)norephedrine}].^[33] The N-Ru-O bond angle (around Ru1A, 79.1(2)°; around Ru1B, 78.6(2)°) also closely resemble the reported values of 78.3(2)° in [(*p*-cymene)RuCl(η^2 -*N*,*O*-(1*S*,2*R*)-amino-1,2-diphenylethanolato)]^[30] and 80.6(8)° in [(*p*-cymene)RuCl(η^2 -*N*,*O*-(1*S*,2*R*)-*N*-(4-biphenylmethyl)norephedrine)].^[33]

2

3

5

6

Consistent with the structure, the ¹H NMR spectrum of **3** showed four ethylene proton signals of the ethanolamine group at $\delta = 2.34, 2.62, 3.16$, and 3.35 ppm. The ${}^{13}C{}^{1}H{}$ NMR spectrum showed two signals at $\delta = 63.1$ and 45.6 ppm for the ethanolamine group. The proton signal of the bridging hydrogen could not be located in the spectrum, presumably due to the exchange of this proton with those of water in solution. The solution NMR data are also consistent with mononuclear the complex [(p-cymene)RuCl(NH₂CH₂CH₂-OH)] or the situation that there is a fast equilibrium between complex 3 and the two monomeric complexes [(p-cymene)RuCl(NH₂CH₂CH₂OH)]+ and

 $[(p\text{-cymene})\text{RuCl}(\text{NH}_2\text{CH}_2\text{CH}_2\text{O})]$. In our view, conversion of **3** into only the mononuclear complex [(p-cymene)R- $\text{uCl}(\text{NH}_2\text{CH}_2\text{CH}_2\text{O}\text{H})]$ in a neutral aprotic solvent such as dichloromethane is unlikely because addition of a proton is required for the process. On the other hand, we cannot rule out the possibility that there is a fast equilibrium between complex **3** and the two monomeric complexes $[(p\text{-cyme-}ne)\text{RuCl}(\text{NH}_2\text{CH}_2\text{CH}_2\text{O}\text{H})]^+$ and $[(p\text{-cymene})\text{RuCl}-(\text{NH}_2\text{CH}_2\text{CH}_2\text{O})]$ in solution.

H/D exchange reactions with complex 3: With complex 3 in hand, we examined its catalytic performance in the H/D exchange reaction of phenethyl alcohol with D₂O. The H/D exchange reaction was performed neat at 80 °C in the presence of 3 mol% of the complex. Consistent with the screening results discussed above, complex 3 was found to be catalytically active for the regioselective H/D exchange reaction. Thus, deuterated 2-phenylethanol with 80% D at the βcarbon was obtained when a mixture of 2-phenylethanol, D₂O, KOH, and 3 (in a molar ratio of 1:7.24:0.15:0.03) was heated at 80 °C for 5.5 h. The deuterium content of 80% found at the β-carbon of 2-phenylethanol was very close to the theoretical maximum value of 82.1% (Table 3, entry 1).

To further demonstrate that complex **3** behaves in a similar way to the species generated in situ, H/D exchange reactions between D_2O and several other alcohols were investigated. The reactions were conducted with 3 mol% **3** and 15 mol% KOH, neat at 80 °C. As shown in Table 3, the performance of catalyst **3** was similar to that of the catalytic system [{(*p*-cymene)RuCl₂}]/ethanolamine.

Mechanistic considerations: A plausible pathway for the H/ D exchange reactions catalyzed by [{(p-cymene)RuCl₂]₂]/ ethanolamine/KOH is shown in Scheme 7, using 1-phenyle-

Table 3.	The H/D	exchange	reactions of	alcohols	with D ₂	O catal	vzed by	3 . ^[a]
					· · · · 2			

Substrate	D_{theo}	t	Product
	[%] ^[b]	[h]	D _{inc} [%] ^[c]
2-phenylethanol (S1)	82.1	5.5	80% CD ₂ OD
N-(2-hydroxyethyl)morpholine (82)	89.9	9.25	0 N_66% CD ₂ OD
N-(3-hydroxypropyl)morpholine (S11)	88.2	8	0 N_CD ₂ _OD
1-phenylethanol (S3)	82.7	6.5	OD CD ₃ 81%
1,2,3,4-tetrahydronaphthalen-1-ol (86)	89.2	6	OD CD ₂ 72%
tetrahydrofuran-3-ol (S12)	90.5	8.5	62% OD D ₂ C O O 49%

[a] Reagents and conditions: complex 3 (1.5 mol%), KOH (15 mol%), N₂, 80 °C in a Schlenk tube. [b] D_{theo} is the statistical percentage of D considering the hydrogen atoms associated with water, KOH and alcohols. [c] D_{inc} is the percentage of deuterium determined experimentally by ¹H and ²D NMR spectroscopic analysis.

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Scheme 7. Proposed mechanism for the H/D exchange reaction of alcohols.

thanol as an example. Because 3, which can be isolated from the reaction of $[\{(p-cymen)RuCl_2\}_2]$ with ethanolamine, has a performance similar to that of $[\{(p-cymen)RuCl_2\}_2]/$ ethanolamine in the catalytic reactions, we believe complex 3 is generated as a precatalyst in the reaction mixture. Complex 3 can react with KOH to give the alkoxyamido species 3A as the true catalyst. Complex 3A reacts with 1-phenylethanol to give hydride complex 3B and acetophenone through a six-membered cyclic transition state such as A, which is a generally accepted pathway for hydrogen transfer reactions. Acetophenone then undergoes H/D exchange with D₂O in the presence of KOH through keto–enol tautomerization. The deuterated acetophenone is then reduced by complex 3B to give deuterated 1-phenylethanol and the active species 3A is regenerated for the next reaction cycle.

In agreement with the proposed mechanism, acetophenone regioselectively deuterated at the β -carbon position was readily obtained by heating a mixture of acetophenone and D₂O in the presence of 20.7 mol% KOH at 80 °C. The result indicates that a H/D exchange reaction through ketoenol tautomerization can indeed proceed in the presence of a catalytic amount of KOH. The observation that tertiary alcohols do not undergo H/D exchange reactions also supports the proposed hydrogen transfer mechanism and eliminates a direct C–H bond activation mechanism.



Scheme 8. Correlation between the activity of alcohols towards H/D exchange reactions and the acidity of the protons of the corresponding carbonyl compound at the carbon adjacent to the carbonyl group.

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Consistent with the mechanism, the rate for deuterium incorporation into the substrates is closely related to the acidity of protons of the corresponding carbonyl compounds. H/ D exchange occurs less readily when an electron-donating group is attached to the β -carbon of the substrate alcohol. For example, 1-phenylethanol (Table 2, entry 3) underwent H/D exchange reaction more readily than cyclohexanol (Table 2, entry 8). The order of reactivity was determined to be the same as the order of acidity of the corresponding carbonyl compounds (Scheme 8).^[34]

Conclusion

We have developed a convenient method for regioselective H/D exchange between D_2O and alcohols at the β -carbon position using the catalytic system [{(*p*-cymene)RuCl₂]₂]/ ethanolamine/KOH.

The present H/D exchange reactions proceed through an oxidation/modification/reduction reaction sequence. Alcohols are first temporarily oxidized to carbonyl compounds by the hydrogen transfer catalyst. The carbonyl compounds then undergo deuteration at the carbon adjacent to the carbonyl group by keto–enol tautomerization in the presence of D_2O and a catalytic amount of base. The deuterated carbonyl compounds are then reduced to produce deuterated alcohols.

This method is applicable for deuteration of both primary and secondary alcohols. A well-defined bimetallic ruthenium precatalyst **3** was isolated from the reaction of $[{(p-cyme$ $ne)RuCl_2}_2]$ with ethanolamine. The activity of this complex is similar to that of $[{(p-cymene)RuCl_2}_2]$ /ethanolamine.

Experimental Section

All manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques unless otherwise stated. Solvents were distilled under nitrogen from sodium/benzophenone (*n*-hexane, diethyl ether, THF), sodium (benzene), or calcium hydride (dichloromethane). Other solvents were purged with nitrogen for 10 min before use. [(*p*-cymene)RuCl(NH₂CH₂CH₂NTs)]Cl (1),^[28] [RuCl₂(PPh₃)₂(ampy)] (**2**; ampy = 2-(aminomethylene)pyridine),^[29] and [[(η^6 -arene)RuCl₂]₂]^[35] were synthesized according to reported procedures. Deuterium oxide (99.9 atom % D), was purchased from Aldrich Chemical Co. and used as received. All other reagents were used as purchased from Aldrich Chemical Co., Acros Organics, International Laboratory USA, or Kodak. ¹H and ¹³C{¹H} NMR spectra were recorded with a Bruker AX 400 MHz spectrometer. ²D NMR spectra were recorded with a Bruker AV 400 MHz spectrometer.

General procedure for the H/D exchange reactions between alcohols and D₂O in the screening experiments (in NMR tubes): A mixture of ligand (2 equiv relative to [{(p-cymene)RuCl₂}₂]), [{(p-cymene)RuCl₂}₂] (9.2 mg, 15 µmol), KOH in D₂O (5.07 M, 29.5 µL, 0.15 mmol), phenylethanol (120 µL, 1.0 mmol), and D₂O (210 µL, 11.7 mmol) was heated at 80 °C for 2 h. The resulting solution was analyzed by ¹H NMR spectroscopy using CDCl₃ as the solvent.

General procedure for H/D exchange reactions between alcohols and D₂O catalyzed by [{(p-cymene)RuCl₂)₂/KOH/ethanolamine conducted on a preparative scale: Ethanolamine (36 μ L, 1.66 μ in D₂O, 60 μ mol), D₂O (397.5 μ L, total D₂O added=397.5 + 36 + 89=522.5 μ L,

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29.2 mmol) and KOH in D₂O (89 μ L, 3.38 M, 0.3 mmol) were added to a Schlenk tube charged with [{(*p*-cymene)RuCl₂]₂] (18.4 mg, 0.03 mmol) and 2-phenylethanol (240 μ L, 2.0 mmol). The mixture was heated at 80 °C for a defined period of time. The progress of the reaction was monitored by ¹H NMR spectroscopic analysis. When the reaction was complete, the product was extracted with diethyl ether, washed with water, and purified by column chromatography.

X-ray crystallographic analysis for 3: Crystals of 3 that were suitable for X-ray diffraction studies were obtained by cooling an acetonitrile solution of 3. Two molecules of CH₃CN co-crystallized with 3. The diffraction intensity data of 3 was collected with a Bruker Smart APEX CCD diffractometer with monochromated $Mo_{K\alpha}$ radiation ($\lambda\!=\!0.71073$ Å) at 100 K. Lattice determination and data collection were carried out by using SMART V.5.625 software. Data reduction and absorption correction were performed with SAINT V.6.26 and SADABS V.2.03. Structure solution and refinement were performed with the SHELXTL V.6.10 software package. It was solved by direct methods and refined by full-matrix least squares on F^2 . All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were introduced at their geometric positions and refined as riding atoms. The crystal data and refinement details are given in Table 4. CCDC-826106 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 4. X-ray crystallographic data for 3.2 CH₃CN.

formula	$C_{28}H_{47}Cl_3N_4O_2Ru_2$
$M_{ m r}$	780.19
λ [Å]	0.71073
<i>T</i> [K]	100(2)
crystal system	triclinic
space group	$P\bar{1}$
a [Å]	10.379 (2)
<i>b</i> [Å]	12.367 (3)
c [Å]	14.172 (3)
α [°]	97.136 (5)
β[°]	97.748 (4)
γ [°]	107.608 (4)
V [Å ³]	1691.6(6)
Ζ	4
$ ho_{ m calcd} [m Mgm^{-3}]$	1.532
F(000)	796
crystal size [mm ³]	$0.25 \times 0.10 \times 0.08$
θ range [°]	1.47 to 26.50
reflns collected	9656
independent reflns	6709 [R(int) = 0.0661]
final R indices $[I > 2\sigma(I)]$	$R_1 = 0.0631, wR_2 = 0.1388$
R indices (all data)	$R_1 = 0.1386, wR_2 = 0.1700$
largest diff. peak/hole [e Å ⁻³]	1.211/-1.320

General procedure for the preparative scale H/D exchange reactions between alcohols and D₂O catalyzed by complex 3: D₂O (0.17 mL, 9.38 mmol) and KOH in D₂O (2.0 M, 0.13 mL, 0.26 mmol) were added in subsequence to a Schlenk tube charged with complex 3 (20.0 mg, $25.9 \mu \text{mol}$) and 1-phenylethanol ($200 \mu \text{L}$, 1.66 mmol). The mixture was heated at 80 °C for a defined period of time. During the reaction, the progress was monitored by ¹H NMR spectroscopic analysis. When the reaction was complete, the product was extracted with diethyl ether, washed with water, and purified by column chromatography.

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