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Simple and Efficient Catalytic Reaction for the Selective Deuteration of Alcohols

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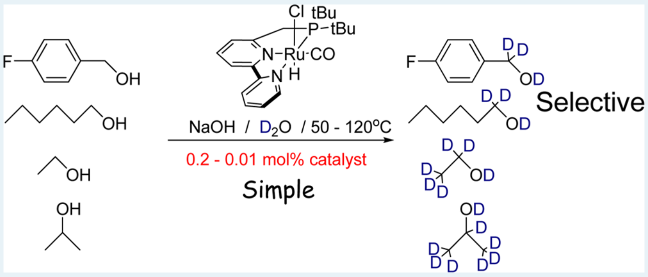
Supporting Information

ABSTRACT: A highly efficient system for the catalytic deuteration of α and β CH bonds of primary and secondary alcohols has been developed. The deuterium source is D_2O. Together with the low catalyst loadings and the simple experimental setup, the reaction has direct application to the synthesis of bioactive isotopologues and the direct synthesis of fully deuterated substrates, such as ethanol-d_6. The current system represents a significant advance in practicality for homogeneous metal catalyzed systems that carry out H/D exchange in organic substrates with water.



KEYWORDS: *H/D exchange, Ru pincer catalyst, alcohols, D_2O, selective deuteration, homogeneous catalysis*

Selective deuteration of alcohols is of importance for a range of uses, such as the preparation of deuterated pharmaceuticals and other biologically active compounds that have properties similar to their nondeuterated analogues, but would differ in rates of metabolism.[1] The alcohol functionality reacts with a broad range of enzymes, including dehydrogenase enzymes in the liver, producing aldehydes with often substantial kinetic isotope effects. Although the greatest use of selectively deuterated alcohols might be in biochemical enzymatic rate studies,[1a] uses in new materials may also become important.[1a]

A quick survey of the literature shows that even in recent articles,[2] authors use the reaction of esters or aldehydes with alkali metal deuteride salts to obtain the desired labeled alcohol. The prices of α-deuterated alcohols, relatively simple substrates such as benzyl alcohol-d_3, and even deuterated ethanol, can become prohibitive on large scales, but deuterated water, the original source of deuterium in all deuterated products, including metal deuteride reactants, remains inexpensive.[3]

Although catalytic deuteration of simple hydrocarbons by exchange with D_2O is an established reaction,[1] direct and selective catalytic deuteration of alcohols is more rare. Koch and Stuart reported on stereoselective deuteration of carbohydrate derivatives with large amounts of hot Raney nickel (>100 mol %), with some substrates being isomerized or remaining unreacted under the reaction conditions.[4] Cioffi reported a milder method of deuteration with Raney nickel by utilizing microwave and sonication methods.[5,6] However, because of the difficulty of preparing deuterated Raney nickel and the necessity of using >100 mol % metal with respect to the substrate, the method still suffers from serious drawbacks.

There are only a few reports on metal-catalyzed selective deuteration of alcohols.[7] The interesting heterogeneous system described by Sajiki[7c] uses high catalyst loadings, especially for primary alcohols (20 wt % Ru) and the reaction must be carried out under hydrogen atmosphere. Baratta reported an effective homogeneous system that utilizes osmium or ruthenium pincer catalysts[7a] at only 1% catalyst loadings, but requires deuterated isopropyl alcohol as solvent. Takahashi and Matsubara reported a homogeneous Ru-based system that under microwave irradiation gave good and selective deuterium incorporation at 5% catalyst loadings for alcohols.[7d] A molybdenum-based system shows poor activity for nonbenzylic substrates, and the benzylic ones require large amounts (5% and more) of catalyst.[7e,f] Yamada[8] reported a cobalt-catalyzed (1 mol % catalyst loading) reduction of aldehydes with $NaBD_4$ that leads to entantioselective deuteration at the α carbon position of the product alcohol. Using a homogeneous Ru system (3 mol % catalyst), deuteration exclusively at the β position of the substrate was recently reported.[9] All these reports concern monofunctional substrates, except for a recent report by Sajiki on the stereoselective α-deuteration of sugars[7b] using a heterogeneous Ru-based system (5 mol % loading) under hydrogen atmosphere.[7c]

We have previously reported on Ru-based pincer systems that catalyze transformation of alcohols and amines to esters, amides, imines, and other substrates in open, organic solvent systems while releasing H_2 gas [10] or perform the reverse reaction in a closed vessel under mild hydrogen pressure.[11] Here, we report on a selective deuteration system that utilizes D_2O as a deuterium source and an air-stable Ru precatalyst **1** (Figure 1) at low loadings (typically 0.2 mol %, but activity can be seen at 0.01 mol % loadings) in the presence of ~20 mol % NaOH. The experimental setup is a simple closed system that is heated to 50−120 °C, depending on the substrate, under

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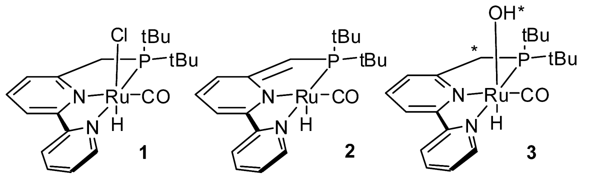


* these positions deuterated if D_2O is used

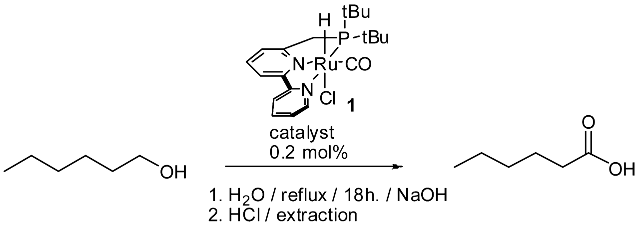
Figure 1. Ru-pincer complexes relevant to the current study.

nitrogen atmosphere. We find, however, that air can be used with no detrimental effects.

The crux of the discovery lies in the fact that unlike earlier systems reporting metal-catalyzed H/D exchange, our system is very practical. It can be used without large amounts of air-sensitive or expensive metal catalyst and can be envisaged as being adoptable for large scale synthesis of industrially relevant substrates. Upon complete deuteration, most alcohols can be easily separated from the reaction medium and the catalyst by neutralizing the reaction mixture and extracting the relevant alcohol in an organic solvent, such as diethyl ether. Smaller alcohols that form azeotropes with water, such as ethanol, need to be separated from water and dried using well established industrial and household methods.

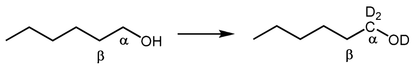
Significantly, similar conditions were utilized in our very recently reported catalytic transformation of primary alcohols to carboxylic acid salts, utilizing water as an oxygen source, with concomitant evolution of hydrogen gas (Scheme 1).[12] In the current work, the reaction is performed in a closed system, preventing dihydrogen removal from the reaction vessel, and often requires less than stoichiometric amounts of base and lower catalyst loadings, especially for secondary alcohols.

Scheme 1. Catalytic Transformation of Alcohols to Carboxylic Acids



In addition to low catalyst loadings and relative simplicity of use, our system is tolerant of a number of functional groups that do not react with aqueous warm base, including amines, unactivated double bonds and CF bonds.[13] Impurities are also well tolerated, as all substrates tested were used "as is" from the manufacturer's bottle without further purification. In a typical reaction, 0.2% of the catalyst and 20% NaOH was put into a 2.5 mL NMR Young tube, to which the substrate and 0.4 mL of D_2O were added (note: higher loadings of D_2O lead to higher deuteration percentages). The reaction conditions were optimized for the substrate 1-hexanol, for which the optimal conditions led to full (highest percentage possible) deuteration at the α carbon and small amounts of side deuteration at the β position (Table 1). Temperature and amount of base play a significant role in the selectivity, with the optimal conditions differing depending on the substrate. For 1-hexanol, 10% NaOH loadings gave the best selectivity, but reactivity was slightly compromised. Really high base loadings (≥110%) showed that it is possible to get significant deuteration at the β position, albeit with a side reaction producing ~1% sodium hexanoate. In an open system, with evolution of hydrogen gas, sodium hexanoate would be the major product as per our recent report (Scheme 1).[12] It is easy to separate out this byproduct by performing a simple extraction in an organic solvent, such as diethyl ether, of the alcohol substrate, with the acid salt remaining in the aqueous layer. However, in most cases when the base loading is less than 100 mol %, a very small trace of acid salt is obtained, or it is not detected.

Table 1. Optimization with 1-Hexanol[a]



entry	conditions	deuteration (% yield) α; β (max % yield)
1	1 mol % **2**, 120 °C, 24 h	0; 0 (96.5)
2	10 mol % **2**, 120 °C, 24 h	80; 0 (96.5)
3	0.2 mol % **1**, 110 mol % NaOH, 120 °C, 24 h	94; 20 (94.1)[b]
4	0.2 mol % **1**, 10 mol % NaOH, 120 °C, 24 h	78; 0 (96.5)
5	1 mol % **1**, 300 mol % NaOH, 120 °C, 24 h	94; 14 (94.1)[b]
6	no catalyst, 110 mol % NaOH, 120 °C, 24 h	no deuteration
7	0.2 mol % **1**, 20 mol % NaOH, 120 °C, 24 h	92; 10 (94.1)
8	as in entry 7 under air, 0.1 mol % **1**	90; 10 (94.1)[b]

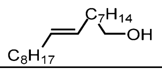
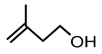
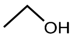
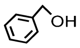
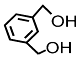
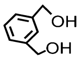
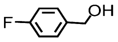
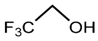
[a] Yields obtained by NMR via integration of unreactive CH_3 groups or dioxane internal standard. In parentheses is the theoretical maximum/equilibrium deuteration possible with 0.4 mL of D_2O. [b] Trace (~1%) of sodium hexanoate was also formed.

For most applications, the presence of deuterium in the β position is not deleterious, and thus, we decided to utilize the optimal 1-hexanol conditions (Table 1; entry 7) for most of the primary alcohols. These conditions led to the full deuteration of ethanol in both the α and β positions, which is particularly interesting if the desired product is ethanol-d_6 (Table 2; entry 3). A number of functional groups proved to be tolerant to the deuteration conditions. For example, the amine substrate (Table 2; entry 7) showed no deuteration at the carbons next to the amine moiety, as checked by deuterium NMR, although the overall deuteration at the alcohol was limited to only ~35%, meaning that for the amine entry, the catalytic efficiency was compromised.

Secondary alcohols proved much more active (Table 3). At room temperature, some deuteration at the α position was already in evidence after 3 h; however, most of the precatalyst remains insoluble and, thus, unactivated at room temperature. Heating to 50 °C overnight allowed for full catalyst activation and subsequent full deuteration of both the α and β positions. Thiols and very electron-poor alcohols, such as CF_3CH_2OH, showed almost no activity in deuteration, probably because of a stronger Ru−O or Ru−S bond that stabilizes an intermediate species. In contrast, electron-rich alcohols, including electron-rich benzyl alcohol and 1,3-bis(hydroxymethyl)benzene, gave full deuteration after just 18 h of heating under the standard primary alcohol conditions.

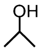
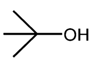
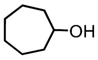
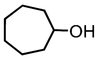
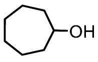
Base is essential for the reaction to proceed under low catalyst loading, although it was found that the activated complex **3**, prepared by the reaction of dearomatized **2** with D_2O,[14] could catalyze the deuteration of 1-hexanol at 10 mol %

Table 2. Deuteration of Primary Alcohols[a]

Entry	Substrate	Conditions	Deuteration (%yield) α ; β (max %yield)
1		0.2mol% **1** 20mol% NaOH 120°C 24 hrs	25 ; 20 (94.1)
2		as in entry 1	14 ; ~2 (96.5)
3		0.2mol% **1** 20mol% NaOH 120°C 40 hrs	~93 ; ~93 (92.9)
4		as in entry 1	~96.5 ; --- (96.5)
5		as in entry 1	~93 ; --- (92.9)
6		no catalyst 20mol% NaOH 120°C 24 hrs	no deuteration
7		as in entry 1	36 ; 34 (91)
8		as in entry 1	~96.5 ; --- (96.5)
9		1mol% **1** 20mol% NaOH 135°C 40 hrs	18 ; --- (96.5)

[a] See Table 1, footnote a.

Table 3. Deuteration of Secondary Alcohols[a]

Entry	Substrate	Conditions	Deuteration α ; β (max %yield)
1		0.2mol% **1** 20mol% NaOH 50°C 40 hrs	~92 ; ~92 (91.9)
2		0.2mol% **1** 20mol% NaOH 120°C 24 hrs	no deuteration
3		0.2mol% **1** 20mol% NaOH 50°C 60 hrs	~93 ; ~93 (92.9)
4		0.2mol% **1** 20mol% NaOH 120°C 24 hrs	~93 ; ~93 (92.9)
5		0.01mol% **1** 20mol% NaOH 120°C 36 hrs	~97 ; ~97 (97.1)
6	α-D-Glucose	as in entry 1	decomposition

[a] See Table 1, footnote a.

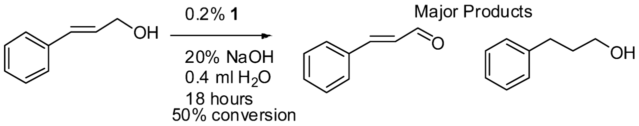
loading in the absence of added base. Introducing 20 mol % of base to 0.2 mol % of **3** allowed deuteration to take place as well, although slightly less efficiently than by utilizing precatalyst **1**. We believe that although **3** and no other complex is always visible in ^{1}HNMR throughout the reaction, no matter if **1** or **3** is used as the initial catalytic species, the difference in reaction outcome is due to the fact that water-insoluble **1** is activated slowly over time with NaOH, thus creating a steady amount of active catalyst. However, we do not have evidence that **3** decomposes to any other inactive species.

Although 0.2 mol % catalyst was used for convenience, because it is difficult to weigh out very small amounts of the catalyst and it is insoluble in water so a stock solution cannot be used, the catalyst loading can be substantially reduced when working on larger scales without sacrificing reactivity. Thus, a reaction with 0.01 mol % of **1** carried out on a large amount of cycloheptanol with 2 mL of D_2O, both of which enabled an amount of solid catalyst to be weighed out that equaled 0.01 mol %, gave full deuteration at both the α and β positions after 36 h of heating at 120 °C.

By utilizing a number of different substrates, we gained insight into the possible catalytic mechanism. When carrying out the catalytic reaction of hexanol in a vessel with a large amount of headspace volume (i.e., "open system") with H_2O, a large sample of the gaseous phase showed the presence of hydrogen in GC/TCD. However, the open system led to large amounts of carboxylic acid salt being observed, probably because of the inability of hydrogen to recombine with intermediate aldehyde before its capture by OH^- and further dehydrogenation.

Although no trace of aldehyde was detected with 1-hexanol, systems that produce relatively stable conjugated aldehydes that have time to react via a different pathway proved the intermediacy of aldehydes. Thus, crotyl alcohol decomposed into the retro-aldol condensation product acetaldehyde under the reaction conditions, which was detected by NMR. Cinnamic alcohol underwent 50% decomposition to give cinnamic aldehyde and 3-phenyl-propanol as major products (Scheme 2) and the minor products benzaldehyde and benzyl alcohol.[15] When D_2O was utilized, the remaining non-decomposed cinnamic alcohol was found to be fully deuterated at the α position.

Scheme 2. Decomposition of Cinnamic Alcohol under Catalytic Reaction Conditions

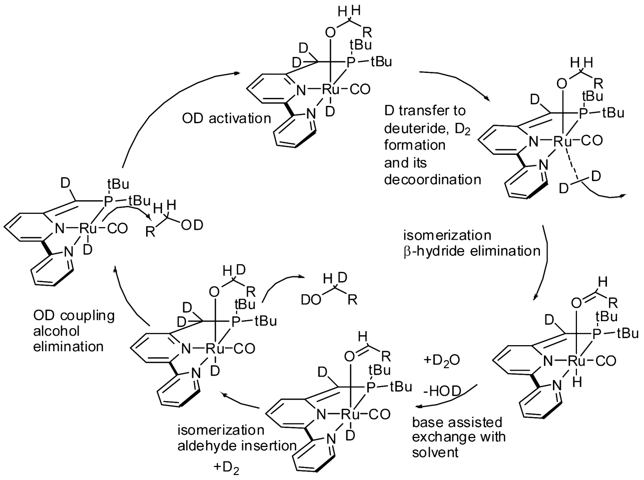


The major products of decomposition suggest that the mechanism proceeds through dehydrogenation to an aldehyde and H_2, with the latter reacting via the complex with cinnamic alcohol to form 3-phenylpropanol. In contrast, when cinnamic aldehyde was used as a starting material under the standard reaction conditions, benzaldehyde was formed as the only major product with acetaldehyde detected by NMR and no further minor products.

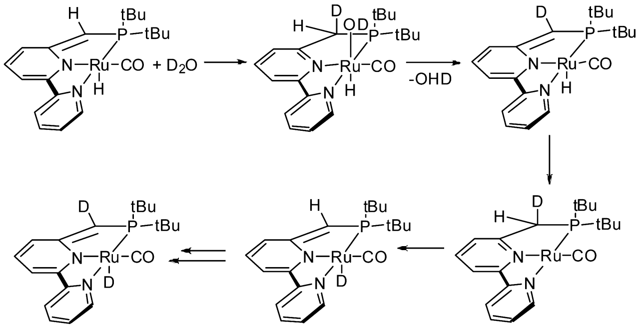
A possible catalytic cycle for the deuteration reaction is shown in Scheme 3, and a mechanistic scheme for deuterium scrambling into all positions of the complex is provided in Scheme 4, where an intermediate Ru(0) complex may be responsible for deuterium scrambling into the metal hydride position.

^{1}H NMR of the ethanol deuteration taken during the reaction clearly indicated the presence of geminal coupled H peaks (J_{HD} ~ 2.5) in both the α and β positions. Thus, the substrate was sequentially deuterated at each position and showed the presence of CHD groups. However, 4-amino-butanol, which did not reach the theoretical deuteration maximum, displaying only 35% of deuteration in both the α and β positions after 40 h at 120 °C even though **3** was still present in solution, showed only the presence of either CH_2 or CD_2 groups, but never CHD. ^{2}D NMR showed the presesnce

Scheme 3. Possible Catalytic Cycle



Scheme 4. Pathway for Deuterium Scrambling into Complex 2



of only two aliphatic peaks corresponding to the α and β CH_2 groups.

The cycle in Scheme 3 can help explain the preference for either CHD intermediates or for the direct CD_2 formation. The intermediacy of a coordinated aldehyde and its lifetime will directly affect the presence of either one species or another. A short-lived aldehyde-bound complex that rapidly undergoes β hydride insertion to form the parent alcohol and is then quickly released will give one deuterium at the α position. Depending on whether this alcohol is quickly released or reverts back to the bound aldehyde, CHD can be observed as an intermediate outcome, or CD_2 is directly formed after just one catalytic cycle in the α position. The exact result will depend on the equilibria between the species.

A sterically hindered or otherwise long-lived aldehyde may also dissociate and undergo H/D exchange at the β positions via keto/enol tautomerism. An example is 4-aminobutanol, which shows only the presence of CD_2 at the β carbon, or more sterically demanding secondary alcohols, which are deuterated nonselectively. Decoordination of the aldehyde intermediate may also be promoted by a higher concentration of NaOH because the selectivity in deuteration of 1-hexanol between the α and β positions is diminished upon reaction with ≥110 mol % of base.

These results mean that in all cases, deuteration proceeds via a temporary transformation of the alcohol to a carbonyl species, and stereochemical information would thus be lost. Therefore, the current method is not appropriate for chiral alcohols, unlike the Sajiki mothod,[7b] which proceeds by a fundamentally different mechanism, but that would be difficult to implement practically, despite its heterogeneous nature, because of high Ru loading and a requirement for a hydrogen atmosphere. Stereochemical information is also lost in the α position in β-selective deuteration in the system developed by Jia and co-workers.[9]

In conclusion, we have developed a catalytic deuteration reaction of primary and secondary alcohols under simple conditions with low catalyst loadings and utilizing D_2O as the deuterium source. The reactions can be run under air. We believe this reaction will be of significant utility because it represents a simple way to produce substrates deuterated at the α CH_2 position, useful for kinetic studies. For a particular substrate that is desired in large amounts, it should be optimized with regard to the amount of base and reaction time because these were found to vary in optimality depending on the substrate. Simple substrates that can be further used as NMR solvents, such as ethanol and isopropyl alcohol, are also efficiently deuterated. We believe that complex **1** is a highly practical and a highly active green catalyst for H/D exchange and alcohol to carboxylic acid salt transformation catalysis.[12]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures, synthesis details of **3**, sample relevant NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org. A typical catalytic procedure is available in ref 16.

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Notes

The authors declare no competing financial interest.

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(13) Very recently, selective deuteration of tertiary amines catalyzed by the Shvo Ru catalyst (using a catalyst loading of 5% for the optimized reaction conditions) has been reported: Norbert, L.; Michalik, D.; Baehn, S.; Imm, S.; Neumann, H.; Atzrodt, J.; Derdau, V.; Holla, W.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 12239−44.

(14) Characterization of complex **3** is available in the Supporting Information. For another PNN−Ru(H)(OH) complex implicated in water splitting, see: Kohl, S. W.; Weiner, L.; Schwartsburd, L.; Konstantinovski, L.; Shimon, L. J. W.; Ben-David, Y.; Iron, M. A.; Milstein, D. *Science* **2009**, *324*, 74−7.

(15) Some other minor products formed during the course of the reaction included hydrocarbons that are identified only by their GC/MS spectra, contain a C3 tail, and are as of yet unexplained, since they cannot result from decarbonylation reactions; they may be of interest as an example of CO cleavage in organic substrates. However, they represent <2% of total products, and we cannot adequately explain the mechanism by which they form, except to note their presence. It is worthwhile to further explore the reactivity of complex **3** in this direction at a later time.

(16) Typical catalytic procedure: In a typical experiment, 0.5 mg of complex **1** (0.001 mmol) and 100 equiv of NaOH (4.2 mg; 0.1 mmol) were added to a J. Young NMR tube; 500 equiv of substrate alcohol (0.5 mmol) was subsequently added as well as 0.4 mL of D_2O. The Young tube was closed, leaving ~2.5−3 mL of free headspace volume. The tube was then immersed in an oil bath preheated to 120 °C and left for 18 h. Before and after, ^1H NMR spectra were used to compare the level of deuteration if nondeuterable CH_2 or CH_3 groups were present in the molecule. For substrates such as ethanol, 1,4 dioxane (5 μL) was added as an internal standard, and the intensity of the peaks was compared with the standard.