

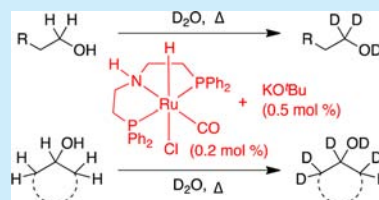
Ruthenium Catalyzed Selective α - and α,β -Deuteration of Alcohols Using D₂O

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Supporting Information

ABSTRACT: Highly selective ruthenium catalyzed α -deuteration of primary alcohols and α,β -deuteration of secondary alcohols are achieved using deuterium oxide (D₂O) as a source of deuterium and reaction solvent. Minimal loading of catalyst (Ru-macho), base (KO^tBu), and low temperature heating provided efficient selective deuteration of alcohols making the process practically attractive and environmentally benign. Mechanistic studies indicate the D–O(D/R) bond activations by metal–ligand cooperation and intermediacy of carbonyl compounds resulting from dehydrogenation of alcohols.



Synthesis of deuterium labeled alcohols with a high percentage of deuteration and selectivity is an important transformation in organic synthesis, as deuterated pharmaceuticals and bioactive organic molecules play a vital role in the metabolism of alcohols and enzymes, in addition to the regular use as NMR solvents and also as reliable chemical probes.¹ All the deuterium atoms present in the commercially available or synthesized chemicals are either directly or indirectly derived from deuterium oxide. Selectively deuterated alcohols are currently synthesized from elongated multistep procedures using reductive reagents such as NaBD₄, LiAlD₄, and SiDMe₂Ph/F[−] from aldehyde or carbonyl derivatives of alcohols, which result in enormous hazardous waste, and the cost of the deuterated alcohols becomes prohibitively high.² Thus, direct synthesis of selectively deuterated alcohols from H/D exchange reactions with cheap deuterium oxide is highly attractive.

Selective efficient deuteration and activation of CH bonds under mild reaction conditions is a tantalizing task.^{3–5} Iridium³ and molybdenum⁴ based catalytic systems were reported, and they required a higher loading of catalyst (5 mol %). While Ir-catalyzed deuteration of alcohols required expensive benzene-d₆ as a deuterium source (reaction solvent), a Mo-based catalyst is effective for only benzylic protons of alcohols.⁴

Both homogeneous and heterogeneous ruthenium catalysts received great attention for the H/D exchange reaction of alcohols.⁵ Ru on carbon support is reported to catalyze selective deuteration of the protons at the α -position of alcohols with the catalyst loading of 20% of Ru (relative to the substrate) and under the atmosphere of hydrogen.^{5d} Ru and Os pincer complexes catalyzed the selective deuteration of alcohols using 2-propanol-d₈ as the deuterium source.^{5b} Under microwave irradiation, a Ru-based soluble catalyst provided selective deuteration of alcohols with a 5% catalyst load.^{5e} Exclusive deuteration at the β -positions also occurred with 3 mol % of an *in situ* generated Ru catalyst ligated by aminoalcohol.^{5f}

Very recently, Milstein reported an interesting selective deuteration of alcohols catalyzed by a bipyridine derived PNN (6-di-*tert*-butylphosphinomethyl-2,2'-bipyridine) ruthenium

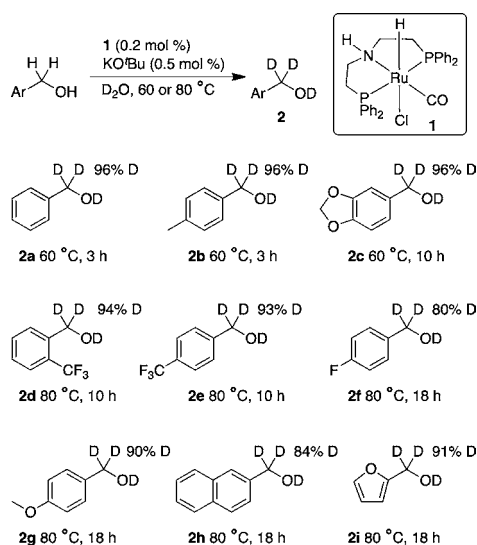
pincer complex,^{3a} which exhibited remarkable reactivity as a result of metal–ligand cooperation.⁶ However, in general ruthenium catalyzed deuteration of alcohols required high temperature—refluxing deuterium oxide conditions (120–150 °C) and a higher loading of base (15 to 20 mol % relative to substrate). Except for the Milstein system, all other ruthenium catalyzed H/D exchange reactions also require a higher loading of catalyst (1–20 mol %).⁵ The Ru-macho catalyst, which exhibits amine–amide metal–ligand cooperation, is reported to catalyze a wide range of organic transformations including dehydrogenation of methanol under aqueous basic conditions.⁷ Inspired by these reports, we explored the H/D exchange of alcohols using the Ru-macho catalyst. Herein, we report the facile and highly efficient selective α -deuteration of primary alcohols, and the selective α,β -deuteration of secondary alcohols catalyzed by Ru-macho using deuterium oxide.

At the outset, deuteration of aryl methyl alcohols was tested. When benzyl alcohol (0.5 mmol) was reacted with the Ru-Macho catalyst (0.2 mol %) with KO^tBu (0.5 mol %) in deuterium oxide, a facile and highly selective α -deuteration is observed at 60 °C. While 96% deuteration occurred at the α -position to provide benzyl alcohol-d₃ in only 3 h, no detectable H/D exchange is observed with aryl protons.⁸ Under similar experimental conditions catalyst 1 selectively deuterated the α -CH₂ protons of other benzyl alcohols such as 4-methylbenzyl alcohol and piperonyl alcohol (Scheme 1). Other aryl methanols and heteroaryl methanols required heating the reaction mixture at 80 °C for a prolonged period. The percentage of deuterium also largely depends on the substrate; the reaction conditions may be further optimized for the individual alcohols to obtain higher deuteration. Upon completion of the reaction, the α -deuterated alcohols were easily separated from the reaction mixture by extraction with dichloromethane.

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Scheme 1. Selective α -Deuteration of Aryl Methanols Catalyzed by Ru-macho 1^a



^aConditions: Alcohol (0.5 mmol), catalyst **1** (0.001 mmol), KO^tBu (0.0025 mmol), and D₂O (0.4 mL, 20 mmol) were charged in a screw cap NMR tube under a nitrogen atmosphere, and the reaction mixture was heated at the indicated temperature. The percentage of deuterium incorporation was monitored by integration of residual signals of ¹H NMR spectroscopy. Maximum possible % deuteration for these aryl methanols is 96.4%.

Deuteration of linear aliphatic alcohols catalyzed by **1** is investigated and the results are summarized in Table 1. In

Table 1. Selective α -Deuteration of Linear Alcohols^a

entry	alcohol	time (h)	temp (°C)	α : β (%) deuteration
1 ^b		24	100	87; 86
2		18	80	94; 9
3		12	80	94; 12
4		16	80	92; 12
5		16	80	92.5; 10
6		5	80	90; 10
7		18	80	95; 20
8		20	80	66
9		12	80	95.5; --
10		10	80	95; --

^aConditions: as indicated in the footnote of Scheme 1. ^b1,4-Dioxane (0.05 mmol) is used as an internal standard.

general, aliphatic alcohols, Ru-macho **1** (0.2 mol %), and KO^tBu (0.5 mol %) in deuterium oxide are heated at 80 °C over the period indicated. Linear alcohols such as 1-butanol, 1-hexanol, 1-heptanol, and 1-octanol underwent facile deuteration predominantly at the α -position (92 to 94%); however, among these alcohols deuteration at the β -position of alcohols is also observed in the range of 9–12% (Table 1, entries 2–5). Progress of the α -

deuteration of 1-butanol catalyzed by **1** in D₂O is monitored using ¹H NMR spectroscopy (Figure 1a). However, when

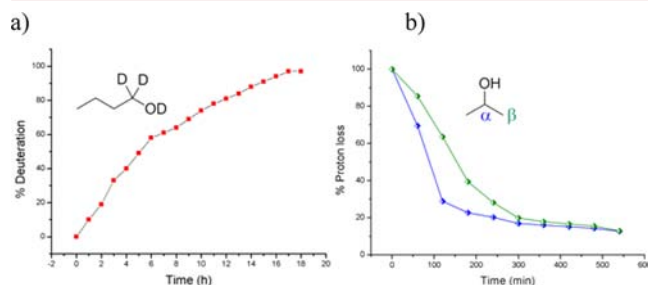


Figure 1. (a) ¹H NMR monitoring of % D incorporation in α -position of 1-butanol (0.5 mmol) in D₂O (0.4 mL). Integration of α -position is done taking integration of δ -CH₃-protons of 1-butanol as a standard. (b) ¹H NMR monitoring of rate of proton loss of 2-propanol at 80 °C.

ethanol was subjected to the reaction, deuteration occurred nonselectively; 87% and 86% deuteration were observed at the α - and β -positions of ethanol, respectively (Table 1, entry 1).

Linear alcohols appended with aryl and heteroaryl ring systems provided selectivity for α -deuteration in the range of 90–95% (Table 1, entries 6–7), while 10–20% β -deuteration occurred as observed similarly in other linear alcohols. Selective α -deuteration alone was also observed for functionalized and sterically hindered alcohols (Table 1, entries 8–10).

Further to expand the substrate scope, diols were tested in the selective deuteration reaction catalyzed by Ru-macho catalyst **1**. Benzene-1,4-dimethanol and pyridine-2,6-dimethanol were reacted with **1** (0.2 mol %) and KO^tBu (0.5 mol %) and D₂O, which delivered the corresponding (both α -positions)-deuterated diols. No detectable deuterium incorporation among aryl protons was observed (Figure 2). Surprisingly, when acyclic diols

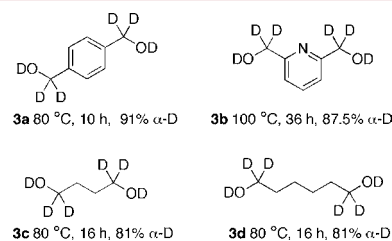


Figure 2. Selective α -deuteration of diols.

such as 1,4-butanediol and 1,6-hexanediol were subjected to deuteration under standard conditions, deuteration occurred selectively only at both α -positions to the hydroxyl functionality (81%). No deuteration was observed at the β -positions of these substrates (Figure 2).

Upon reaction with Ru-macho **1** under standard reaction conditions, secondary alcohols underwent efficient deuteration at both α - and β -positions, contrary to the α -selective deuteration observed in primary alcohols. Perhaps the intermediate ketones were more long-lived than aldehydes, resulting in the effective β -deuteration by H/D exchange via keto–enol tautomerism and the subsequent hydrogenation providing α,β -deuterated secondary alcohols. 2-Propanol underwent 88% and 87% α,β deuteration, respectively (maximum possible deuteration is 90.9%, Table 2, entry 1). The incorporation of deuterium in the α,β -positions of 2-propanol was unambiguously demonstrated by monitoring the progress of the H/D-exchange

Table 2. Selective α,β -Deuteration of Secondary Alcohols^a

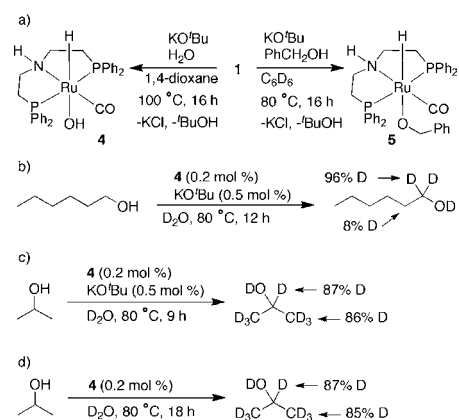
entry	diol	time (h)	temp (°C)	α ; β (%) deuteration
1 ^b		9	80	88; 87 (90.9)
2		12	80	94; 94 (94)
3		10	80	80; 10 (92)
4		12	80	97 (97.6)
5		10	80	90; 89 (93)
6		12	80	90; 89 (93)
7		16	80	86; 85 (93)

^aConditions: as indicated in the footnote of Scheme 1. ^b1,4-Dioxane (0.5 mmol) is used as an internal standard. Maximum possible % deuteration of substrates is given in the parentheses.

reaction (Figure 1b). 1-Phenylethanol exhibited both α,β deuteration at 94% (entry 2). While 2-hexanol showed predominantly selective α -deuteration like linear alcohols, diphenylmethanol provided 97% α -deuteration. Under the standard experimental conditions, cyclic secondary alcohols also afforded effective α,β -deuteration with excellent selectivity and efficiency (Table 2, entries 5–7).

Stoichiometric reactions were performed to obtain mechanistic insight. Upon reaction of complex 1 with water and base, a Ru(II) complex 4 (³¹P NMR δ = 57.3 ppm) with a hydroxyligand is obtained (Scheme 2a).⁹ A similar reaction of 1 with

Scheme 2. Synthesis and Reactivities of Intermediates



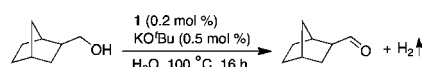
benzyl alcohol provided benzyloxy-ligated complex 5; interestingly, the presence of a benzaldehyde coordinated ruthenium complex (9%) is also found in the reaction mixture.¹⁰ These reactions involve a base promoted, in situ formed unobserved amide-ligated unsaturated intermediate (6, Scheme 4), which reacted with H₂O and BnOH to provide 4 and 5, respectively, as a result of O–H activation by metal–ligand cooperation.^{6,11}

When isolated complex 4 (0.2 mol %) is used as a catalyst in the presence of base using D₂O, selective 96% α -deuteration of 1-hexanol (Scheme 2b, along with 8% D at the β -position; see Table 1, entry 3) and 87% and 86% α,β -deuteration of 2-propanol occurred in 12 h and 9 h, respectively (Scheme 2c; see

Table 2, entry 1). These observations indicate the comparable reactivity of Ru–OH complex 4 compared to that of Ru-macho catalyst 1 and its potential involvement in the reaction. In principle, complex 4 does not require a base to catalyze the H/D exchange reaction between alcohols and D₂O. Thus, deuteration of 2-propanol was carried out using 4 under neutral conditions. As anticipated, the reaction proceeded in the absence of a base; however only after 18 h similar % deuteration as that of basic conditions was obtained (Scheme 4d). This observation indicates that a base may promote the H/D exchange reactions with a solvent and catalytic system in one or more steps.

Attempts were made to observe the intermediates, if any, from alcohol dehydrogenation during the catalysis.¹² When 2-norbornanemethanol was reacted with H₂O using catalyst 1 (0.2 mol %) and base (0.5 mol %) under open conditions, formation of the corresponding aldehyde was observed in the reaction mixture (Scheme 3).¹³ Since the reaction is performed

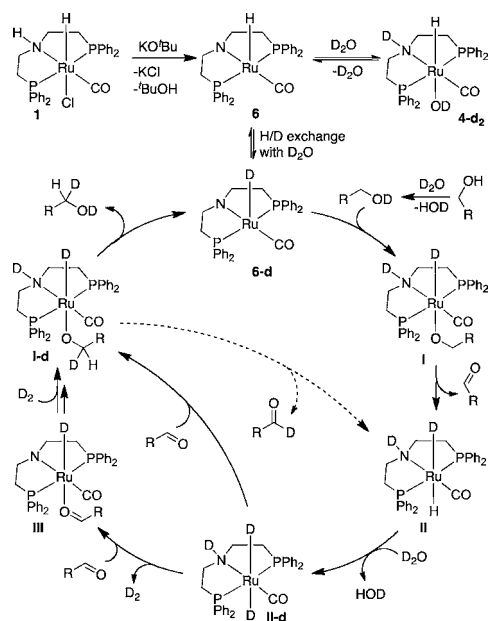
Scheme 3. Dehydrogenation of 2-Norbornanemethanol by 1



with a minimal amount of base using water as a solvent, potential competing pathways such as subsequent dehydrogenation of aldehyde to carboxylic acid¹⁴ or coupling with alcohol to provide the corresponding self-coupled esters^{7d} are minimized and the formation of intermediate aldehyde in the reaction mixture was observed (Scheme 3).

Although more evidence is required based on the above observations, a possible catalytic cycle for the selective deuteration of alcohols is postulated in Scheme 4. The reaction

Scheme 4. Proposed Catalytic Cycle



of complex 1 with a base provided the unsaturated Ru(II) intermediate 6, which reacts with D₂O by “amine–amide” metal–ligand cooperation^{6,10} and results in complex 4-d₂ as observed in the reaction of complex 1 with H₂O (Scheme 2). Under experimental conditions, 6 is in equilibrium with 4-d₂ and 6-d by O–D activation or Ru–H/D exchange with D₂O,

respectively. Perhaps, base assisted H/D exchange or involvement of a Ru(0) intermediate cannot be ruled out, which may also play a crucial role in the deuterium scrambling. Complex **6-d** further reacts with alcohols (RCH₂OD) to provide saturated intermediate **I** (as observed in stoichiometric reaction, Scheme 2a). Further, β -hydride elimination of alkoxide ligand can result in Ru-dihydride **II**. Base assisted Ru–H/D exchange of **II** with solvent (D₂O) provides **II-d**. Either by direct aldehyde insertion into a Ru–D bond of **II-d** or by D₂ liberation followed by aldehyde coordination (**III**)/decoordination pathways, monodeuterated alkoxy-ligated intermediate **I-d** was generated. Reductive elimination of alcohols from intermediate **I-d** can provide alcohols with monodeuteration at the α -position, regenerating **6-d** to complete one cycle. Alternatively, **I-d** may also undergo β -hydride elimination to result in **II** and the subsequent transformations would result in **I-d₂** that can reductively eliminate alcohols with complete deuteration at the α -position of alcohols (RCD₂OD).

In conclusion, Ru-macho catalyzed highly efficient selective deuterations of assorted primary and secondary alcohols are developed using deuterium oxide, the cheapest source of deuterium. While primary alcohols underwent deuteration predominantly at the α -position, the secondary alcohols were deuterated at both α - and β -positions. The reaction proceeded by O–D activation of deuterium oxide and alcohols by the Ru-macho catalyst, and subsequently the alkoxide ligands were dehydrogenated to the carbonyl compounds via amine–amide metal–ligand cooperation. While the catalytic hydrogenation of the carbonyl motif resulted in α -deuteration, β -deuteration perhaps occurred via keto–enol tautomerization, which was varied based on substrate and steric hindrance. High percentage selective deuteration, mild experimental conditions, and the low loading and commercial availability of the catalyst make the process highly attractive for both laboratory and large-scale preparation of useful deuterated alcohols.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.5b02254](https://doi.org/10.1021/acs.orglett.5b02254).

Experimental Procedures, ¹H, ²H, ¹³C, and ³¹P NMR spectra and characterization data of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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