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A Convenient and Effective Method for the Regioselective Deuteration of Alcohols

Tomohiro Maegawa,[a] Yuta Fujiwara,[a] Yuya Inagaki,[a] Yasunari Monguchi,[a] and Hironao Sajiki[a,*]

[a] Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, Mitahora-higashi, Gifu 502-8585, Japan
Fax: (+81)-58-237-5979; e-mail: sajiki@gifu-pu.ac.jp

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Abstract: The convenient and regioselective deuteration of hydroxy groups on vicinal carbons was achieved by the combination of 5% ruthenium on carbon (Ru/C), hydrogen gas and deuterium oxide (D_2O).

Keywords: alcohols; deuteration; heterogeneous catalysis; regioselectivity; ruthenium

Deuterium-labeled compounds are highly useful in a variety of scientific fields including the analysis of metabolism, reaction mechanisms and kinetics.[1] The new utilization of deuterated compounds is also increasing in the material and analytical science fields such as the raw material of optical fibers[2] and the internal standard for quantitative analysis.[3] According to the new demand for suitably deuterated compounds, the development of diverse and selective synthetic methods of deuterated materials is desired.

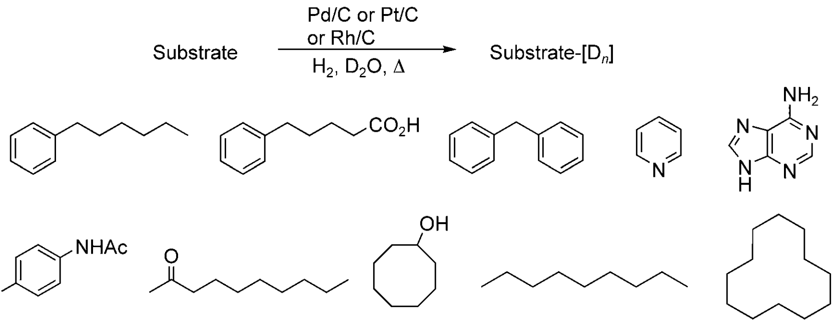
Deuterium-labeled alcohols can be widely utilized in the biochemistry and biophysical fields,[4] especially, deuterated carbohydrates and glycoconjugates play pivotal roles in revealing the mechanisms of cell recognition and receptor functions.[5] Regioselectively deuterated compounds are applicable for the conformational analysis of complex molecules using ^{1}H NMR spectroscopy because of the simplified spectrum[6] and the elucidation of the chemical or enzymatic reaction pathways.[7] Conventional methods to prepare regioselectively deuterated alcohols involve reduction with metal deuteride reagents ($NaBD_4$ and $LiAlD_4$, etc.) or the deuterogenation with D_2 gas of unsaturated compounds,[8] although the construction of the starting substrates for the reductive deuteration may require several steps. On the other hand, the H–D exchange reaction is an easy and straightforward way to obtain regioselectively deuterated alcohols using the target compound itself as a substrate. Efficient and simple methods to substitute a hydrogen with a deuterium on the C–H bond on carbon atoms vicinal to hydroxy groups in carbohydrates have been reported using Raney Ni in D_2O with heat,[9] ultrasonication[10] and microwave irradiation.[11] Other transition metals such as Ru[12] and Mo[13] can also catalyze the regioselective deuterium incorporation at the α-position to hydroxy groups, but these methods often require harsh reaction conditions with an unsufficient deuterium efficiency.

We have recently established the efficient and multiple deuteration of various organic molecules catalyzed by a heterogeneous platinum metal group system such as Pd/C,[14] Pt/C[15] and Rh/C[16] in D_2O under an H_2 atmosphere (Scheme 1).

During the continuous study to further improve deuteration methods, we developed the regioselective deuterium incorporation method of alcohols catalyzed by Ru/C in the presence of H_2 gas in D_2O with a high deuterium efficiency. We now report the regioselective deuteration at the α-positions to hydroxy groups under mild reaction conditions.

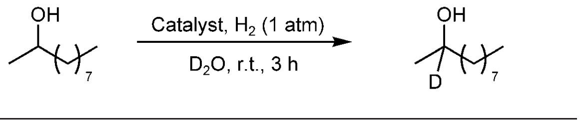
We first examined the catalyst efficiency of several activated carbon-supported metal catalysts using 2-decanol as the substrate (Table 1). Only Ru/C was effective for the reaction, and regiospecific and efficient deuterium incorporation was achieved at the α-position at room temperature in 3 h.

The metal content of the heterogeneous catalyst is important to achieve an efficient deuterium incorporation (entries 5–7) and 20 wt% (vs. substrate) of 5% Ru/C gave the best result. The application of heat accelerated the deuteration and the reaction was completed within only 1 h at 50 °C. Regioselective deuterium incorporation on the vicinal carbon of the secondary alcohol was achieved in a nearly quantitative efficiency (Table 2, entries 1–4). Only 2-adamantanol



Scheme 1. Deuteration by the Pd/C (Pt/C or Rh/C)-H_2-D_2O system of various organic molecules.

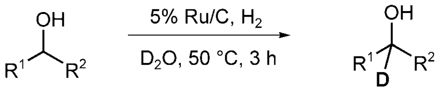
Table 1. Effect of the catalyst.[a]

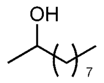
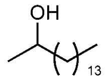
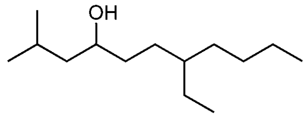
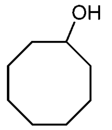
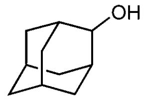


Entry	Catalyst	D content [%]
1	10% Pd/C, 10 wt%	0
2	10% Rh/C, 10 wt%	0
3	10% Ir/C, 10 wt%	0
4	10% Pt/C, 10 wt%	0
5	10% Ru/C, 10 wt%	87
6	5% Ru/C, 10 wt%	60
7	5% Ru/C, 20 wt%	97

[a] The reaction was conducted with 0.5 mmol of the substrate and catalyst in 2 mL of D_2O at room temperature under a H_2 atmosphere of 1 atm for 3 h. The D content was determined by ^1H NMR and ^2H NMR using an internal standard.

Table 2. Regioselective deuteration at the α-position to hydroxy groups in secondary alcohols catalyzed by Ru/C in D_2O.[a]



Entry	Substrate	D content [%]	Yield [%]
1[b]		97	87
2[c]		100	97
3		100	94
4[c]		94	72
5		0	N.D.[d]

[a] The reaction was conducted with 0.25 mmol or 0.5 mmol of the substrate and 20 wt% of 5% Ru/C in 2 mL of D_2O at 50 °C under 1 atm of H_2 for 3 h.
[b] The reaction was performed at room temperature.
[c] A slight deuterium incorporation on the other carbons was observed.
[d] Not determined.

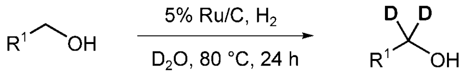
possessing a rigid basic skeleton was not affected under these reaction conditions (entry 5). The deuterated alcohols were spectromerically pure and no chromatographic purification was needed.

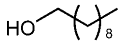
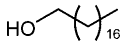
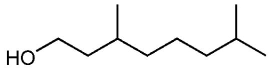
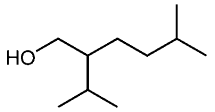
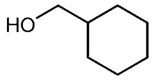
We next investigated the deuteration of primary alcohols. The deuteration of 1-decanol selectively proceeded at the α-position to the hydroxyl group whereas the efficiency of the deuterium incorporation was moderate (~80%) at 50 °C even after 36 h (Table 3, entry 1). We then attempted a further optimization of the deuteration of primary alcohols. Consequently, an increase in temperature to 80 °C improved the reaction efficiency and a variety of primary alcohols were regioselectively deuterated under the reaction conditions with nearly quantitative deuterium efficiency (entries 2–6).

Furthermore, the deuteration of diol and triol derivatives in a regioselective manner is also possible, and multi-deuterated products at the α-positions should be useful as deuterium-labeled synthons (Table 4).

Next, the reaction of (*R*)-2-decanol (97% *ee*) using 5% Ru/C in H_2O under an H_2 atmosphere (H–H exchange reaction conditions) was conducted to investigate the reaction mechanism. As a result, the product was racemized after 3 h [Eq. (1), only 1.8% *ee*]. When the reaction with 2-decanone was performed under the same conditions, the Ru/C catalyzed the reduction of the aliphatic ketone smoothly and 2-decanol was obtained in an 81:19 ratio [Eq. (2)]. Since the generation of a trace amount of ketones during the deuteration of secondary alcohols could be detect-

Table 3. Regioselective deuteration at the α-position to hydroxy groups in primary alcohols catalyzed by Ru/C in D_2O.[a]

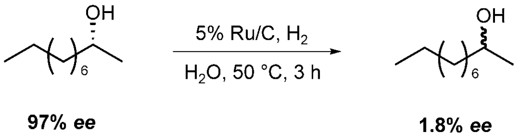


Entry	Substrate	D content [%]	Yield [%]
1[b]		81	97
2		99	88
3[c]		100	95
4		100	100
5[c]		98	78
6		99	86

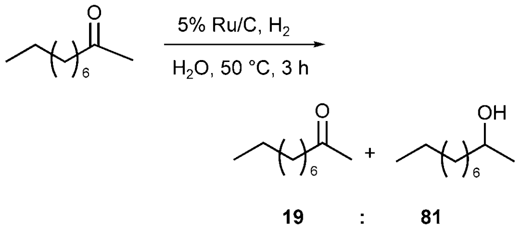
[a] The reaction was conducted with 0.25 mmol or 0.5 mmol of the substrate and 20 wt% of 5% Ru/C in 2 mL of D_2O at 80 °C under 1 atm of H_2 for 24 h.

[b] The reaction was performed at 50 °C for 36 h.

[c] A slight deuterium incorporation on the other carbons was observed.



(1)



(2)

ed, a redox reaction is more likely the mechanism for the present deuteration, while the direct C–H insertion cannot be entirely ruled out.

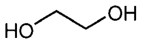
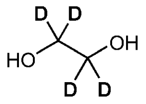
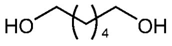
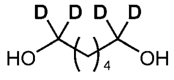
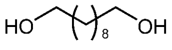
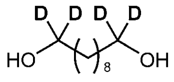
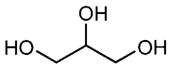
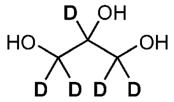
In conclusion, we have developed a convenient and efficient method for the regiospecific deuteration at the α-positions to hydroxy moieties. The reaction proceeded with a high deuterium efficiency and regioselectivity. This method is applicable to the deuteration of various aliphatic alcohols including diol and triol derivatives. Further applications to ethers and amines are now underway.

Experimental Section

General Procedure for the Regioselective Deuteration of Alcohols

A suspension of 5% Ru/C (20 wt% of substrate), substrate (0.25 or 0.5 mmol) and D_2O (2 mL) in a test-tube was stirred at the appropriate temperature under a hydrogen atmosphere. After completion, the mixture was cooled to room temperature and filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm). The filtrate was extracted with diethyl ether (2×10 mL), washed with water (2×30 mL) and brine (30 mL) and dried with Mg_2SO_4 followed by concentration under reduced pressure to furnish the deuterated alcohol. The details of experiments and the data (^{1}H and ^{2}H NMR and mass spectra) are available in the Supporting Information.

Table 4. Regioselective deuteration at the α-position to hydroxy groups in diols and triols catalyzed by Ru/C in D_2O.[a]

Entry	Substrate	Product	D content [%]	Yield [%]
1			97	89
2[b]			82	90
3			75	89
4			98	100

[a] The reaction was conducted with 0.25 mmol or 0.5 mmol of the substrate and 20 wt% of 5% Ru/C in 2 mL of D_2O at 80 °C under 1 atm of H_2 for 24 h.

[b] A slight deuterium incorporation on the other carbons was observed.

Acknowledgements

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