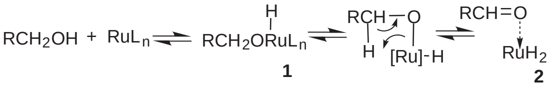
Ruthenium Catalyzed Deuterium Labelling of α-Carbon in Primary Alcohol and Primary/Secondary Amine in D_2O

Masaaki Takahashi, Koichiro Oshima, and Seijiro Matsubara*
Department of Material Chemistry, Graduate School of Engineering, Kyoto University,
Kyoutodaigaku-katsura, Nishikyo-ku, Kyoto 615-8510

(Received November 11, 2004; CL-041358)

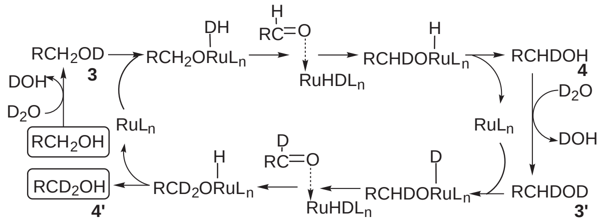
Primary alcohols and primary/secondary amines are labelled with D atom at α-position regioselectively by means of deuterium oxide and ruthenium catalyst.

In the field of selective oxidation of alcohol,[1] the chemoselective oxidation of primary vs. secondary alcohol has been investigated intensively. While an electron transfer type reagent oxidizes a secondary alcohol selectively,[2] the selective oxidation of a primary alcohol into an aldehyde was accomplished by hydrogen transfer type oxidation using $RuCl_2(PPh_3)_3$.[3,4] The reason why the $RuCl_2(PPh_3)_3$ oxidizes a primary alcohol selectively in the presence of a secondary one is the formation of ruthenium alkoxide **1** as an initial reaction complex (Scheme 1). The preferential formation of alkoxide with a primary alcohol in the presence of a secondary one explains the chemoselectivity.[4] Elimination of ruthenium hydride **2** from the alkoxide **1** will afford an aldehyde. In the case of a catalytic reaction, the hydrogen in **2** will be removed by oxidants or by a hydrogen acceptor such as enone. We have reported that treatment of a primary alcohol with catalytic amounts of $RuCl_2(PPh_3)_3$ and 3-buten-2-one under microwave irradiation gave an aldehyde in good yield.[5] The reaction was performed without solvent. In this non-solvent reaction, we have noticed that addition of some water inhibited the oxidation reaction. This observation means that the equilibrium of the reaction path in Scheme 1 inclines to the alcohol in the presence of water.



Scheme 1. An oxidation of primary alcohols with $RuCl_2(PPh_3)_3$.

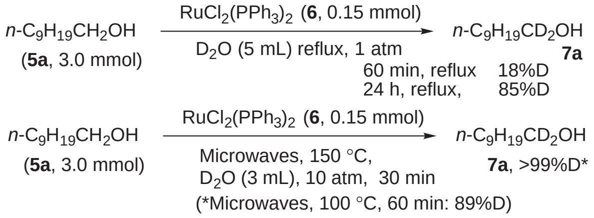
When water is replaced with deuterium oxide, an exchange of the acidic proton in the hydroxyl group with deuterium oxide will occur (**3** and **3′**). Through the catalytic process shown in Scheme 2 as a working hypothesis, α-protons of alcohol will be replaced with D atom (**4** and **4′**). Here, we wish to report a catalytic process for the labelling of the α-position of primary alcohols[6] and primary/secondary amines.



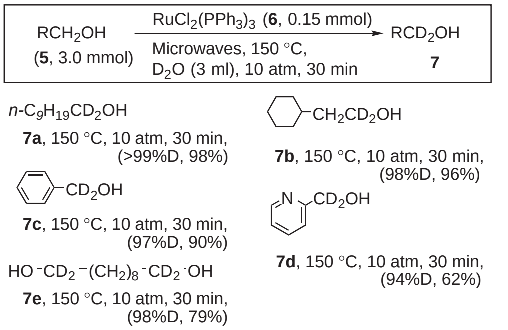
Scheme 2. Working hypothesis for H–D exchange reaction of primary alcohol with D_2O and $RuCl_2(PPh_3)_3$.

As shown in Scheme 3, *n*-dodecanol (**5a**, 3.0 mmol) and $RuCl_2(PPh_3)_3$ were heated under reflux of deuterium oxide (5 mL) for 60 min. Although the deuterium proportion is not high, some regioselective deuteration at α-position (**7a**) was observed. The longer duration of heating (24 h) improved the proportion up to 85%. The ratio of deuterium content was determined by ^1H NMR and ^2H NMR. Use of microwave irradiation accelerated the exchange reaction. We used Discover system from CEM corporation,[7] as the microwave system. In a 10-mL pressure vial which can be sealed by a septum, a mixture of alcohol (**5a**, 3.0 mmol) and $RuCl_2(PPh_3)_3$ (**6**, 0.15 mmol) in deuterium oxide (3.0 mL) was placed. Microwaves (100 W) irradiated the vial while the temperature was maintaining at 150 °C. The internal pressure reached to around 10 atm. After the irradiation was continued for 30 min, 1,1-dideuteriodecanol was obtained quantitatively. The ratio of deuterium atom on α-position of alcohol was more than 99%. Other examples are shown in Scheme 4. A secondary alcohol, 2-octanol, was also examined as a substrate, but it was not converted into the labelled compound. The result was quantitative recovery of starting material after an irradiation by microwaves for 30 min at 150 °C.

The protecting group, such as a benzyl, acetyl, *t*-butyldimethylsilyl, or MOM group cannot survive the reaction condition which had been applied for the primary alcohols in Scheme

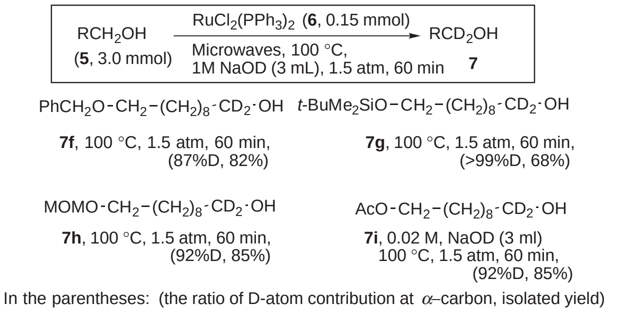


Scheme 3. Regioselective H–D exchange of **5a** with $RuCl_2(PPh_3)_3$.



In the parentheses: (the ratio of D-atom contribution at α-carbon, isolated yield)

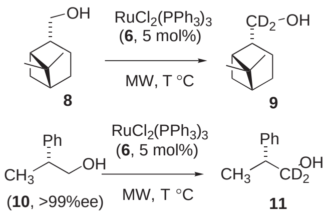
Scheme 4. Regioselective H–D exchange of primary alcohols under microwave irradiation.



Scheme 5. Regioselective H–D exchange of primary alcohols in basic condition under microwave irradiation.

4, because a mixture of deuterium oxide and **6** generates DCl. When the reactions were operated in basic deuterium oxide, these groups were intact and H–D exchange on the α-carbon of alcohol proceeded selectively, as shown in Scheme 5.

Optically active primary alcohols with the stereogenic center at β-position were also examined for this exchange reaction. As shown in Scheme 6, (1*S*, 2*S*, 5*S*)-(–)-myrtanol (**8**) and (*R*)-2-phenylpropanol were treated with $RuCl_2(PPh_3)_3$ (**6**) and deuterium oxide at 150 °C under microwave irradiation. The exchange proceeded in both cases to give the labelled alcohol, but some epimerisation at β-position was observed. In these cases, a partial deuteration was also observed at β-position (**9**: 38%D, **11**: 30%D). Tuning the reaction temperature solved this racemization problem. The reaction below 100 °C with microwaves (internal pressure 1.5 atm) did not cause the epimerisation. When the substrate was treated with the catalyst **6** in refluxing deuterium oxide (bp. 101.4 °C, 1.0 atm) for 1 h by simple external heating, only slight deuteration on α-carbon was observed (12%). Irradiation by microwaves is different from simple external heating, because polar species such as catalyst **6** and ruthenium alkoxide are heated selectively by microwave irradiation.[8,9]



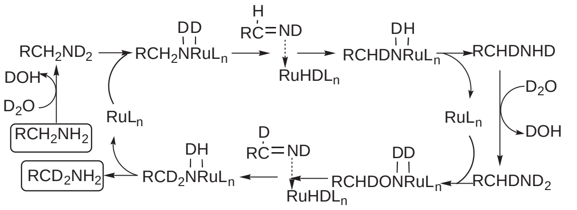
T°C	D%	Yield% of 9	β/α of 9
150, 10 min	100	95	15/85
100, 60 min	93	90	<1/>99

T°C	D%	Yield% of 11	%ee of 11
150, 10 min	100	95	80
100, 60 min	87	90	>99

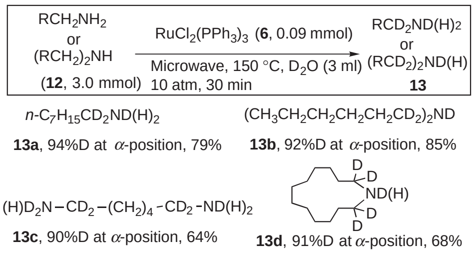
Scheme 6. Deuteration of Optically Active Alcohols.

The same working hypothesis as in Scheme 2 may be applicable for primary and secondary amines.[10] As shown in Scheme 7, it may be possible that H–D exchange on α-carbon of primary/secondary amines is induced by the same condition as in Scheme 4.

As shown in Scheme 8, primary and secondary amines were examined for the H–D exchange reaction. In all cases, H–D exchange reactions were observed on α-carbon selectively. The deuterium proportion on nitrogen atom in **13** was variable according to the aqueous work-up procedure. A work-up with 1 M NaOD gave the high contents of deuterium on nitrogen atom. As a tertiary amine, trihexylamine was examined for the reaction. A small amount of H–D exchange was observed, but the deuterium distribution was less than 12%.



Scheme 7. Working hypothesis for H–D exchange reaction of primary amine with D_2O and $RuCl_2(PPh_3)_3$.



Scheme 8. Regioselective ruthenium catalyzed H–D exchange of primary/secondary amines.

Many examples of H–D exchange reaction in organic compounds based on transition metal-catalyzed direct C–H activation have been reported.[11,12] The present method may also be classed a catalytic C–H activation, but one should recognize that the reaction proceeds as a result of transition metal catalyzed redox equilibrium of primary alcohols in water. The method may be applied for the regioselective labelling for more complex compounds such as sugar or DNA. This is now underway.

References

1 M. Edmonds and A. Abell, in "Modern Carbonyl Olefination," ed. by T. Takeda, Wiley-VCH, Weinheim (2003).
2 H. Tomioka, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, **23**, 539 (1982); Y. Ueno and M. Okawara, *Tetrahedron Lett.*, **17**, 4597 (1976); B. M. Trost and Y. Masuyama, *Tetrahedron Lett.*, **25**, 173 (1984).
3 H. Tomioka, K. Takai, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, **22**, 1605 (1981); S.-I. Murahashi, K.-I. Ito, T. Naota, and Y. Maeda, *Tetrahedron Lett.*, **22**, 5327 (1981).
4 A. Miyata, M. Murakami, R. Irie, and T. Katsuki, *Tetrahedron Lett.*, **42**, 7067 (2001); R. H. Meijer, G. B. W. L. Ligthart, J. Meuldijk, J. A. J. M. Vekemans, L. A. Hulshof, A. M. Mills, H. Kooijman, and A. L. Spe, *Tetrahedron*, **60**, 1065 (2004); T. Naota, H. Takaya, and S. Murahashi, *Chem. Rev.*, **98**, 2599 (1998).
5 M. Takahashi, K. Oshima, and S. Matsubara, *Tetrahedron Lett.*, **44**, 9201 (2003).
6 C. Balzarek and D. R. Tyler, *Angew. Chem., Int. Ed. Engl.*, **38**, 2406 (1999).
7 B. L. Hayes, in "Microwave Synthesis," CEM Publishing, Matthews (2002).
8 M. Yamamoto, K. Oshima, and S. Matsubara, *Chem. Lett.*, **33**, 846 (2004).
9 A. R. Katritzky and S. M. Allin, *Acc. Chem. Res.*, **29**, 399 (1996).
10 S. E. Diamond, G. M. Tom, and H. Taube, *J. Am. Chem. Soc.*, **97**, 2661 (1975); T. Kondo, T. Okada, and T. Mitsudo, *J. Am. Chem. Soc.*, **124**, 186 (2002); K. Yamaguchi and N. Mizuno, *Angew. Chem., Int. Ed. Engl.*, **42**, 1480 (2003).
11 S. R. Klei, J. T. Golden, T. Don Tilley, and R. G. Bergman, *J. Am. Chem. Soc.*, **124**, 2092 (2002); L. P. Kingston, W. J. S. Lockley, A. N. Mather, E. Spink, S. P. Thompson, and D. J. Wilkinson, *Tetrahedron Lett.*, **41**, 2705 (2000); G. J. Ellames, J. S. Gibson, J. M. Herbert, W. J. Kerr, and A. H. McNeill, *Tetrahedron Lett.*, **42**, 6413 (2001); F. A. L. Anet and M. St. Jacques, *J. Am. Chem. Soc.*, **88**, 2585 (1966); J. L. Ganett and R. J. Hodges, *J. Am. Chem. Soc.*, **89**, 4545 (1967); O. Desponds and M. Schlosser, *Tetrahedron Lett.*, **37**, 47 (1996); H. Sajiki, K. Hattori, F. Aoki, K. Yasunaga, and K. Hirota, *Synlett*, **2002**, 1149; C. Hardacre, J. D. Holbrey, and S. E. J. McMath, *Chem. Commun.*, **2001**, 367; J. G. Atkinson, M. O. Luke, and R. S. Stuart, *Can. J. Chem.*, **45**, 1511 (1967); J. R. Jones, W. J. S. Lockley, S.-Y. Lu, and S. P. Thompson, *Tetrahedron Lett.*, **42**, 331 (2001).
12 S. Matsubara, Y. Yokota, and K. Oshima, *Chem. Lett.*, **33**, 294 (2004); S. Matsubara, Y. Yokota, and K. Oshima, *Org. Lett.*, **6**, 2071 (2004); M. Yamamoto, Y. Yokota, K. Oshima, and S. Matsubara, *Chem. Commun.*, **2004**, 1714.

Published on the web (Advance View) January 15, 2005; DOI 10.1246/cl.2005.192