Retention of Optical Purity in H-D Exchange Reactions Catalysed by Cobalt-Aluminium Alloy in Na_2CO_3-D_2O

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(Received October 9, 1995)

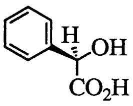
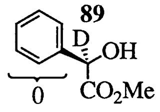
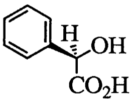
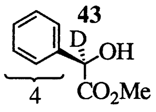
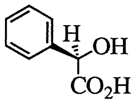
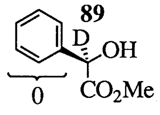
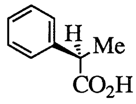
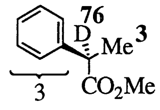
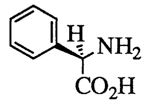
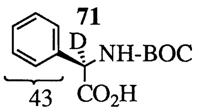
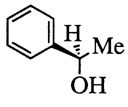
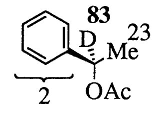
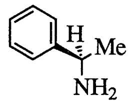
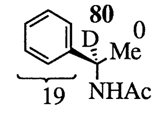
Co-Al alloy in a sodium carbonate-deuterium oxide solution catalyzes the H-D exchange reaction of optically active benzylic hydrogen atom without racemization.

Previously optically active compounds deuterated at a chiral center of methine hydrogen at the benzylic position were obtained by resolution of racemic deuterated compounds[1] and asymmetric synthesis.[2] It was recently reported that heterogeneous catalytic hydrogen-deuterium (H-D) exchange reaction of α-substituted toluene using cobalt-aluminium (Co-Al) alloy[3] in an Na_2CO_3-D_2O solution takes place at benzylic position without any additional incorporation of deuterium atoms into the benzene ring.[4] The present article reports novel findings that the treatment of (*R*)-mandelic acid, (*R*)-2-phenylpropanoic acid, (*R*)-phenylglycine, (*R*)-α-methylbenzylalcohol, and (R)-α-methylbenzylamine by Co-Al alloy in an Na_2CO_3-D_2O solution gave the α-deuterated optically active compounds in one step.

Experimental procedures are simple and do not need a special apparatus. For example, a mixture of (*R*)-mandelic acid (1.0 mmol), Co-Al alloy (50:50 wt%, 0.50 g), Na_2CO_3 (1.0 g) and D_2O (99.9 atom%D, 5.0 ml) was heated at 60 °C under argon atmosphere for 2 h under ultrasonication.[5] Then the insoluble materials were filtered off. The filtrate was acidified with conc. HCl to pH 1, and extracted with ether. The extract was treated with CH_2N_2 ether solution and the product was purified with column chromatography (Wakogel C-300). Enantiomeric excess and absolute configuration of the products were determined by HPLC using chiral column and deuterium contents were determined by ^1H NMR spectroscopy. As shown in Table 1, lowering of the reaction temperature improves the ee in run 2, and ultrasonication increases the deuterium content of benzylic position; in run 3, (*R*)-mandelic acid gave methyl α-^2H-(*R*)-mandelate in high deuterium content (89%) with complete retention (99% ee). We assume that ultrasonication would assist to develop the uniform metal surface and to remove the passivating surface impurities as previously reported.[6] Similarly, (*R*)-2-phenylpropanoic acid provided methyl α-^2H-(*R*)-phenylpropanoate in high deuterium content with complete retention (run 4). The H-D exchange reactions of (*R*)-phenylglycine, (*R*)-α-methylbenzylalcohol, and (*R*)-α-methylbenzylamine were suffered by racemization as shown in runs 5-7. Furthermore in runs 5 and 7, additional deuterium atoms of 43 and 19% were incorporated into the benzene ring. These results suggest that the catalytic intermediate, a π-benzyl adsorbed species[7] undergoes the steleoselective substitution reaction with deuterium on the catalyst surface and the adsorbed state depends upon the substituents.[8]

The authors wish to thank Tohwa university for financial support.

Table 1. H-D Exchange reactions of optical active compounds using Co-Al alloy in Na_2CO_3-D_2O[a]

run	Substrate[b]	Isolated product D content/%[c]	yield/%	ee/%[d,e]
1[f]			59	51
2[g]			89	> 99
3			77	> 99
4			97	> 99
5			73	85
6			87	46
7			94	79

[a] The reaction was carried out at 60 °C under ultrasonication. [b] All the substrates were *R*-form. [c] Determined by ^1H-NMR spectroscopy. [d] Determined using chiral HPLC (Chiralcel OD, Sumichiral OA 5000). [e] The ee of a mixture of deutero and protio form were given. [f] The reaction was carried out at 90 °C under no ultrasonication. [g] The reaction was carried out at 60 °C under no ultrasonication.

References and Notes

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3 The use of the nickel-aluminum alloy resulted in the cleavage of carbon-oxygen and carbon-nitrogen in benzylic position precedence over H-D exchange reaction[9]; the hydrogenolysis afforded the product which substitutes to deuterium.

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