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RHODIUM-CATALYZED STEREOSELECTIVE DEHYDROGENATION OF *CIS*- AND *TRANS*-METHYLCYCLOHEXANOLS BY MOLECULAR OXYGEN

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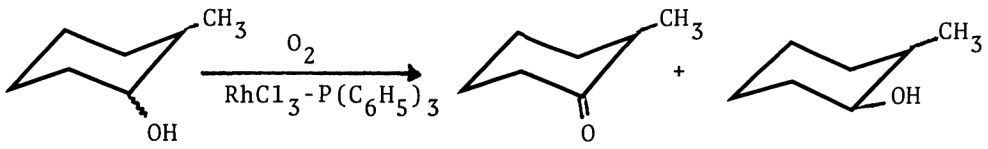
Methylcyclohexanols were dehydrogenated stereoselectively by rhodium phosphine catalyst and molecular oxygen. The less stable stereoisomers were consumed preferentially.

Dehydrogenation of alcohols has been used frequently for the syntheses of aldehydes and ketones. In response to the increasing demand for selective reactions in organic syntheses, various reagents were developed for regio- and chemoselective dehydrogenation of alcohols lately.[1] However, little is known about the stereoselectivity of the reaction. Whitesides et al. reported the transhydrogenation of cis- and trans-1,2-cyclododecanols by ruthenium phosphine complex in the presence of α,β-unsaturated ketone at 195 °C, but the yields of ketones from both stereoisomers were in a similar order.[2] In the course of study for a new effective catalyst of dehydrogenation, we found that the rhodium phosphine complex worked effectively as the catalyst of oxidation by molecular oxygen,[3] and that the catalysis showed stereoselectivity. In this letter we communicate a rhodium-catalyzed stereoselective dehydrogenation of methylcyclohexanols by molecular oxygen.



(50% cis, 50% trans) (77%) (17%)

In a typical reaction, $RhCl_3 \cdot 3H_2O$ (0.067 mmol), $P(C_6H_5)_3$ (0.076 mmol), and a mixture of cis- and trans-2-methylcyclohexanols (a commercial 1:1 mixture, 8.1 mmol) was stirred at 95 °C under the atmospheric pressure of oxygen. At the con-

version of 83%, 2-methylcyclohexanone was formed in a yield of 77% and the remaining substrate was exclusively the trans isomer. When the reaction was interrupted at the earlier stage of 52% conversion, a mixture of 2-methylcyclohexanone (40% yield), cis-2-methylcyclohexanol (6% recovery), and trans-2-methylcyclohexanol (42% recovery) was obtained. A system of molecular oxygen and ruthenium catalyst was less effective and less selective under the present reaction conditions, and chromic acid-sulfuric acid (Jones reagent) showed a higher reactivity and selectivity of dehydrogenation, but the stereoselectivity was modest. The results are summarized in Table 1.

Under these reaction conditions, the substrate was recovered intact in the absence of catalyst or under the anaerobic condition in the presence of $RhCl_3$-$P(C_6H_5)_3$ at 100 °C for 15 h. This result makes a sharp contrast to the report on

Table 1. Dehydrogenation of Alkylcyclohexanols[a)]

Cyclo-	NMR, ppm[b)]		Initial ratio[c)]	Reagent for	Ketone	Recovered alcohol	
hexanol	cis	trans	of cis/trans	dehydrogenation	Yield/%[d)]	%[e)]	cis/trans[f)]
H				O_2-$RhCl_3$-$P(C_6H_5)_3$	45 (54)[g)]	17	
2-Me	3.78	3.12	50/50	O_2-$RhCl_3$-$P(C_6H_5)_3$	77 (93)[h)]	17	0/100
				O_2-$RhCl_3$-$P(C_6H_5)_3$	40 (83)[g)]	48	13/87
				O_2-$RuCl_3$-$P(C_6H_5)_3$	18 (72)	75	46/54
				$RuCl_3$-$P(C_6H_5)_3$[i)]	0.4 (1)	50	51/49
				H_2CrO_4-H_2SO_4[j)]	50 (98)	49	42/58
3-Me	3.57	4.05	70/30	O_2-$RhCl_3$-$P(C_6H_5)_3$	38 (69)	45	87/13
4-Me	3.95	3.54	32/68	O_2-$RhCl_3$-$P(C_6H_5)_3$	33 (60)	45	18/83
				O_2-$RuCl_3$-$P(C_6H_5)_3$	12 (-)	-	31/69
4-t-Bu	4.04	3.54	31/69	O_2-$RhCl_3$-$P(C_6H_5)_3$	4 (33)	88	33/67

a) Reaction conditions: $RhCl_3$, 0.067 mmol; $P(C_6H_5)_3$, 0.076 mmol; cyclohexanol, 8.1 mmol; 85 °C; 15 h. b) NMR signal of carbinyl hydrogen. c) NMR ratio of cis and trans isomers in the substrate used. d) Yield of ketone based on the amount of alcohol used. The value in the parenthesis shows the yield on the basis of alcohol consumed. e) Recovery of alcohol. f) Isomer ratio of recovered alcohol determined by NMR. g) 16 h. h) 95 °C, 16 h. i) 1-Phenyl-1-buten-3-one was used as the hydrogen acceptor in place of O_2. j) Stoichiometric reaction, no O_2.

isomerization by Raney nickel under hydrogen, where thermodynamic equilibrium was attained at around 100 °C.[4] Obviously, the isomer distribution in the presented rhodium-catalyzed oxidation was not controlled by thermodynamic equilibrium but under the kinetic control.

The relative reactivities of two stereoisomers can be estimated when the reactivities of both isomers in the side reaction(s)[5] are accessible. In the case of the reaction with a 52% conversion of substrate presented above, the reactivity ratio of cis and trans isomers for dehydrogenation is calculated to be 4/1 if only the cis isomer was consumed in the side reaction(s).[6] In fact, it seems likely that both isomers are consumed nonselectively in the side reaction(s) (vide infra). Therefore, the ratio of reactivities of the two isomers for dehydrogenation would be about 19/1, which is calculated on the basis of equal reactivities of both isomers in side reaction(s).[6] Here, the less stable isomer with two substituents in axial and equatorial positions of the ring was dehydrogenated preferentially. Similarly, less stable isomers were dehydrogenated more quickly with 3- and 4-methylcyclohexanols although the results were less unequivocal because of the uneven distributions of stereoisomers in the starting substrate mixtures. On the contrary, crowded 4-t-butylcyclohexanol, which was dehydrogenated more slowly than methylcyclohexanols, showed poor chemo- and stereoselectivity of the reaction. It should be noted that the distribution of cis- and trans-4-t-butylcyclohexanols was almost unaffected by the reaction. This tendency was more distinctive in the reaction of 2-methylcyclohexanol in the presence of 1-phenyl-1-buten-3-one and $RuCl_3$-$P(C_6H_5)_3$ (Sasson and Blum's transhydrogenation system).[7] At the low temperature of present work, Blum's transhydrogenation did not proceed, and the substrate was consumed to give unknown side product(s) nonstereoselectively. The results are interpreted as indicating that the dehydrogenation of alcohol proceeded stereoselectively for the less stable isomer but the accompanied side reaction(s) took place nonstereoselectively.

A tentative mechanism for the observed selectivity is presented as follows: By coordination on the metal, a hydroxy group is converted into a bulky metal alkoxide, which must occupy preferentially the equatorial position on the ring. Then the methyl substituent in the less stable isomer of methylcyclohexanol should be forced into the axial position. The driving force to release the steric hindrance around the methyl group would be expected to facilitate the dehydrgenation.

However, for the more stable isomer, which has diequatorial substituents, no similar steric acceleration is expected. Thus the high reactivity of less stable isomer is rationalized. On the contrary, in the reaction of cis-4-t-butylcyclohexanol, the t-butyl group may persist in the equatorial position even in the metal-alkoxide complex, leading to a small formation constant of the complex and, subsequently, little acceleration and selectivity. In addition, the results suggest that the distance between the alkyl and the hydroxy groups also influences the selectivity. The shorter the distance, the more selective was the reaction.

Although stereoselectivity of dehydrogenation might be less important than regio- or chemoselectivity in organic syntheses, this report would contribute, as the first example of metal-catalyzed homogeneous stereoselective dehydrogenation of alcohol, for selective organic syntheses by transition-metal catalysis.

References

1) K. Oshima, J. Synth. Org. Chem. Jpn., 41, 337 (1983), and references cited therein.
2) S. L. Regan and G. M. Whiteside, J. Org. Chem., 37, 1832 (1972).
3) $RhCl_3$ was reported to be a poor catalyst for dehydrogenation of alcohols with molecular oxygen. However, the reaction of secondary benzylic or allylic alcohols proceeded smoothly by $RhCl_3$-$P(C_6H_5)_3$-O_2. The system itself was less effective for primary alcohols, but addition of proton sponge gave good results in this case; T. Okamoto and S. Oka, unpublished results.
4) G. Chiurdoglu and W. Masschelein, Bull. Soc. Chim. Belg., 70, 782 (1961); E. L. Eliel and R. S. Ro, J. Am. Chem. Soc., 79, 5992 (1957).
5) Lower yields of ketones than 100% on the consumed substrate basis indicate the presence of some side reaction(s). Dehydration, for example, took place in some extent depending on the substrate and reaction conditions.
6) The recovered substrate contained 6% of cis and 42% of trans isomers on the basis of the amount of substrate used. If only cis isomer was consumed in the side reaction(s) (12%), 32% of cis and 8% of trans isomers should be consumed in dehydrogenation to give 2-methylcyclohexanone. Reactivity ratio of cis and trans isomers in dehydrogenation can be calculated as 32/8, or 4/1. In the case when cis and trans isomers were consumed nonselectively in the side reaction(s), the corresponding relative ratio of reactivities was (50-6-6)/(50-42-6), or 19/1.
7) Y. Sasson and J. Blum, Tetrahedron Lett., 1971, 2176; Y. Sasson and J. Blum, J. Org. Chem., 40, 1887 (1975).

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