CHEMISTRY LETTERS, pp. 1179-1182, 1982. 

# CATALYTIC ENANTIOTOPOS DIFFERENTIATING DEHYDROGENATION OF PROCHIRAL DIOLS USING RUTHENIUM COMPLEX WITH DIOP

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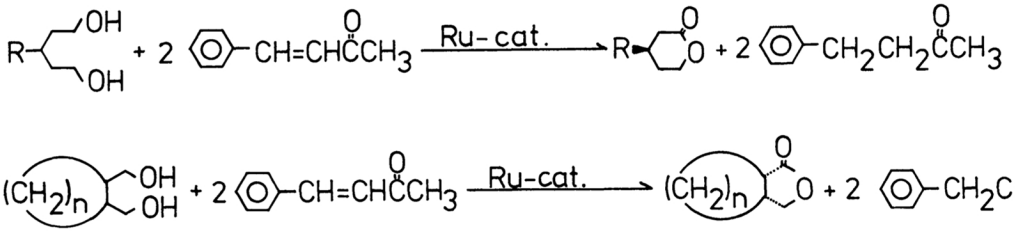
Optically active δ- and γ-lactones are obtained by the homogeneous catalytic dehydrogenation of prochiral diols using $Ru_2Cl_4((-)\text{-DIOP})_3$ in the presence of benzalacetone as a hydrogen acceptor and triethylamine.

Catalytic enantioface differentiating reaction, such as catalytic asymmetric hydrogenation of prochiral olefins,[1] has been extensively studied in the last decade. On the contrary, there have been only a few examples about enantiotopos differentiating reaction,[2] where one of enantiotopic groups in a prochiral molecule undergoes stereoselective transformation by a chiral catalyst to give a chiral molecule, although such enantioselective reactions are commonly found in enzymatic processes.[3] As an example of such reactions, we have previously reported the catalytic asymmetric reduction of one of enantiotopic carbonyl groups in cyclic anhydrides to afford optically active lactones.[4] In this paper, we wish to report the chiral ruthenium complex catalyzed dehydrogenation of one of enantiotopic hydroxymethyl groups of prochiral 1,5- and 1,4-diols in the presence of hydrogen acceptors to give optically active δ- and γ-lactones, respectively.

The ruthenium catalyzed dehydrogenation of alcohols which proceeds in the presence of hydrogen acceptor such as olefin or carbonyl compound has been well known as the hydrogen transfer reaction.[5] Chiral ruthenium catalysts were employed for the transfer hydrogenation of prochiral olefins and the kinetic optical resolution of racemic chiral alcohols.[6] Recently it was reported that $RuH_2(PPh_3)_4$[7] and $Ru_3(CO)_{12}$[8] catalyzed the dehydrogenation of 1,4- and 1,5-diols in the presence of adequate hydrogen acceptors to give the corresponding γ- and δ-lactones, respectively. It can be expected that a similar reaction of 3-alkyl-1,5-

pentanediols or cis-1,2-bis(hydroxymethyl)cycloalkanes(meso type) yields optically active products when a chiral ruthenium complex is used as a catalyst. In these regards $Ru_2Cl_4((-)\text{-DIOP})_3$[9] was examined as a catalyst for the enantioselective dehydrogenation of diols to obtain optically active lactones. ((-)-DIOP = (-)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane[10])

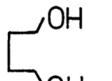
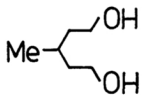
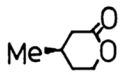
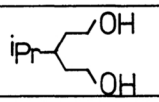
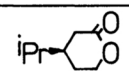
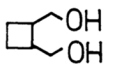
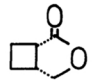
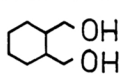
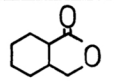



The reaction conditions and obtained results are listed in Table. In a typical case, 3-methyl-1,5-pentanediol(5 mmol), benzalacetone(10 mmol), $Ru_2Cl_4((-)\text{-DIOP})_3$(0.1 mmol), and triethylamine(0.12 $cm^3$) were dissolved in 25 $cm^3$ of dry toluene under nitrogen or argon atmosphere and refluxed for 10 h, during which time the color of the solution changed from green to dark brown. The reaction mixture was extracted several times with 10 % aqueous NaOH, the combined extracts being washed with ether and then acidified with conc. HCl to pH 1. The mixture was extracted several times with chloroform. The solvent was removed and the residue was distilled under reduced pressure to give 3-methylvalerolactone (1.9 mmol), which was identified by its IR and $^1H$-NMR spectra. The optical purity was determined to be 10.8 %e.e. with (R)-configuration by comparing the optical rotation of the product with that of the optically pure lactone.[11] In the reaction mixture 2-hydroxy-4-methyltetrahydropyran(hemiacetal) was also detected by GLC analysis. Its IR spectrum was identical with that of the authentic sample obtained by the reduction of 3-methylvalerolactone with diisobutylaluminum hydride.[11a)]

Similar reactions of other prochiral diols also gave optically active corresponding lactones as shown in the Table. The yields and optical purities of the products were affected by the reaction temperature. In the reaction carried out at 140°C or higher temperatures, lactone formation was completed within relatively short time(ca. 5 h) and no hemiacetal was detected at all,although optical yields of the lactones were apparently lowered.

This lactone formation reaction is supposed to proceed via the dehydrogenation of one of the hydroxy groups in a diol, followed by the hemiacetal formation and

Table

| Entry | Diol | Lactone | Temp.(°C) | Time(h) | Yield(%)[a] | %e.e.[b] | Confign.[b] |
|---|---|---|---|---|---|---|---|
| 1 |  |  | 190 | 5 | 81 | | |
| 2[c] | | | 190 | 5 | 3 | | |
| 3[d] | | | 140 | 4 | 62 | | |
| 4 |  |  | 180 | 5 | 73 | 2.0 | (R) |
| 5 | | | 140 | 5 | 86 | 2.3 | (R) |
| 6 | | | 110 | 10 | 66 | 10.8 | (R) |
| 7 |  |  | 150 | 5 | >90 | 2.5 | (R) |
| 8 | | | 110 | 10 | 60 | 15.2 | (R) |
| 9 |  |  | 150 | 5 | 86 | 6.4 | (1S,2R) |
| 10 | | | 110 | 10 | 35 | 9.6 | (1S,2R) |
| 11 | | | 110 | 19.5 | 62 | 8.3 | (1S,2R) |
| 12 |  |  | 150 | 5 | >90 | ([α]$_D$= +3.40) | |
| 13 | | | 110 | 20 | 90 | ([α]$_D$= +5.88) | |

a) GLC yield based on the starting diol using propiophenone or acetophenone as an internal standard. b) See ref. 11). c) $NEt_3$ was not added. d) $RuH_2(PPh_3)_4$(0.2 mmol) catalyst.

subsequent dehydrogenation, as proposed for similar oxidations of diols using ruthenium catalysts.[7a] It should be noted that in this $Ru_2Cl_4$((-)-DIOP)$_3$ catalyzed reaction, lactones were scarcely obtained in the absence of triethylamine, though the considerable hydrogenation of benzalacetone and the decrease of the amount of diols were observed. This forms a sharp contrast to the results that no additives were needed in $RuH_2(PPh_3)_4$ or $Ru_3(CO)_{12}$ catalyzed reactions.[7,8] Probably it is because hydrogen chloride, which is formed through the reaction of the catalyst with alcohols,[12] promotes the acetal formation[7c] and/or the polymerization[7b] of formed hemiacetals and consequently suppresses the lactone formation.

The lactones listed in the Table can be also obtained by the hydrogenation of corresponding prochiral cyclic anhydrides in comparable stereoselectivities to the present dehydrogenation reaction using $Ru_2Cl_4$((-)-DIOP)$_3$ catalyst as shown in our previous paper.[4] It should be noted that γ-butyrolactone derivatives obtained in these two reactions catalyzed by $Ru_2Cl_4$((-)-DIOP)$_3$ showed the opposite configuration with each other, while the dehydrogenation of 3-alkyl-1,5-pentanediols gave 3-alkylvalerolactones with the same configuration to that obtained in the hydrogenation of anhydrides. This stereoselectivity of the dehydrogenation of

1,4- or 1,5-diols should be determined at the first stage of the reaction where the chiral discrimination of prochiral hydroxy groups by ruthenium coordinated with DIOP takes place to give an optically active hemiacetal. An enzyme[11] or some bacteria[13] were reported to be highly effective for similar asymmetric dehydrogenations of prochiral diols and our reaction is interesting as a competing chemical approach with these biochemical reaction processes.

Now we are continuing to study to improve the stereoselectivity of the reaction employing other chiral phosphine ligands and to clarify the detailed mechanism of asymmetric induction.

Acknowledgement: This work was supported by a Grant-in-Aid for Developmental Scientific Research from the Ministry of Education of Japan (56850201).

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(Received May 26, 1982)