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CATALYTIC ASYMMETRIC HYDROGENATION OF CYCLIC ANHYDRIDES USING RUTHENIUM(II) CHIRAL PHOSPHINE COMPLEX

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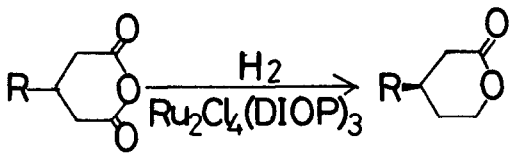
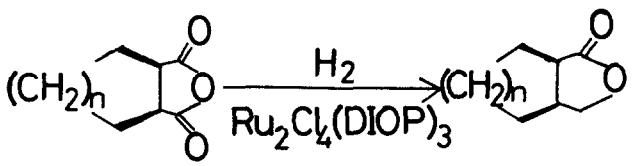
Summary: Optically active γ- and δ-lactones are obtained by the hydrogenation of five- and six-membered cyclic anhydrides using a Ru(II) complex with chiral phosphine ligand, DIOP, as a catalyst.

Catalytic asymmetric hydrogenation with transition metal complexes has been extensively studied in the last decade. Most reports have concerned the stereoselective addition of a hydrogen molecule to either of the prochiral faces of a double bond, such as C=C, C=O, and C=N, using transition metal complexes with chiral phosphine ligands as catalyst. Little was known about the transition metal complex catalyzed stereoselective transformation of enantiotopic groups attached to a prochiral center[1], although these enantioselective reactions are commonly found in enzymatic processes. A typical example is the enantiodifferentiating dehydration of citric acid with aconitase in the presence of Fe^{2+}. Similar enzyme catalyzed asymmetric reactions of unnatural substrates have also been reported, such as the hydrolysis of a carboethoxy group of 3-substituted diethyl glutarate or 2-substituted diethyl malonate with α-chymotrypsin[2], or the dehydrogenation of a hydroxy group of 3-substituted 1,5-pentanediol with horse liver alcohol dehydrogenase[3].

In this paper we wish to report the asymmetric synthesis of chiral lactones by the enantioselective reduction of a carbonyl group in the cyclic anhydrides with a prochiral carbon atom or with two carbon centers of opposite chirality (meso type), using a chiral ruthenium(II) complex as catalyst. Previously we have reported the stepwise formation of γ-lactones from the



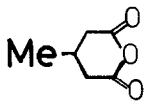
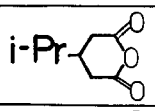
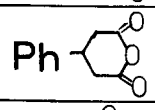
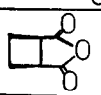
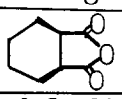


five-membered cyclic anhydrides and $RuH_2(PPh_3)_4$, where the initially formed intermediates 3-aldo-carboxylate ruthenium(II) complexes were susceptible to the reduction at the aldehyde group to give the corresponding γ-lactones upon contact with hydrogen, hydrogen chloride, or carbon monoxide[4]. We also found that this reaction proceeded regioselectively when 2-substituted succinic anhydrides were used. With these regards we initiated the investigation of asymmetric hydrogenation of prochiral cyclic anhydrides using a ruthenium complex with chiral phosphine ligand as catalyst. The hydrogenation of 3-substituted glutaric anhydrides, which have a prochiral center at C-3 position, with $Ru_2Cl_4(DIOP)_3$[5] actually gave the optically active δ-lactones, where DIOP stands for (-)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane[6].

The contact of toluene solution of 3-methylglutaric anhydride(1)(1.40g, 10.9mmol) containing catalytic amount of $Ru_2Cl_4(DIOP)_3$(0.10g, 0.054mmol) and triethylamine(0.12g, 1.19mmol) with 10 kg/cm^2 of hydrogen at 100°C caused the change of color of the reaction mixture from green to orange. The reaction mixture was further stirred for five hours at this temperature until hydrogen uptake was completed. The hydrogenated product was obtained by distillation under reduced pressure, and identified as 3-methyl-δ-lactone by its IR, ^{1}H-NMR, and MS spectra. The optical purity of the product, determined by comparing the optical rotation value with that of the optically pure lactone[3], was 16.4%e.e. with (R)-configuration.

Similarly hydrogenation reactions of 3-isopropylglutaric anhydride(2) and 3-phenylglutaric anhydride(3) also gave the corresponding δ-lactones with optical purities of 6.0%e.e. and 17.7%e.e. respectively. In all these

Table Asymmetric Hydrogenation of Cyclic Anhydrides[a)]

Substrate	Addition[b)]	Yield(%)	$[\alpha]_D$ (Conc.)[c)]	%e.e.[d)]	Confign.
 (1)		32	+4.53°(c=25.3)	16.4	(R)
	PPh_3	61	+5.34°(c=29.6)	19.4	(R)
	DIOP	48	+3.86°(c=30.0)	14.0	(R)
 (2)		27	+4.64°(c=44.8)	6.0	(R)
	PPh_3	79	+3.54°(c=55.9)	5.4	(R)
 (3)		28	-0.67°(c=43.4)	17.7	(R)
	PPh_3	56	-0.76°(c=50.2)	20.0	(R)
 (4)		35	-15.2°(c=32.4)	12.8	(1R,2S)
 (5)		42	-12.4°(c=35.8)		

a) 0.5mol% $Ru_2Cl_4(DIOP)_3$, NEt_3/Ru=10-13 b) Phosphine/Ru=3.0

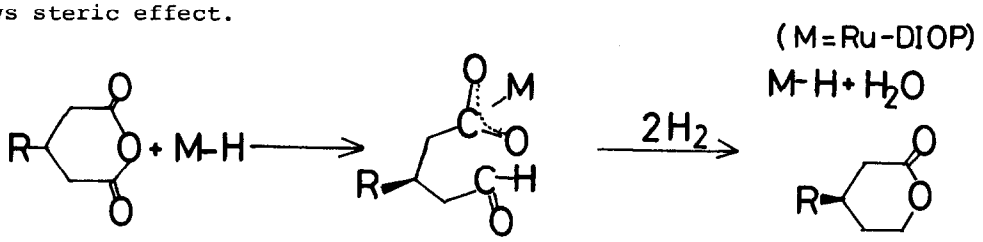
c) measured in $CHCl_3$ d) see ref. 3) and 9)

reactions the obtained lactones contained (R)-enantiomer in excess. The hydrogenation of cis-1,2-cyclobutanedicarboxylic anhydride(4), which has meso structure, gave cis-(2-hydroxymethyl)cyclobutanecarboxylic lactone containing (1R,2S)-form prior to (1S,2R)-form in the enantioselectivity of 12.8%e.e. Similarly cis-hexahydrophthalic anhydride(5)was hydrogenated to give optically active cis-hexahydrophthalide, the optical purity of which is now under investigation[7)].

Of interest is that in the absence of triethylamine this hydrogenation did not occur. Probably triethylamine served to promote the formation of ruthenium hydride species. We have found that a brown ruthenium complex containing DIOP and norbornadiene ligand, prepared by the reaction of DIOP with $[RuCl_2(C_7H_8)]_n$[8)] (C_7H_8=2,5-norbornadiene), exhibited higher catalytic activity for the reaction described above with similar stereoselectivity even in the absence of triethylamine. The addition of a free phosphine such as PPh_3 or DIOP to the reaction mixture did not affect the optical purities of the products, but caused significant increase of the chemical yields.

It is supposed that this asymmetric reaction proceeds via ruthenium aldo-carboxylate complexes formed by the cleavage of C-O bond of cyclic

anhydrides, followed by the formation of aldehyde group from a carbonyl group and a hydride ligand as shown in the previous paper[4], and the absolute configuration of the products is determined by the selectivity of C-O bond cleavage with the chiral ruthenium hydride species, where DIOP coordinated to ruthenium shows steric effect.



The obtained lactones in this reaction can be prepared from the enzyme catalyzed dehydrogenation of corresponding diols in higher stereoselectivity[3)9)]. However it should be noted that there have been only a few reports dealing with the asymmetric reaction from preferential reaction at either of the prochiral groups in a molecule using transition metal complex catalyst similar to the title reaction[10)]. The application of this asymmetric reaction to other system seems to be attractive from the viewpoint of synthetic chemistry. The further studies on the detail of this asymmetric reaction mechanism are now in progress, and will be published soon as a full paper.

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