STUDIES ON

KINETIC RESOLUTION AND ASYMMETRIC HYDROGENATION

BY CHIRAL TRANSITION METAL COMPLEXES

(キラル遷移金属錯体による動力学分割および不斉水素化反応に関する研究)

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PREFACE

The works in this thesis were carried out under the guidances of Professor Katsutoshi Ohkubo at Faculty of Engineering of Kumamoto University from 1975 to 1980, and of Professor Taketoshi Kito at Faculty of Engineering of Kyushu Institute of Technology from 1981 to 1983.

The objects of the work are to develop effective processes and chiral catalysts to obtain optically active compounds.

The author believes that the work will be able to contribute to the development in a field of catalytic asymmetric reaction by transition metal complexes.

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LIST OF PUBLICATIONS

Contents in this thesis are published in following papers.

1. Asymmetric Intramolecular Hydrogenation of an Unsaturated Alcohol by Ruthenium(II) and Rhodium(I) Chiral Phosphine Complexes

   Katsutoshi Ohkubo, Tsutomu Ohgushi, Tsugihiko Kusaga, and Kohji Yoshinaga, *Inorg. Nucl. Chem. Lett.*, 13, 631 (1977).

2. Enantioselective Dehydration of Racemic 1,3-Butanediol by the Catalytic System of $RhCl_3$ and Chiral Phosphine

   Katsutoshi Ohkubo, Kyoshiro Hori, and Kohji Yoshinaga, *Inorg. Nucl. Chem. Lett.*, 13, 634 (1977).

3. Asymmetric Dehydrogenation of Secondary Carbinols by Ruthenium(II) Chiral Phosphine Complexes

   Katsutoshi Ohkubo, Takayuki Shoji, and Kohji Yoshinaga, *J. Catal.*, 54, 166 (1978).

4. The Enantioselective Dehydrogenation of Racemic Secondary Alcohols Catalyzed by Dimeric Ruthenium(II) Chiral Diphosphine Complexes

   Katsutoshi Ohkubo, Ikuhiro Terada, and Kohji Yoshinaga, *Bull. Chem. Soc. Jpn.*, 51, 2807 (1978).

5. Enantioselective Dehydrogenation of Racemic 1-Phenylethanol by Rhodium(I) Chiral Phosphine Complexes

   Katsutoshi Ohkubo, Tsutomu Ohgushi, and Kohji Yoshinaga, *J. Coord. Chem.*, 8, 195 (1979).

6. Relationships between Activation Enthalpies and Entropies of the Enantiomer-differentiating Dehydrogenation of Racemic 1-Phenylethanol by Rhodium(I)-chiral Phosphine Complex

   Kohji Yoshinaga, Taketoshi Kito, and Katsutoshi Ohkubo, *Nippon Kagaku Kaishi*, 1982, 1838.

7. Asymmetric Hydrogenation of Prochiral Ketones by Homogeneous and Heterogeneous Rhodium-chiral Diphosphine Catalytic Systems

   Kohji Yoshinaga, Taketoshi Kito, and Katsutoshi Ohkubo, *Nippon Kagaku Kaishi*, 1983, 345.

8. Asymmetric Transfer Hydrogenation of Prochiral α,β-Unsaturated Acids and their Esters by Alcohols with Binuclear Ruthenium(II) Chiral Diphosphine Complexes

   Kohji Yoshinaga, Taketoshi Kito, and Katsutoshi Ohkubo, *Bull. Chem. Soc. Jpn.*, 56, 1786 (1983).

9. A Kinetic Study on Asymmetric Transfer Hydrogenation of Unsaturated Acids and Esters by Alcohols with Binuclear Ruthenium(II) Chiral Diphosphine Complexes

   Kohji Yoshinaga, Taketoshi Kito, and Katsutoshi Ohkubo, *J. Chem. Soc., Perkin Trans. 2*, 1984, 469.

10. Catalytic Ability of Cobalt(II) and Nickel(II) Chiral Diphosphine Complexes for Asymmetric Hydrogenation of Prochiral Unsaturated Esters

    Kohji Yoshinaga, Taketoshi Kito, Hiroshi Oka, Shigeyoshi Sakaki, and Katsutoshi Ohkubo, *J. Catal.*, 87, 517 (1984).

CONTENTS

INTRODUCTION

Optically active compounds are of growing importance in up-to-date organic chemistry. In order to obtain the compounds, the reagents or the media to be used are required to contain at least one center of asymmetry as chiral source. Therefore, preparation of optically active compounds by means of the asymmetric synthesis or the optical resolution utilizing chiral catalyst, in which chiral source is able to create a larger amount of the compounds, is most effective and practical.

In this regard, the enantio-differentiating reaction catalyzed by chiral transition metal complexes has received considerable attention, since the asymmetric hydrogenation of prochiral olefins by rhodium(I) chiral phosphine complexes has been first reported by Knowles[1] and Hornor[2] in 1968, independently. Asymmetric induction by the transition metal complexes, especially rhodium(I) chiral phosphine ones, in the hydrogenation of prochiral olefins has been extensively investigated, and great effort in the development of efficient chiral ligands has successfully enable to produce optically active amino acid derivatives with over 95% enantiomeric excess in the hydrogenation of dehydro-amino acid derivatives.[3] Recently, much attention has also been paid to interesting type of asymmetric syntheses with chiral organometallic compounds, such as the cyclopropanation by chiral cobalt(II) or nickel(II) complexes,[4] the Grignard cross-coupling reaction by chiral nickel(II) or palladium(II) complexes,[5] and the allylic rearrangement by chiral ruthenium(II) or rhodium(I) complexes.[6]

Enantiomer-differentiating reaction (kinetic resolution) of racemates with chiral catalyst, another type of asymmetric reaction, can be used as a method of obtaining optically active compounds. However, there have been only limited investigations on this type of reaction, even though enantiomer-differentiating epoxidation of racemic allylic alcohols by chiral titanium(IV) complex with extreme high enantio-selection has been recently reported by Sharpless.[7)]

On the other hand, optically active alcohols as significant starting materials have been recognized. For example, Mukaiyama[8)] has developed an efficient and convenient conversion of chiral alcohols to the corresponding amines, thiols, or halides by the reaction with 2-halopyridinium or 2-halobenzothiazolium compounds. In many cases, the asymmetric hydrogenation of ketones by rhodium(I) chiral phosphine complexes afforded optically active alcohols with low yield and low enantiomeric excess, although high enantio-selection has been attained in noncatalytic reduction of ketones with chiral organo-lithium hydride complex[9)] and chiral organo-aluminium complex,[10)] or catalytic hydrosilylation by rhodium(I) chiral phosphine complexes.[11)]

Part 1 describes the kinetic resolution of racemic alcohols in the dehydrogenation of secondary ones by ruthenium(II) chiral phosphine complexes (Chapter 1 and 2) and by rhodium(I) chiral phosphine complexes (Chapter 3), in the intramolecular hydrogen transfer of a racemic unsaturated alcohol by chiral ruthenium(II) and rhodium(I) complexes (Chapter 4), and in the dehydration of a racemic 1,3-diol by chiral rhodium(III) complexes (Chapter 5).

Part 2 describes the asymmetric hydrogenation by chiral

transition metal complexes, which has been investigated with the intention of developing practical processes and catalysts. In Chapter 6 is presented asymmetric transfer hydrogenation of prochiral olefins by alcohols with ruthenium(II) chiral phosphine complexes. The author has also investigated the kinetics of the reaction to elucidate its mechanism (Chapter 7). Furthermore, asymmetric hydrogenation of prochiral ketones by homogeneous and heterogeneous chiral rhodium(I) complexes (Chapter 8), and of prochiral esters by cobalt(II) and nickel(II) chiral phosphine complexes (Chapter 9) have also been investigated.

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PART 1

KINETIC RESOLUTION OF RACEMIC ALCOHOLS

BY CHIRAL RUTHENIUM AND RHODIUM COMPLEXES

CHAPTER 1 ENANTIOMER-DIFFERENTIATING DEHYDROGENATION OF SECONDARY ALCOHOLS BY RUTHENIUM(II) CHIRAL MONOPHOSPHINE COMPLEXES

1-1 Introduction

Asymmetric hydrogenation of prochiral olefins catalyzed by rhodium(I) chiral phosphine complexes, a procedure originally developed in 1968, has been extensively investigated.[1] A number of chiral phosphines were synthesized to examine their effectiveness for the asymmetric induction in terms of their structural effect on the optical purity of the hydrogenated products. In an early stage, chiral monophosphine having an asymmetric phosphorus atom, various and bulky ligands, such as (+)-*o*-methoxyphenylcyclohexylmethylphenylphosphine,[2] were shown to be more efficient in the rhodium(I) complex-catalyzed asymmetric hydrogenation of dehydro-amino acid derivatives than ones containing chiral carbon atoms in the ligands, such as (+)-neomenthyldiphenylphosphine.[3]

The author has prepared some ruthenium(II) chiral monophosphine complexes, and examined their enantiomer-differentiating ability for the dehydrogenation of racemic secondary alcohols. It is also discussed that how the enantio-selective ability of the ruthenium complexes depends on the structure of the chiral ligand and unsaturated additives, and on reaction temperature.

1-2 Experimental

Measurements.

Elemental analyses were carried out with Yanagimoto MT-2.

^{1}H NMR spectra were recorded on JEOL MH-100. Gas-chromatographic measurements were made with Hitachi 063 equipped with a 1-m column packed with Tween 80 on Celite 545. Optical rotations were measured with a Union PM-101 digital polarimeter.

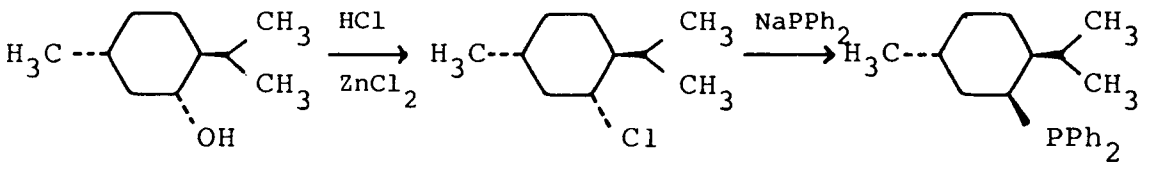
Materials.

Ruthenium trichloride trihydrate ($RuCl_3 \cdot 3H_2O$) was commercially available. Dichlorotris(triphenylphosphine)ruthenium(II) ($RuCl_2(PPh_3)_3$) and dichlorotetrakis(triphenylphosphine)ruthenium (II) ($RuCl_2(PPh_3)_4$) were prepared according to the literature method.[4)]

Racemic alcohols were distilled before use. Unsaturated compounds for the dehydrogenation of alcohols were used after recrystallization or distillation.

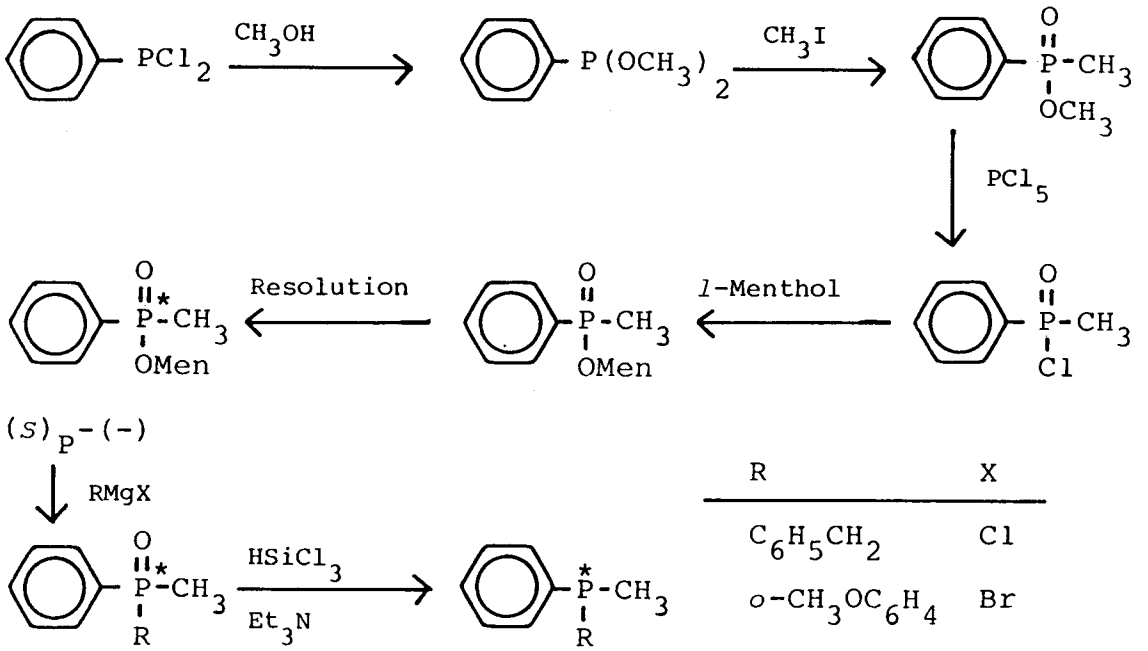
Preparation of Optically Active Phosphines.

(+)-Neomenthyldiphenylphosphine (nmdp). According to the method reported by Morrison,[3)] this phosphine was synthesized from *l*-menthyl chloride and sodium diphenylphosphide (Scheme 1); $[\alpha]_D^{23}$ +93.95° (*c* 1.27, CH_2Cl_2), lit.[3)] $[\alpha]_D^{23}$ +94.4° (*c* 1.26, CH_2Cl_2).



Scheme 1.

(+)-Benzylmethylphenylphosphine (bmpp). Starting from phenyldichlorophosphine, $(S)_P$-(-)-menthyl methylphenylphosphinate was first prepared along the route in Scheme 2; $[\alpha]_D^{23}$ -93.5° (*c* 0.5, C_6H_6), lit.[5] $[\alpha]_D^{23-26}$ -94° (*c* 1-3, C_6H_6). (+)-Benzylmethylphenylphosphine oxide was given by the reaction of the phosphinate with benzyl magnesium chloride in benzene; $[\alpha]_D^{24}$ +50.32° (*c* 1, CH_3OH), lit.[6] $[\alpha]_D^{23-26}$ +51.4° (*c* 1-3, CH_3OH). The oxide was reduced by trichlorosilane in the presence of triethylamine to give (+)-benzylmethylphenylphosphine, which was immediately supplied for the preparation of the chiral ruthenium complex because of extreme air sensitivity.



Scheme 2.

(-)-o-Methoxyphenylmethylphenylphosphine (*o*-ampp), *(-)-p-methoxyphenylmethylphenylphosphine* (*p*-ampp), *and (-)-propylmethylphenylphosphine* (pmpp). In a similar manner described above, these chiral phosphines were synthesized by the reduction of corresponding chiral phosphine oxides, (-)-*o*-methoxyphenylmethylphenylphosphine oxide ($[\alpha]_D^{24}$ -19.3° (*c* 0.46, CH_3OH)), (-)-*p*-methoxyphenylmethylphenylphosphine oxide ($[\alpha]_D^{24}$ -9.96° (*c* 0.53, CH_3OH); lit.[6] $[\alpha]_D^{22-24}$ -9.8° (*c* 1-3, CH_3OH)), and (+)-propylmethylphenylphosphine oxide ($[\alpha]_D^{24}$ +16.3° (*c* 0.45, CH_3OH); lit.[6] $[\alpha]_D^{22-24}$ +17° (*c* 1-3, CH_3OH)) respectively, which were also immediately supplied for the preparation of the chiral ruthenium complexes.

Preparation of Chiral Ruthenium Complexes.

Dichlorotris((+)-benzylmethylphenylphosphine)ruthenium(II). Two grams (1.6 mmol) of $RuCl_2(PPh_3)_3$ was suspended in hexane (100 cm^3) containing (+)-benzylmethylphenylphosphine (1.5 g, 7.0 mmol). The suspension was refluxed for 6 h in a nitrogen atmosphere to give dark yellow crystals (1.6 g).[7] After the crystals were thoroughly washed with hexane, and dried *in vacuo*, giving $RuCl_2$((+)-bmpp)$_3$: ^1H NMR ($CDCl_3$) δ=1.60 (3H, broad), 3.45 (2H, broad), and 6.30-7.37 (10H, m); $[m]_D^{24}$ -685° (*c* 0.1, C_6H_6). Found: C, 62.01; H, 5.64; Cl, 8.61%. Calcd for $C_{42}H_{45}Cl_2P_3Ru$: C, 61.92; H, 5.57; Cl, 8.70%.

Dichlorobis((-)-o-methoxyphenylmethylphenylphosphine)(triphenylphosphine)ruthenium(II), dichlorobis((-)-p-methoxyphenylmethylphenylphosphine)(triphenylphosphine)ruthenium(II), and dichlorotris((-)-propylmethylphenylphosphine)ruthenium(II).

These complexes were prepared from $RuCl_2(PPh_3)_3$ and respective phosphines in the same manner described above. Analytical characterizations of the complexes are as follows.

$RuCl_2((-)\text{-}o\text{-ampp})_2(PPh_3)$: yellow crystal; ^1H NMR ($CDCl_3$) δ= 1.54 (6H, broad), 3.75 (6H, s), and 6.20-7.30 (33H, m); $[m]_D^{24}$ -2600° (*c* 0.1, C_6H_6). Found: C, 61.80; H, 5.14; Cl, 7.82%. Calcd for $C_{46}H_{45}Cl_2O_2P_3Ru$: C, 61.74; H, 5.03; Cl, 7.94%.

$RuCl_2((-)\text{-}p\text{-ampp})_2(PPh_3)$: dark brown crystal; ^1H NMR ($CDCl_3$) δ=1.65 (6H, broad), 3.75 (6H, s), and 6.35-7.45 (33H, m); $[m]_D^{24}$ -26.7° (*c* 0.1, C_6H_6). Found: C, 61.17; H, 5.38; Cl, 7.71%. Calcd for $C_{46}H_{45}Cl_2O_2P_3Ru$: C, 61.74; H, 5.03; Cl, 7.94%.

$RuCl_2((-)\text{-pmpp})_3$: pale yellow crystal; ^1H NMR ($CDCl_3$) δ= 0.80 (6H, broad), 1.77 (4H, broad), and 7.10-7.30 (5H, m); $[m]_D^{24}$ +260° (*c* 0.1, C_6H_6). Found: C, 53.82; H, 6.57; Cl; 10.35%. Calcd for $C_{30}H_{45}Cl_2P_3Ru$: C, 53.74; H, 6.77; Cl, 10.58%.

Since the complex from $RuCl_2(PPh_3)_3$ and (+)-nmdp was unable to be isolated, ruthenium-(+)-nmdp complexes were prepared *in situ* to supply for the dehydrogenation of alcohols directly.

Reaction Procedure and Analyses.

A typical reaction was carried out as follows. The chiral ruthenium complex (0.16 mmol) was charged into a two-neck flask (50 cm^3) with a condenser and a nitrogen inlet. The flask was purged with nitrogen gas, and then 1-phenylethanol (10 g, 82 mmol) and benzylideneacetone (10 g, 69 mmol) was put into it. The reaction temperature was controlled within $\pm$1°C. After the desired conversion of the reaction was attained, the unreacted alcohol was fractionally distilled under a reduced pressure and

subjected to optical rotation measurement. In the dehydrogenation of achiral alcohols such as benzyl alcohol with the ruthenium chiral phosphine complexes, it was confirmed that distilled alcohols were never contaminated with any optically active compounds such as the chiral ruthenium complex, chiral ligand, and their decomposed products. Measurement of the optical rotation for the alcohol enriched with one enantiomer was repeated four times and the average value thus obtained was employed to determine its optical purity.

1-3 Results and Discussion

Characteristic Features of Enantio-selective Dehydrogenation of Racemic Alcohols.

In principle, the progress of the reaction during the kinetic resolution always brings about the elevation of the optical purity of the unreacted substrate, as shown in Fig. 1, which is produced in a straight manner from the following equation;

$$\frac{k_R}{k_S} = \frac{\frac{1}{t}\ln([R]_0/[R])}{\frac{1}{t}\ln([S]_0/[S])} = \frac{\ln(1-C)(1-O.P.)}{\ln(1-C)(1+O.P.)} \qquad (1)$$

starting from the equation for first-order kinetics; $-d[R]/dt=k_R \times [R]$, and $-d[S]/dt=k_S[S]$. Where C is the fraction of consumption of racemates, O.P. (optical purity of the unreacted substrate) is %O.P./100, R and S are enantiomers, the square brackets signify the concentration, and subscript zero represents the initial state. Thus, the optical purity of the unreacted substrate is

an inadequate estimate for enantio-selectivity in the kinetic resolution. The relative rate-constant ratio (k_R/k_S) of three variables in Fig. 1 is appreciably independent on the reaction time, so that it can be used as a measure of the extent of enantio-selectivity.

When the dehydrogenation of 1-phenylethanol (1) by the chiral ruthenium(II) complexes was carried out at 180°C with or without benzylideneacetone as hydrogen donor, the optical purity of unreacted 1 enriched with the (*R*)-(+) or (*S*)-(-)-enantiomer monotonously increased with increasing in conversion of the alcohol. Plots of $\ln[R]_0/[R]$ and $\ln[S]_0/[S]$ calculated from Equation (1) against the reaction time showed a good linear relationship (Fig. 2), indicating to obey pseudo-first-order rate law, which was also reflected in the constant k_R/k_S ratio during the reaction. Therefore, the extent of enantio-selectivity in the present reaction can be defined by the ratio of the rate constant for each enantiomer.

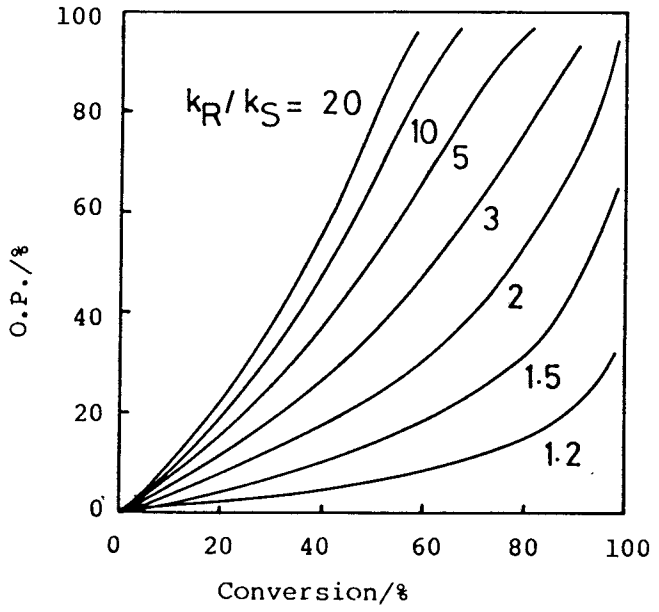


Fig. 1. Relation between the relative rate ratio and the optical purity of unreacted alcohol.

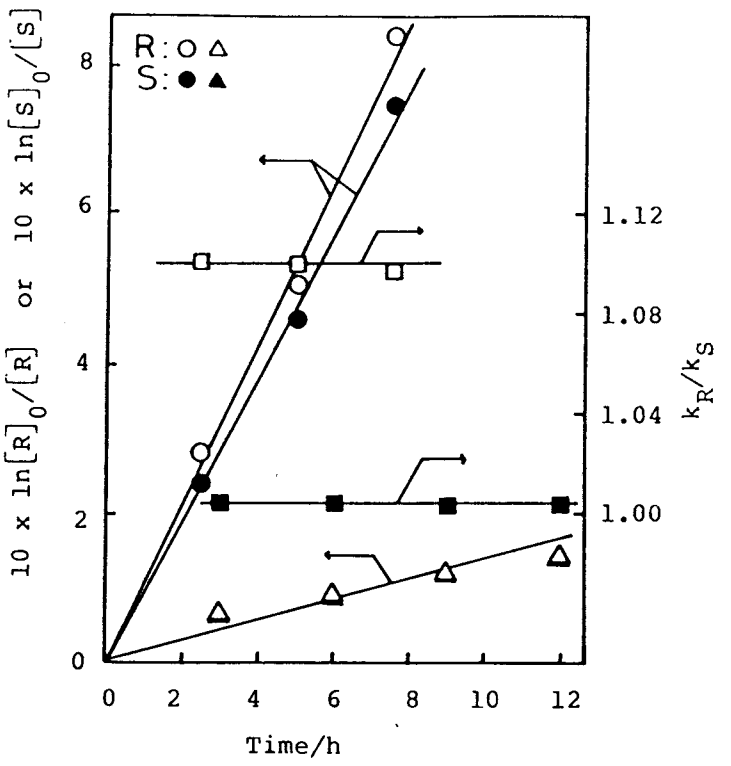


Fig. 2. Plots of reaction time *vs.* $\ln[R]_0/[R]$ or $\ln[S]_0/[S]$, and k_R/k_S for the dehydrogenation of 1 by Ru(II)-(+)-nmdp complex at 180°C with (○, ●, □) or without (△, ▲, ■) benzylideneacetone.
(+)-nmdp/$RuCl_2(PPh_3)_3$=6; $RuCl_2(PPh_3)_3$, 2 or 8 mmol dm^{-3} with or without the olefin, respectively.

In the case of the dehydrogenation of 1 without hydrogen acceptor, the enantio-selectivity is very low (k_R/k_S=1.003-1.004) but reproducible with the products consisted of acetophenone (AP)(45-48 mol%), racemic and meso bis(1-phenylethyl) ether (PEE)(32-34 mol%), ethylbenzene (11-15 mol%), and styrene (4-5 mol%).

The addition of a hydrogen acceptor such as benzylideneacetone to the reaction system showed a considerable increase in

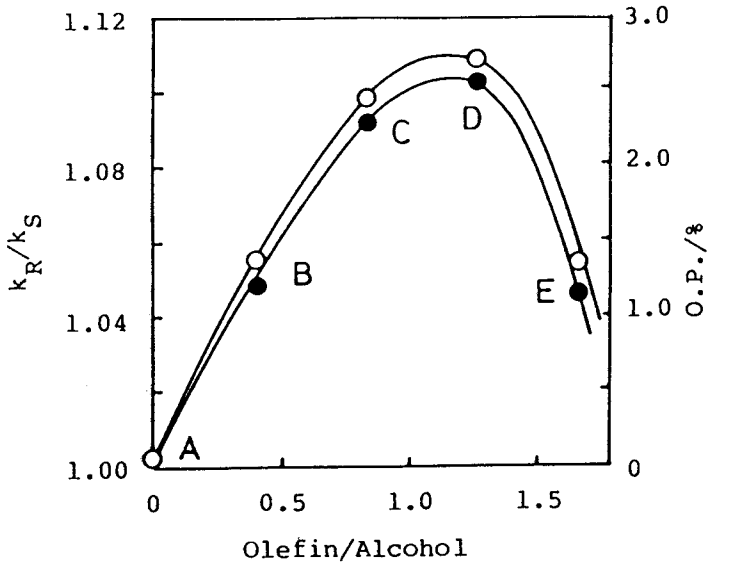


Fig. 3. Effects of mole ratio of benzylideneacetone/1 on enantio-selectivity (O) and optical purity (●) in the dehydrogenation of 1 by Ru(II)-(+)-nmdp complex at 180°C for 5 h. $RuCl_2(PPh_3)_3$, 8 mmol dm^{-3}; (+)-nmdp/$RuCl_2(PPh_3)_3$=6. Conv. (%), AP (mol%), PEE (mol%): A(19.4, 42.0, 47.3); B(36.7, 85.6, 10.2); C(38.2, 95.7, trace); D(38.5, 96.4, trace); E(37.0, 93.2, trace).

the reaction rate and the enantio-selectivity (Fig. 3), but these reduced somewhat in the excess olefin concentration. In this reaction system, formation of the byproducts, especially PEE, was remarkably decreased with increasing amount of the additive, and AP was preferentially produced with comprizing over 95 mol% of the products in the reaction with the ratio of benzylideneacetone/1>0.84 (Fig. 3). Probably, the enhancement of the enantio-selectivity due to addition of the unsaturated compound is attributable to the promotion of the dehydrogenation of 1 to AP with the enantio-differentiating process by the ruthenium complex (discussed later).

Table 1. Enantio-selective Abilities of Ru(II) Chiral Phosphine Complexes in the Dehydrogenation of 1 with Benzylideneacetone[a)]

Complex	Time / h	Conv / %	O.P.[b)] / %	k_R/k_S
$RuCl_2(PPh_3)_3$-(+)-nmdp	5	38.2	2.28	1.10
$RuCl_2$((-)-*o*-ampp)$_2$(PPh_3)	14	38.1	1.30	1.06
$RuCl_2$((+)-bmpp)$_3$	9	49.3	0.90	1.03
$RuCl_2$((-)-pmpp)$_3$	3	40.5	0.24	1.01
$RuCl_2$((-)-*p*-ampp)$_2$(PPh_3)	5	63.5	0.37	0.993

a) Benzylideneacetone/1=0.84; the reaction temperature, 180°C; the ruthenium complex, 8 mmol dm^{-3} except for $RuCl_2$((-)-pmpp)$_3$ (4 mmol dm^{-3}).

b) Calculated from the specific rotation for the (*S*)-(-)-alcohol; $[\alpha]_D^{23}$ -52.5° (*c* 2.27, CH_2Cl_2).[8)]

Enantio-selective Ability of Chiral Ruthenium(II) Complexes.

The dehydrogenation of 1 by chiral ruthenium(II) complexes was carried out at 180°C in the presence of benzylideneacetone. Results are shown in Table 1. The enantio-selectivity was substantially dependent on the structure of the chiral phosphine, and in the following order: $RuCl_2(PPh_3)_3$-(+)-nmdp>$RuCl_2$((-)-*o*-ampp)$_2$(PPh_3)>$RuCl_2$((+)-bmpp)$_3$>$RuCl_2$((-)-pmpp)$_3$>$RuCl_2$((-)-*p*-ampp)$_2$(PPh_3). The chiral phosphine possessing different and bulky substituents seems to be efficient.

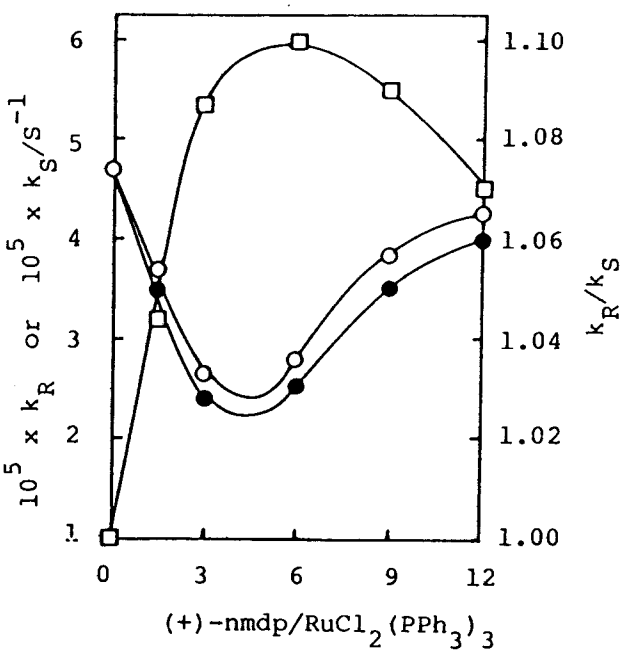


Fig. 4. Effects of mole ratio of (+)-nmdp/$RuCl_2(PPh_3)_3$ on catalytic activity (k_R, O ; k_S, ●) and enantio-selectivity (k_R/k_S, □) in the dehydrogenation of 1 by Ru(II)-(+)-nmdp complex. Reaction conditions were the same as in Fig. 3, except for benzylideneacetone/1=0.84.

The enantio-selective ability of the most effective $RuCl_2$-$(PPh_3)_3$-(+)-nmdp complex, however, considerably suffered the concentration effect of (+)-nmdp, and the selective ability was the greatest around (+)-nmdp/$RuCl_2(PPh_3)_3$=6 (Fig. 4). This phenomenone is presumably relevant to the following equiliblium in the reaction system:

$$RuCl_2(PPh_3)_3 \rightleftharpoons RuCl_2(PPh_3)_2 + PPh_3 \qquad (2a)$$

$$RuCl_2(PPh_3)_2 + n\ (+)\text{-nmdp} \overset{-PPh_3}{\rightleftharpoons} RuCl_2(PPh_3)((+)\text{-nmdp}) +$$

$$(n\text{-}1)\ (+)\text{-nmdp} \overset{-PPh_3}{\rightleftharpoons} RuCl_2((+)\text{-nmdp})_2 + (n\text{-}2)\ (+)\text{-nmdp} \rightleftharpoons$$

$$RuCl_2((+)\text{-nmdp})_3 + (n\text{-}3)\ (+)\text{-nmdp}. \qquad (2b)$$

In the case of n=(+)-nmdp/$RuCl_2(PPh_3)_3$<6, the presence of (+)-nmdp in the coordination sphere of $RuCl_2(PPh_3)_3$ decreases the dehydrolyzing ability of $RuCl_2(PPh_3)_3$ with diminution of the reaction rate, and the ligand exchange between PPh_3 and (+)-nmdp which results in the formation of $RuCl_2(PPh_3)$((+)-nmdp), $RuCl_2$-((+)-nmdp)$_2$ and/or $RuCl_2$((+)-nmdp)$_3$, also gives rise to a retardation of the reaction because the ruthenium(II) complexes possessing (+)-nmdp ligand are catalytically less active than $RuCl_2$-$(PPh_3)_2$. On the contrary, the formation of ruthenium(II) complexes involving (+)-nmdp ligand elevates the enantio-selectivity, and at n=6 the amount of $RuCl_2$((+)-nmdp)$_2$ seems to become largest among the chiral ruthenium complexes.

With excess concentration of (+)-nmdp (n>6), the selectivity was lowered by increasing the (+)-nmdp concentration. The excess free phosphine presumably changes the above equiliblia through the promotion of $RuCl_2$((+)-nmdp)$_2$ formation, and the selectivity is lowered by increasing of the concentration of catalytically inactive $RuCl_2$((+)-nmdp)$_3$. In such situation, the reaction rate increased again, probably owing to increasing basicity of the reaction system by the free phosphine. This basicity effect on the rate enhancement is directly related to the contribution of bases to the dissociation of the oxygen-bound hydrogen of alcohol as proton in Reaction (3a) or (4b).

$$RR'CHOH + (Ru) \xrightarrow{-H^+} [RR'CHO—(Ru)] \quad (3a)$$

$$RR'CHOH + H^+ + [RR'CHO-(Ru)] \xrightarrow{-(Ru)} (RR'CH)_2O + H_2O \quad (3b)$$

Where (Ru) denotes catalytically active species.

Effects of Hydrogen Acceptors.

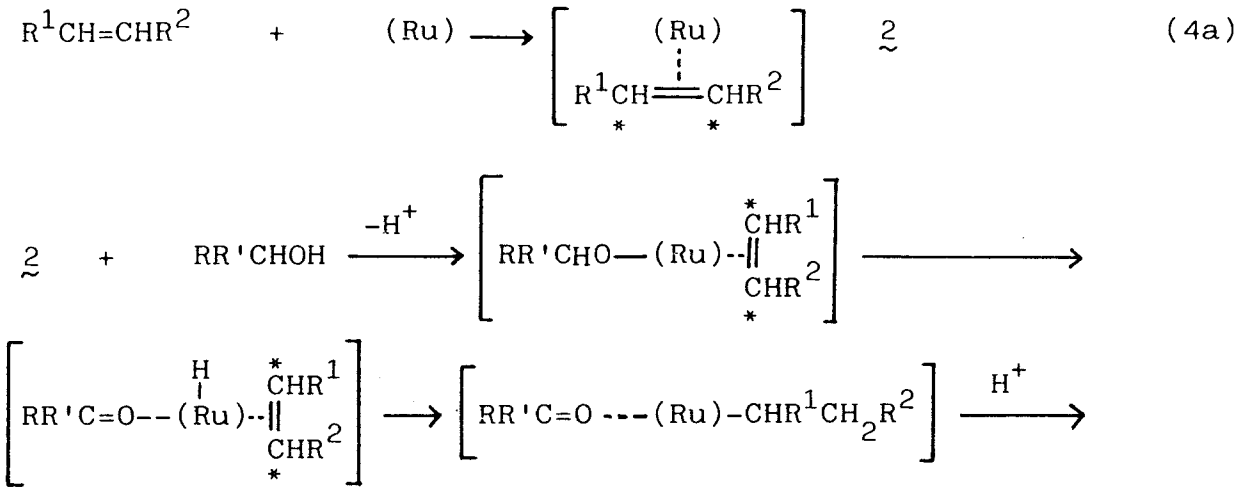
In the present reaction, the enantio-selectivity was affected by the concentration of hydrogen acceptor with respect to the alcohol (Fig. 3). The low olefin concentration presumably prevents the intermediate [RR'CHO—(Ru)] from converting into RR'C=O and the ruthenium hydride complex (Ru-H) because of the lack of the hydrogen acceptor, and it promotes PEE formation in Reaction (3a) and (3b). As also shown in Fig. 3, the gradual increase in olefin concentration makes PEE/AP ratio smaller *via* hydrogen transfer from the alcohol to the olefin in Reaction (3a) and (4b) (see later), and results in higher enantio-selectivity. However, the excess concentration of olefin suppresses the selectivity, probably through a blocking of the active site of the complex by the olefin. In fact, the reaction rate increased monotonously up to benzylideneacetone/$\underset{\sim}{1}$=1.26, but it decreased in excess olefin concentration; (the olefin/$\underset{\sim}{1}$; 10^4k_R, 10^4k_S)=(0; 1.21, 1.19), (0.42; 2.61, 2.47), (0.84; 2.80, 2.55), (1.26; 2.85, 2.56), and (1.68; 2.64, 2.50) under the condition shown in Fig. 3.

The enantio-selectivity was also found to vary from olefin to olefin. Representative results of the dehydrogenation of $\underset{\sim}{1}$ by the ruthenium-(+)-nmdp complex are shown in Table 2. There are possible explanation concerning the structural effect of hydrogen acceptors on the selectivity: (a) the type of the hydrogen acceptor affects the equiliblium of the complex (for example the distribution of $RuCl_2(PPh_3)$((+)-nmdp), $RuCl_2$((+)-nmdp)$_2$, and $RuCl_2$((+)-nmdp)$_3$ in Reaction (2a) and (2b)), and causes different selectivity, and (b) the coordination of the hydrogen acceptor to the chiral ruthenium complex gives rise to a new chiral field.

Table 2. Enantio-selectivity Change in the Dehydrogenation of 1 by Hydrogen Acceptors[a)]

No.	Hydrogen acceptor	Temp °C	Time h	Conv %	O.P. %	k_R/k_S
1	Benzylidene-acetophenone	180	8	17.3	2.01	1.24
		190	8	46.4	4.31	1.15
		195	8	81.2	4.79	1.06
2	Benzylidene-acetone	165	5	18.7	1.17	1.12
		170	5	27.9	1.70	1.11
		180	5	38.2	2.28	1.10
		190	5	60.3	2.11	1.05
3	*trans*-Stilbene	180	8	26.2	0.10	1.04
		195	8	41.8	0.05	1.00_2
4	Ethyl cinnamate	165	8	7.6	0.09	1.02
		180	8	36.1	0.10	1.01
5	Dodecyl methacrylate	180	5	34.2	0.12	1.00_4
6	2-Ethylhexyl methacrylate	170	9	14.0	0.28	1.04
		190	7	36.7	1.63	1.07
7	Hexyl methacrylate	180	8	13.7	0.14	1.02
8	Secobarbital	180	5	18.9	0.72	1.06
9	None	165	5	11.3	0.07	1.01
		180	5	19.4	0.04	1.01

a) Catalyst, $RuCl_2(PPh_3)_3$-(+)-nmdp complex; the ruthenium complex, 8 mmol dm^{-3}; (+)-nmdp/$RuCl_2(PPh_3)_3$=6; Hydrogen acceptor/1=0.84.



$$RR'C{=}O + R^1CH_2CH_2R^2 + (Ru) \qquad (4b)$$

Such effect of the hydrogen acceptor on the selectivity was observed in the case of the dehydrogenation of racemic alcohols by $Ru_2Cl_4((-)\text{-diop})_3$ (diop=2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)-2,3-butanediol); *e.g.*, k_R/k_S=1.11 for benzylideneacetone, 1.06 for 2-ethylhexyl methacrylate, and 1.03 in the absence of olefin (see Chapter 2).[11] From this, explanation (b) seems plausible, even though the induced asymmetry of olefins coordinated with platinum(II) chiral amine complexes has been confirmed only at the temperatures much lower than 160 to 195°C in the present experiment;[12,13] that is, newly formed asymmetric center in the intermediate $\underset{\sim}{2}$ might not be completely diminished *via* epimerization[13] at a temperature range of 160 to 195°C.

Among hydrogen acceptors employed, two unsaturated ketones of benzylideneacetone and benzylideneacetophenone were most effective in terms of the enhancement of the selectivity. Hence, one could propose that, with deliberately chosen acceptors, the

Table 3. Enantiomer-differentiation of Secondary Alcohols by $RuCl_2(PPh_3)_3$-(+)-nmdp Complex with Benzylideneacetophenone[a)]

No.	RR'CHOH		Temp	Time	Conv	O.P.[b)]	k_R/k_S
	R	R'	°C	h	%	%	
10	Ph	Me	160	7	26.2	1.60	1.11
			170	6	34.3	1.54	1.08
			180	5	47.3	1.74	1.05
			190	2	41.5	1.37	1.05
11	Ph	Et	170	7	26.3	1.37	1.09
			180	5	38.7	0.82	1.03
			190	3	36.4	1.00	1.05
12	$PhCH_2$	Me	170	12	31.1	0.09	0.995
			180	6	27.4	0.07	0.993
			190	4	39.9	0.09	0.994

a) Mole ratio of (+)-nmdp/$RuCl_2(PPh_3)_3$, 3; $RuCl_2(PPh_3)_3$, 8 mmol dm^{-3}; benzylideneacetone/alcohol=1.

b) Calculated from the specific rotation: $[\alpha]_D^{17-20}$ +40° (*c* 5, C_6H_6) for (*R*)-(+)-PhCH(Et)OH;[15] $[\alpha]_D^{25}$ -20.2°(*c* 5, $C_2H_5OC_2H_5$) for (*R*)-(-)$PhCH_2CH(Me)OH$.[16]

corresponding phosphobetaine can be expected to form in the reaction of the above ketones with the chiral ligand.[14] Especially in the case of the *in situ* prepared complex, the phosphobetaine ($R''_3\overset{+}{P}CH(Ph)CH=C(R)O^-$) is then bound to the ruthenium complex as a new chiral ligand. The unsaturated esters such as the methacrylates, except 2-ethylhexyl methacrylate which possesses an asymmetric carbon atom, were relatively less effective, probably because negatively charged oxygen of the ester binds to the

ruthenium complex and disturbs the coordination of the chiral ligand in the case of the *in situ* prepared Ru(II) complex.

The free proton participation in Reaction (4b) has already been confirmed in the transfer hydrogenation of benzylideneacetophenone by 1-phenylethanol with $RuCl_2(PPh_3)_3$.[10] Through Reaction (4a) and (4b), the abstraction of α-carbon-bound hydrogen by the ruthenium complex is the rate-determining step.[10]

The structural change of alcohol (RR'CHOH: R, R'=Ph, Me; Ph, Et; $PhCH_2$, Me) varied the reaction rate and the enantio-selectivity (Table 3). The selectivity order was not simply reflected in the bulkiness of the substituents.

Activation Parameter Relationships.

The enantio-selectivity was also dependent on the reaction temperature and raised by lowering the temperature (Table 2 and 3). Presumably, lower temperature makes the interaction among the species in Reaction (4a) and (4b) more stronger. The temperature dependence of the reaction rate in the reaction was expressed by linear Arrhenius relationship for each enantiomer. A typical example is shown in Fig. 5.

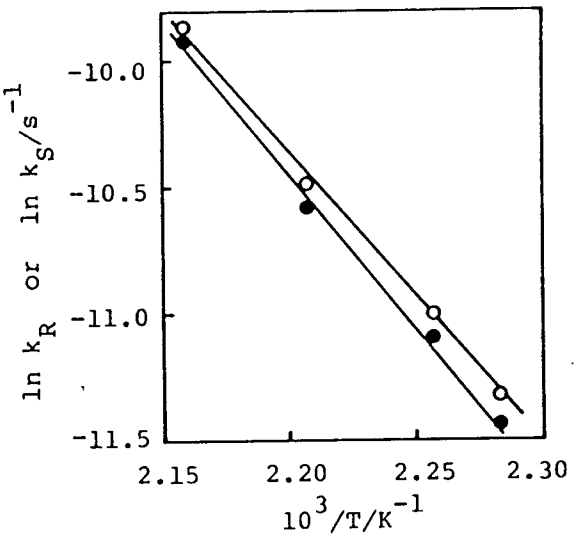
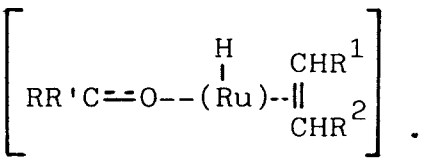


Fig. 5. Arrhenius plots in the dehydrogenation of 1 by Ru(II)-(+)-nmdp complex with benzylideneacetone. R, ○; S, ●. Reaction conditions were the same as in Fig. 3.

Notably, the activation parameters thus obtained, which reflect those for the rate determining process in Reaction (4b), bore isokinetic relationship; that is, the smaller $\Delta H^{\ddagger}$ values for one of enantiomers always required negatively larger $\Delta S^{\ddagger}$ values (Fig. 6). In view of the fact that the $\Delta H_R^{\ddagger}$ (for (*R*)-enantiomer) and $\Delta H_S^{\ddagger}$ (for (*S*)-enantiomer) values are different from each other and require different $\Delta S^{\ddagger}$ ($\Delta S_R^{\ddagger}$ and $\Delta S_S^{\ddagger}$ for respective (*R*) and (*S*)-enantiomer) values in the isokinetic relation, the coordination distance between the carbonyl oxygen and the Ru metal center in the following transition state might be different between enantiomers;



The shorter coordination distance probably makes the $\Delta H^{\ddagger}$ value smaller, requiring the negatively larger $\Delta S^{\ddagger}$ value. If this is true, the difference ($\Delta\Delta H^{\ddagger}$) between $\Delta H_R^{\ddagger}$ and $\Delta H_S^{\ddagger}$ values might have a correlation with the difference ($\Delta\Delta S^{\ddagger}$) between $\Delta S_R^{\ddagger}$ and $\Delta S_S^{\ddagger}$ values. In this regard, there is a linear correlation between the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values with intercept zero (Fig. 7). This correlation strongly suggests the enantiomer-differentiating process controlled by steric factors (reflected by $\Delta S^{\ddagger}$) which compensate electronic ones (reflected by $\Delta H^{\ddagger}$); the hydrogen migration from RR'CHOH to the complex might simultaneously occur in the different coordination distance between the enantiomers.

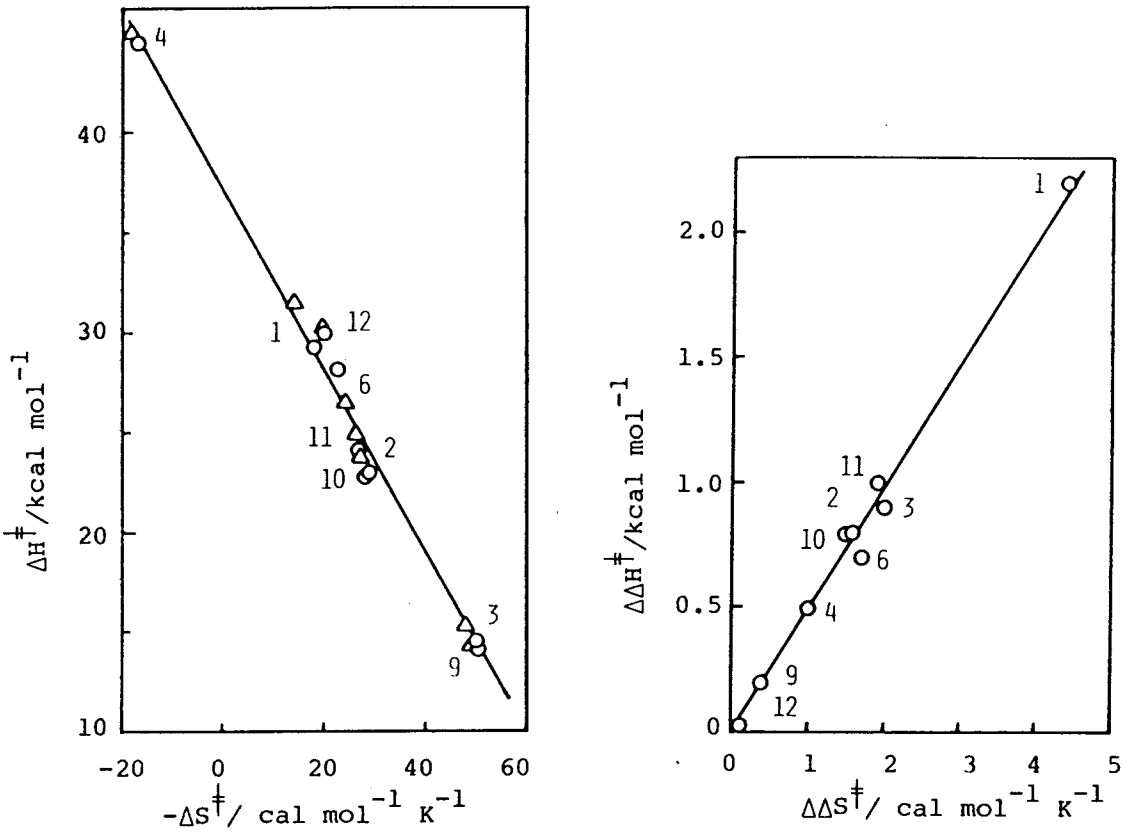


Fig. 6 Isokinetic relationship. Numbers are the same as in Table 2 and 3. R, ○ ; S, △.

Fig. 7 Correlation between $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. Numbers are the same as in Table 2 and 3.

1-4 Summary

Kinetic resolution of racemic secondary alcohols in the dehydrogenation with ruthenium(II) chiral monophosphine complexes was studied. The magnitude of enantio-selectivity was substantially dependent on the structure of the chiral phosphine ligand, the equiliblium of the complex in the reaction system, the asymmetry induced by unsaturated species, and reaction temperature. The linear isokinetic relationship was exhibited between $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values obtained for each enantiomer. There

was also a linear correlation between the differences of the above activation parameters for the enantiomers. These relationships led to an assumption that the enantiomer-differentiating process was controlled by the difference in coordination distance of each enantiomer to the chiral complex.

CHAPTER 2 ENANTIOMER-DIFFERENTIATING DEHYDROGENATION OF SECONDARY ALCOHOLS BY A BINUCLEAR RUTHENIUM(II) CHIRAL DIPHOSPHINE COMPLEX

2-1 Introduction

A chiral diphosphine of (+) or (-)-2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)-2,3-butanediol (diop), first reported by Kagan[17] in 1972, has been accepted as an efficient chiral ligand for rhodium(I)[17] and ruthenium(II)[18,19] complexes catalyzed asymmetric hydrogenation of olefins, for rhodium(I) complex catalyzed asmmetric hydrosilylation of ketones,[20,21] and for nickel(II) complex catalyzed asymmetric Grignard cross-coupling.[22,23]

Therefore, the author has examined the catalytic efficiency of a binuclear ruthenium(II)-(-)-diop complex, $Ru_2Cl_4((-)\text{-diop})_3$, in the enantiomer-differentiating dehydrogenation of racemic secondary alcohols with or without unsaturated compounds as hydrogen donor.

2-2 Experimental

Measurements.

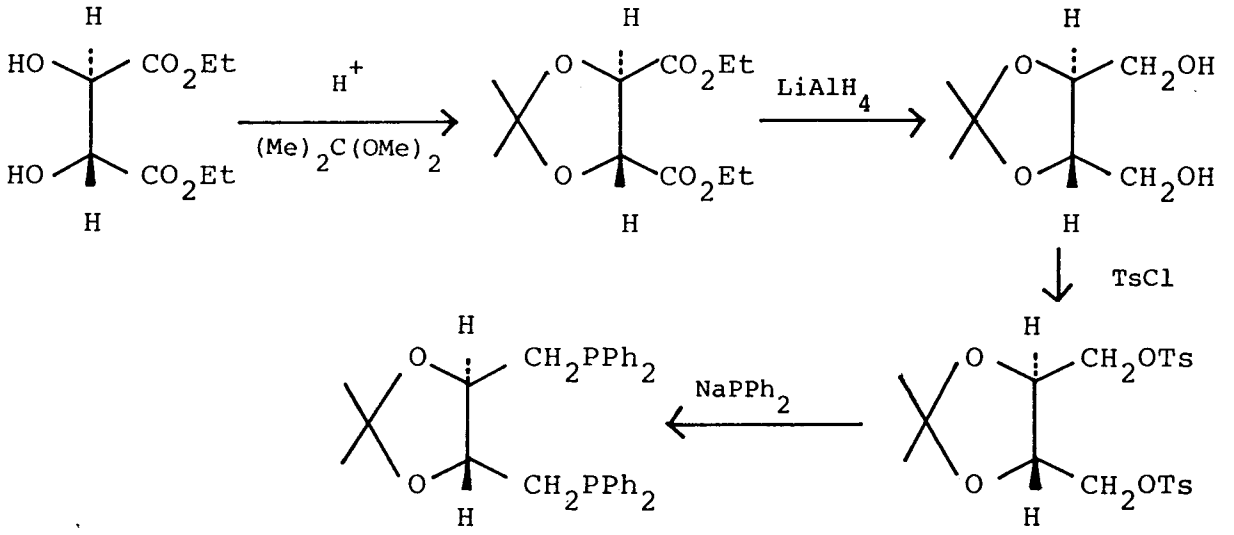
Elemental analyses, records of ^1H NMR spectra, gas-chromatographic analyses and optical rotation measurements were carried out with the same instruments described in Chapter 1.

Materials.

Racemic alcohols were distilled before use. Unsaturated compounds for the dehydrogenation of alcohols were used after

recrystallization or distillation.

The chiral diphosphine of (-)-diop was prepared by Kagan's method[17] (Scheme 1). The chiral phosphines of (-)-*o*-methoxyphenylmethylphenylphosphine (*o*-ampp), (-)-propylmethylphenylphosphine (pmpp), and (+)-benzylmethylphenylphosphine (bmpp) were synthesized according to Mislow's method.[6] (+)-Neomenthyldiphenylphosphine (nmdp) was made by means of the method of Morrison,[3] and ruthenium(II)-(+)-nmdp complex was prepared *in situ* from $RuCl_2(PPh_3)_3$ and (+)-nmdp. The binuclear ruthenium complex, $Ru_2Cl_4((-)\text{-diop})_3$, was prepared by James' method[18] and the other complexes, $RuCl_2((-)\text{-}o\text{-ampp})_2(PPh_3)_3$, $RuCl_2((-)\text{-pmpp})_3$ and $RuCl_2((+)\text{-bmpp})_3$, were made according to the phosphine exchange method.[7] Characterization of $Ru_2Cl_4((-)\text{-diop})_3$ is as follows: ^1H NMR ($CDCl_3$) δ=0.86 (6H, broad), 1.57 (12H, broad), 3.02 (6H, broad), 6.98 (20H, m), and 7.18 (40H, m); IR (CsI), 318 cm^{-1} (Ru-Cl). Found: C, 60.78; H, 5.78; Cl, 7.58%. Calcd for $C_{93}H_{96}Cl_4O_6P_6Ru_2$: C, 60.72; H, 5.22; Cl, 7.22%.



Scheme 1.

Reaction Procedure and Analyses.

The dehydrogenation of secondary alcohol by the ruthenium (II) chiral phosphine complex was carried out in a two-neck flask (50 cm^3) without solvents at 120-195°C under nitrogen atmosphere in the absence or in the presence of hydrogen acceptor. After a desired conversion of the reaction was obtained, the unreacted alcohol was fractionally distilled under reduced pressure and the distillate was subjected to the optical rotation measurement. In the dehyhdrogenation of achiral alcohols such as benzyl alcohol with chiral ruthenium complexes at 120-195°C, the distilled alcohols were confirmed to include no optically active contaminants. In order to determine the optical purity of the alcohol, average value of the optical rotations measured four times was used as the observed one. The distribution of the reaction products was monitored by gas-chromatographic analyses, and some products such as the racemic or meso bis(1-phenylethyl) ether were identified by ^1H NMR after their fractional collection by gas-chromatography.

2-3 Results and Discussion

Propriety to Pseudo-first-order Rate Law.

Dehydrogenation of 1-phenylethanol ($\underset{\sim}{1}$) by $Ru_2Cl_4((-)\text{-diop})_3$ was carried out in the presence of benzylideneacetone as hydrogen acceptor at 165°C. Results are shown in Table 1. The optical purity of the unreacted alcohol increased with increasing in the conversion of $\underset{\sim}{1}$, and the reaction obeyed pseudo-first-order rate law up to 65% conversion; rate constans, k_R and k_S, calculated from the following Equations (1a) and (1b) for each

Table 1. Enantio-selective Dehydrogenation of 1 by $Ru_2Cl_4((-)\text{-diop})_3$ with Benzylideneacetone at 165°C

Time	Conv	$-[\alpha]_D^{23}$	O.P.	10^6k_R	10^6k_S	k_R/k_S	Product/mol%		
h	%	°	%	s^{-1}	s^{-1}		AP	PEE	S,B
2	23.0	0.46	0.88	37.5	35.1	1.07	98.9	1.1	trace
3	32.7	0.65	1.24	37.8	35.5	1.06	83.6	15.5	0.9
4	41.0	0.92	1.75	37.9	35.4	1.07	87.0	12.3	0.7
6	54.9	1.28	2.44	38.0	35.7	1.06	88.0	11.4	0.6
8	65.3	1.49	2.84	37.8	35.8	1.06	88.4	11.2	0.4

a) Catalyst, 2 mmol dm^{-3}; alcohol, 83.4 mmol; olefin, 68.4 mmol.

b) Calculated from the specific rotation; $[\alpha]_D^{23}$ -52.5° (*c* 2.27, CH_2Cl_2) for (*S*)-enantiomer.[8)]

c) AP: acetophenone; PEE: bis(1-phenylethyl) ether; S,B: styrene and ethylbenzene.

enantiomer, were invariable for the reaction period of 8 h, and its ratio (k_R/k_S), which reflects the enantio-selectivity in the present reaction, also unchanged virtually.

$$k_R = \frac{1}{t} \ln[R]_0/[R] = -\frac{1}{t} \ln(1-C)(1-O.P.) \quad (1a)$$

$$k_S = \frac{1}{t} \ln[S]_0/[S] = -\frac{1}{t} \ln(1-C)(1+O.P.) \quad (1b)$$

Where [R] and [S] mean respective concentrations of (*R*) and (*S*)-enantiomer, the subscript zero represents the initial state, C is the fraction of conversion of the racemate, and O.P. (optical purity of the unreacted alcohol) is %O.P./100.

As indicated in Table 1, the present chiral ruthenium complex produced acetophenone (AP) as the main dehydrogenation product of 1, with quantitative saturation of hydrogen acceptor, but small amounts of racemic and meso bis(1-phenylethyl) ether (PEE) were also detected, together with traces of styrene and ethylbenzene.

Efficiency of (-)-diop as Chiral Ligand.

In order to establish the actual efficiency of (-)-diop as a chiral ligand of the ruthenium(II) complex in comparison with other chiral phosphine ligands, the dehydrogenation of 1-phenyl-1-propanol was examined in the presence of benzylideneacetophenone at 165°C with Ru_2Cl_4((-)-diop)$_3$, and $RuCl_2$((-)-*o*-ampp)$_2$-(PPh_3), $RuCl_2$((-)-pmpp)$_3$, $RuCl_2$((+)-bmpp)$_3$, and $RuCl_2(PPh_3)_3$-(+)-nmdp complex (prepared *in situ*). Results are listed in Table 2. Although the enantio-selective ability of Ru_2Cl_4((-)-diop)$_3$ complex is not directly compared with those of the other mononuclear complexes, among the complexes to be tested,

Table 2. Enantio-selective Dehydrogenation of 1-Phenyl-1-propanol by Chiral Ruthenium(II) Complexes with Benzylideneacetophenone at 165°C[a)]

Complex	Time / h	Conv / %	O.P.[b)] / %	k_R/k_S
Ru_2Cl_4((-)-diop)$_3$	24	56.8	11.0	1.30
$RuCl_2$((-)-*o*-ampp)$_2$ (PPh_3)$_3$	78	51.8	0.09	1.00
$RuCl_2$((-)-pmpp)$_3$	3	40.5	0.24	1.01
$RuCl_2$((+)-bmpp)$_3$	70	26.3	1.36	1.09
$RuCl_2(PPh_3)_3$-[c)] (+)-nmdp	72	59.1	0.51	1.01

a) Catalyst, 4 mmol dm^{-3} except for Ru_2Cl_4((-)-diop)$_3$ (2 mmol dm^{-3}); alcohol, 83.4 mmol; olefin, 68.4 mmol.

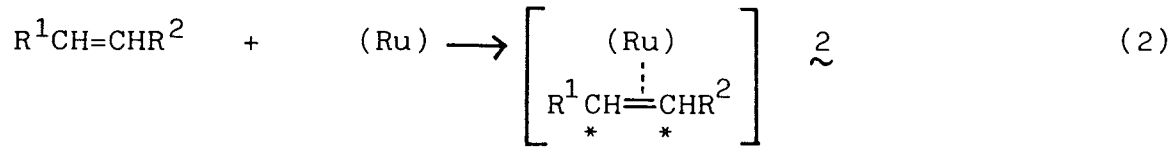
b) Calculated from the specific rotation: $[\alpha]_D^{17-20}$ +40.0° (*c* 5, C_6H_6) for (*R*)-(+)-enantiomer.[15)]

c) Prepared *in situ* (mole ratio of $RuCl_2(PPh_3)_3$/(+)-nmdp, 1/4).

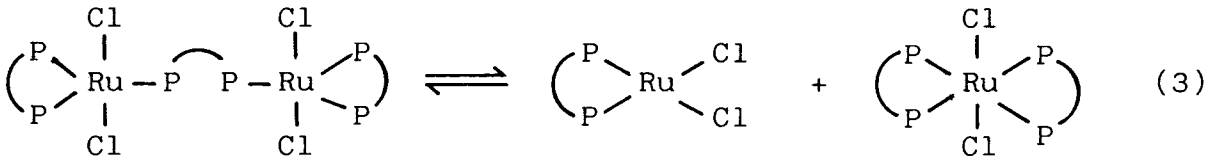
(-)-diop ligand substantially brought about the highest selectivity in the enantiomer-differentiation of the alcohol. Probably the high enantio-selectivity of the ruthenium-(-)-diop complex is attributable to its conformational rigidity due to the seven-membered chelate structure, as compared with other ruthenium(II) chiral monophosphine complexes.

Effects of Hydrogen Acceptors.

Addition of hydrogen acceptors to the reaction system substantially enhanced the enantio-selectivity of the chiral ruthenium complex in comparison with that in the same reaction without hydrogen acceptors, and structure effect of hydrogen acceptors on the enantio-selectivity was observed (Table 3). Such a structure effect of hydrogen acceptors has also been reported in the enantiomer-differentiating dehydrogenation of 1 by *in situ* prepared Rh(I)-(+)-nmdp[24] and Ru(II)-(+)-nmdp complexes.[25] There are two possible explanations of the effect of hydrogen acceptors on the selectivity: (a) the change in the type of hydrogen acceptors affected the equiliblium of $Ru_2Cl_4((-)\text{-diop})_3$ in solution, (b) the coordination of the unsaturated hydrogen acceptor ($R^1CH{=}CHR^2$) to the chiral ruthenium complex gives rise to newly formed asymmetric center, as shown in below;



where (Ru) denotes a catalytically active species supplied from the ruthenium complex. ^{31}P NMR spectroscopy showed the dissociation of bridged type $Ru_2Cl_4((-)\text{-diop})_3$ in solution has been suggested as follows;[26]



where $\overset{\frown}{P\ P}$ denotes (-)-diop. However, it seems unreasonable to explain the effect of hydrogen acceptor on the selectivity only

Table 3. Effect of Hydrogen Acceptors on Enantio-selectivity in the Dehydrogenation of 1 by Ru_2Cl_4((-)-diop)$_3$ [a)]

No.	Hydrogen acceptor	Temp °C	Time h	Conv %	O.P. %	k_R/k_S
1	Benzylideneaceto-phenone	150	22	23.5	0.34	1.02
		170	14	23.9	0.34	1.02
		180	8	37.9	1.03	1.04
		190	5	48.4	3.37	1.11
2	Benzylideneacetone	120	34	18.5	0.29	1.03
		130	24	35.9	0.62	1.03
		150	6	27.1	0.58	1.03
3	*trans*-Stilbene	170	10	12.9	0.71	1.08
		180	10	20.3	1.18	1.10
		190	10	28.3	2.76	1.18
4	Ethyl cinnamate	170	5	22.8	1.14	1.09
		180	5	28.8	1.28	1.08
		190	4	37.9	2.74	1.13
5	2-Ethylhexyl methacrylate	170	5	37.4	5.68	1.28
		180	5	53.4	6.15	1.17
		190	4	72.4	4.27	1.07
6	None	170	8	11.6	0.120	1.02
		180	7	15.7	0.243	1.02
		190	6	21.1	0.294	1.03
7	α-Methylcrotonic acid [b)]	165	8	65.4	4.85	1.09

a) Reaction conditions were the same as in Table 1.

b) The enantiomeric excess of α-methylbutyric acid enriched with (*R*)-enantiomer was 21%.

Table 4. Enantiomer-differentiating Dehydrogenation of 1-Phenyl-1-propanol by $Ru_2Cl_4((-)\text{-diop})_3$ in the Presence of Hydrogen Acceptor[a)]

Hydrogen acceptor	Temp °C	Time h	Conv %	O.P. %	k_R/k_S
Benzylidenaceto-phenone	165	24	56.8	11.0	1.30
	175	11	75.7	14.1	1.22
Benzylideneacetone	165	8	56.3	2.52	1.03

a) Reaction conditions were the same as in Table 1.

on the basis of Explanation (a).

On the other hand, Explanation (b) seems plausible because asymmetric centers induced by the coordination of olefins to chiral metal complexes (*viz.*, Platinum-chiral amine complexes) have already been reported.[12,13] Although, in the case of the platinum amine complexes, Reaction (2) has been established only at temperature much lower than 120-195°C, the newly formed asymmetric centers in the intermediate $\underset{\sim}{2}$ might not be completely disappeared *via* epimerization,[12,13] even in the present temperature range. The possibility of Reaction (2) is supported by the fact that α-methylcrotonic acid used as a prochiral hydrogen acceptor instead of achiral olefins was converted into a chiral species ((*R*)-(-)-$MeCH_2CH(Me)CO_2H$) with enantiomeric excess of 21% in the dehydrogenation of $\underset{\sim}{1}$ by $Ru_2Cl_4((-)\text{-diop})_3$ at 165°C, and simultaneously (*S*)-(-)-$\underset{\sim}{1}$ was obtained with the O.P. of 4.85% (at 68.4% conversion).

In connection with the above effect of hydrogen acceptors on enantio-selectivity, change in the type of racemic alcohol also affected the magnitude of the selectivity to a substantial extent (Table 4).

Reaction Mechanism.

If the induced asymmetry in the intermediate $\underset{\sim}{2}$ plays an important role in the enhancement of enantio-selectivity, the coordination of the hydrogen acceptor to the chiral complex is required before the coordination of the alcohol to the complex can proceed. In this regard, an increase in the concentration of a hydrogen acceptor with respect to that of the alcohol resulted in a monotonous increase in the reaction rate up to the mole ratio of olefin/alcohol≈1, but excess concentration of olefin retarded the reaction rate (Fig. 1). This probably implies that an increase in the olefin concentration raises the concentration of the intermediate $\underset{\sim}{2}$, which, in turn, reacts with the alcohol in following way;

$$\underset{\sim}{2} + RR'CHOH \xrightarrow{-H^+} \left[RR'CHO\text{—}(Ru)\text{--}\overset{*}{C}HR^1 \,\|\, \overset{*}{C}HR^2 \right] \longrightarrow$$

$$\left[RR'C{=}O\text{--}(Ru)\text{--}(H)\,\overset{*}{C}HR^1 \,\|\, \overset{*}{C}HR^2 \right] \longrightarrow \left[RR'C{=}O\text{--}(Ru)\text{-}\overset{*}{C}HR^1CH_2R^2 \right] \xrightarrow{H^+}$$

$$RR'C{=}O + R^1CH_2CH_2R^2 + (Ru). \qquad (4)$$

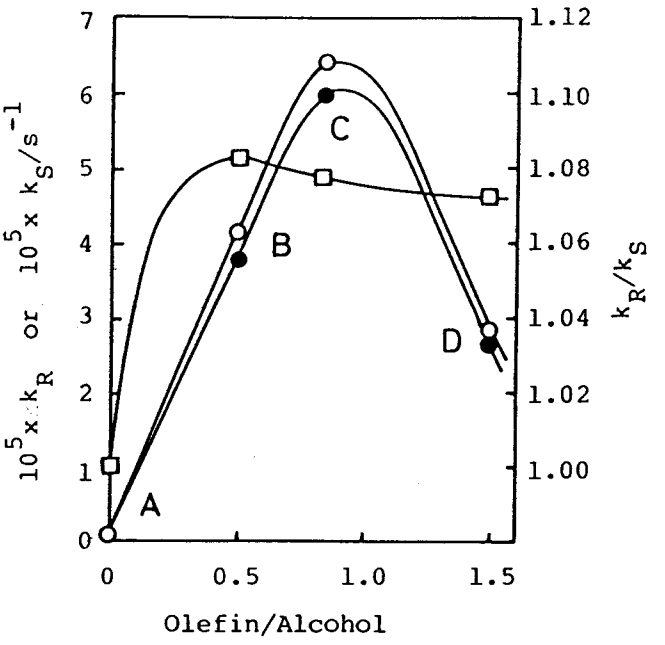


Fig. 1. Effects of mole ratio of benzylideneacetone/1 on reaction rate (k_R, ○ ; k_S, ●) and enantio-selectivity (k_R/k_S, □) in the dehydrogenation of 1 by Ru_2Cl_4((-)-diop)$_3$ (2 mmol dm^{-3}) at 165°C. Conv. (%), AP (mol%), PEE (mol%): A(45.7, 35.2, 64.4); B (25.0, 97.4, trace); C(28.4, 98.8, trace); D(18.2, 98.3, trace).

In the case of using excess of olefin, its shielding of the active site of the intermediate 2 depresses the reaction between the intermediate 2 and the alcohol in Reaction (4). The reaction between the intermediate 2 and the alcohol starts *via* the deprotonation of alcohol. The deprotonation process, comparable with rate-determining step, can be explained by rate enhancement with addition of a base; the dehydrogenation of ethanol by $[Ru_2Cl_3(PEt_2Ph)_6]Cl$ is accelerated by potassium hydroxide,[9] and the transfer hydrogenation of benzylideneacetophenone by PhCH(Me)O$^-$Na$^+$ with $RuCl_2(PPh_3)_3$ is markedly accelerated as compared

with a similar reaction including PhCH(Me)OH.[10]

Activation-parameter Relationships.

The rate of dehydrogenation of the alcohol by the ruthenium (II)-(-)-diop complex is also dependent on reaction temperature between the enantiomers, and enantio-selectivity comes to be affected by the temperature (Table 3). Temperature dependence of the rate constant for each enantiomer can be expressed by the linear Arrhenius relationship (Fig. 2); the activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) obtained for a series of experiments shown in Table 3, which reflect those for the rate-determining hydrogen abstraction process in Reaction (4), exhibited an isokinetic relationship, that is, the smaller $\Delta H^{\ddagger}$ values for one of enantiomers always require larger negative $\Delta S^{\ddagger}$ values (Fig. 3). Such an

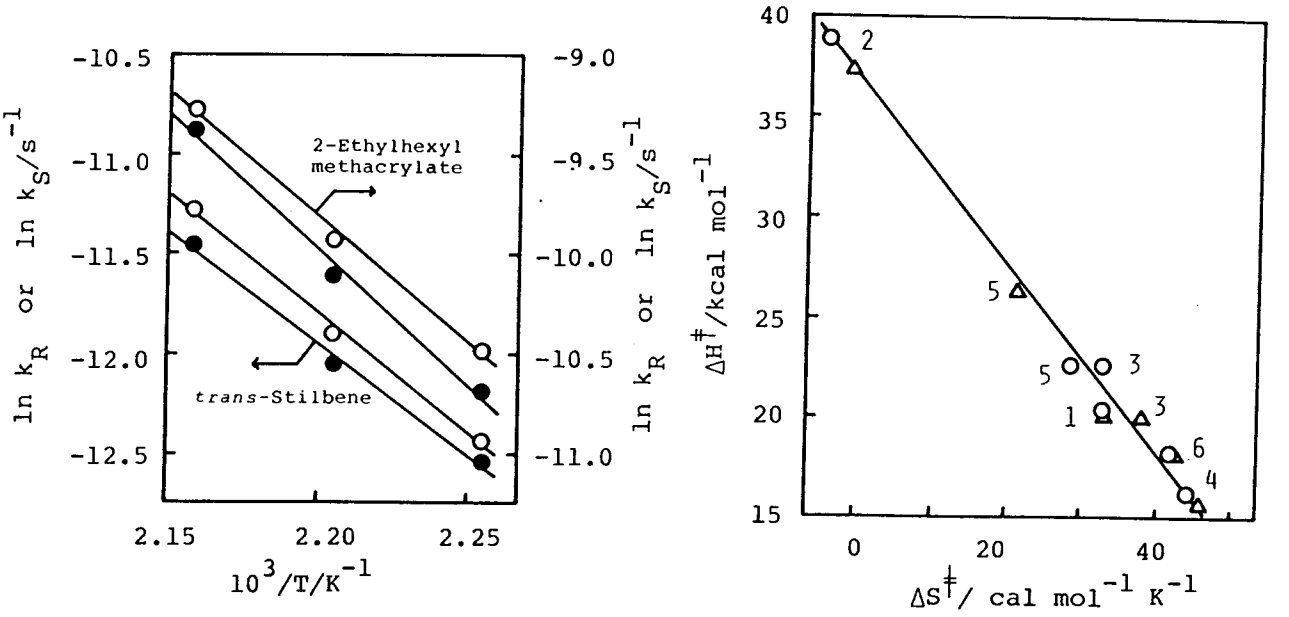


Fig. 2. Typical Arrhenius plots. k_R, ○ ; k_S, ● .

Fig. 3. An isokinetic relationship. Numbers are the same as in Table 3. R, ○ ; S, △ .

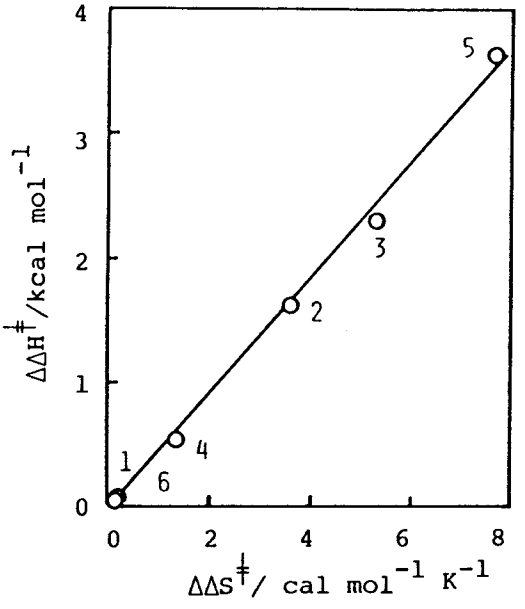


Fig. 4. Correlation between $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. Numbers are the same as in Table 3.

isokinetic relationship indicates that the electronic factors reflecting in $\Delta H^{\ddagger}$ are compensated by the steric factors reflecting in $\Delta S^{\ddagger}$. Hence, the difference in $\Delta H^{\ddagger}$ between the (*R*) and (*S*)-enantiomers ($\Delta H_R^{\ddagger}$ and $\Delta H_S^{\ddagger}$ respectively) leads to the idea that the coordination distance between the oxygen and the ruthenium metal in the transition state might be different between the enantiomers; the shorter coordination distance makes the $\Delta H^{\ddagger}$ values smaller, while it makes negative $\Delta S^{\ddagger}$ ones larger. If this is true, the difference between $\Delta H_R^{\ddagger}$ and $\Delta H_S^{\ddagger}$ values, $\Delta\Delta H^{\ddagger}$, is correlated with that between $\Delta S_R^{\ddagger}$ and $\Delta S_S^{\ddagger}$ (for (*R*) and (*S*)-enantiomer respectively) values, $\Delta\Delta S^{\ddagger}$. In this respect, there is a linear correlationship between $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values with the intercept of zero (Fig. 4). It may be deduced, therefore, that coordination of the alcohol to the chiral ruthenium complex occurs at a different coordination distance between the enantiomers under asymmetric circumstances, *viz.*, stereochemical influence of chiral ligand.

2-4 Summary

The asymmetric dehydrogenation of racemic alcohols by $Ru_2Cl_4((-)\text{-diop})_3$ was investigated with or without hydrogen acceptors at 120-195°C. The magnitude of enantio-selectivity was substantially affected by the structure of the alcohols and hydrogen acceptors, and by reaction temperature. The activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) obtained from the linear Arrhenius dependence of reaction rate constants for each enantiomer bore an isokinetic relationship, and the differences in the parameters of the enantiomers ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) also showed a satisfactory linear correlationship between them.

CHAPTER 3 ENANTIOMER-DIFFERENTIATING DEHYDROGENATION OF A SECONDARY ALCOHOL BY RHODIUM(I) CHIRAL PHOSPHINE COMPLEXES

3-1 Introduction

Rhodium(I) complexes possessing chiral phosphine ligand have been widely utilized as enantio-selective catalyst in asymmetric reaction, such as asymmetric hydrogenation[1] or hydroformylation[27] of prochiral olefins, and asymmeric hydrosilylation of ketones.[21,28] However, there have been no reports on the chiral rhodium(I) complexes utilized in the kinetic resolution of racemates.

This Chapter describes the enantiomer-differentiating dehydrogenation of racemic 1-phenylethanol (1) in the presence of unsaturated species by *in situ* prepared rhodium(I)-(+)-neomenthyldiphenylphosphine (nmdp) or rhodium(I)-(-)-2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)-2,3-butanediol (diop) complexes. Characteristic features of the chiral rhodium(I) complexes in the reaction is shown with respect to the dependence of catalytic enantio-selectivity on the concentration of chiral phosphine and of unsaturated additives, and on reaction temperature.

3-2 Experimental

Measurements.

Records of ^{1}H NMR spectra, gas-chromatographic analyses and optical rotation measurements were carried out with the same instruments described in Chapter 1.

Materials.

The alcohol of 1 was distilled before use. Unsaturated compounds were supplied for the dehydrogenation of the alcohol after distillation or recrystallization.

Chiral phosphines of (+)-nmdp and (-)-diop were synthesized according to Morrison's[3] and Kagan's[17] methods, respectively. Rhodium(I) complexes, $[RhCl(C_2H_4)_2]_2$ and RhH((-)-diop), were prepared by means of the methods of Cramer[29] and Cullen,[30] respectively. The chiral rhodium(I)-(+)-nmdp and rhodium(I)-(-)-diop complexes were prepared *in situ* from $[RhCl(C_2H_4)_2]_2$ and respective phosphines; the mole ratios of (+)-nmdp/$[RhCl(C_2H_4)_2]_2$ and (-)-diop/$[RhCl(C_2H_4)_2]_2$ were 6 and 3, respectively, with some exceptions noticed in this Chapter.

Reaction Procedure and Analyses.

The dehydrogenation of 1 by the rhodium chiral phosphine complexes was carried out in a two-neck flask (50 cm^3) without solvent at 160-190°C under nitrogen atmosphere. After a desired conversion of the reaction was obtained, the unreacted alcohol was fractionally distilled under reduced pressure and then the distillate was subjected to optical rotation measurement. In the dehydrogenation of benzyl alcohol, achiral alcohol, with the chiral rhodium (I) complexes at 180°C, it was confirmed that the distilled alcohol included no optically active contaminants. To determine the optical purity of the alcohol, the average value of the optical rotations measured four times was used as observed one. The distribution of reaction products was monitored by gas-chromatography, and the products were identified by ^1H NMR after their fractional collection by gas-chromatography.

3-3 Results and Discussion

Propriety to Pseudo-first-order Rate Law.

When the dehydrogenation of racemic 1 by the rhodium(I)-(+)-nmdp complex was carried out at 180°C in the presence of benzylideneacetone as hydrogen acceptor, the optical purity (O.P.) of unreacted 1 enriched with (*S*)-(-)-enantiomer increased with increasing in conversion of 1 (Table 1). It was shown that the reaction obeyed pseudo-first-order rate law; rate constants, k_R and k_S, calculated from the following Equations (1a) and (1b) for each enatiomer, where almost invariable for the reaction period of 36 h. The ratios (k_R/k_S), which reflect the enantioselectivity in the present reaction, were also constant virtually.

$$k_R = \frac{1}{t} \ln[R]_0/[R] = -\frac{1}{t} \ln(1-C)(1-O.P.) \qquad (1a)$$

$$k_S = \frac{1}{t} \ln[S]_0/[S] = -\frac{1}{t} \ln(1-C)(1+O.P.) \qquad (1b)$$

Where [R] and [S] mean respective concentrations of (*R*) and (*S*)-enantiomer, the subscript zero represents the initial state, C is the fraction of conversion of the racemate, and O.P. is %O.P./100.

As shown in Table 1, products of the present reaction mainly consisted of acetophenone (AP) and racemic and meso bis(1-phenylethyl) ether (PEE) together with a small amount of styrene and ethylbenzene, including saturated product of the hydrogen acceptor.

Table 1. Enantio-selective Dehydrogenation of 1 by Rh(I)-(+)-nmdp Complex with Benzylideneacetone at 180°C [a]

Time	Conv	$-[\alpha]_D^{23}$	O.P.[b]	$10^6 k_R$	$10^6 k_S$	k_R/k_S	Products/mol%[c]			
h	%	°	%	s^{-1}	s^{-1}		AP	PEE	ST	EB
8	6.1	0.188	0.358	2.32	2.08	1.11	75.6	16.8	6.0	1.6
19	14.3	0.224	0.427	2.32	2.19	1.06	64.5	30.0	3.2	2.3
30	21.6	0.363	0.691	2.31	2.18	1.06	79.8	17.6	1.4	1.2
36	25.2	0.516	0.983	2.32	2.17	1.07	79.9	17.9	1.9	0.3

a) Catalyst was prepared *in situ* from $[RhCl(C_2H_4)_2]_2$ (5 mmol dm^{-3}) and (+)-nmdp (30 mmol dm^{-3}); 1, 83.5 mmol; olefin, 68.5 mmol.

b) Calculated from the specific rotation; $[\alpha]_D^{23}$ -52.5° (*c* 2.27, CH_2Cl_2) for (*S*)-(-)-enantiomer.[8]

c) AP: acetophenone, PEE: bis(1-phenylethyl) ether, ST: styrene, EB: ethylbenzene.

Concentration Effects of (+)-nmdp.

Enantio-selective abilities of *in situ* prepared chiral rhodium(I) complexes, which were very low but reproducible, were dependent on the concentration of the chiral phosphine. Figure 1 indicates concentration effects of (+)-nmdp on the selectivity of the rhodium(I)-(+)-nmdp complex in the dehydrogenation of 1 with benzylideneacetone at 180°C. The selectivity monotonously increased up to the mole ratio of (+)-nmdp/$[RhCl(C_2H_4)_2]_2 \simeq 6$, and thereafter, decreased gradually with increasing in (+)-nmdp concentration. Maximum selectivity obtained with (+)-nmdp/$[RhCl(C_2H_4)_2]_2 \simeq 6$ may be related to the formation of active chlorine-bridged dimer species of $[RhCl((+)\text{-nmdp})_2]_2$ probably *via* following equiliblium;[30]

$$[RhCl(C_2H_4)_2]_2 + 6\ (+)\text{-nmdp} \xrightarrow{-4\ C_2H_4}$$

$$[RhCl((+)\text{-nmdp})_2]_2 + 2\ (+)\text{-nmdp} \rightleftharpoons$$

$$2\ RhCl((+)\text{-nmdp})_3. \qquad (2)$$

Effects of Hydrogen Acceptors.

The enantio-selectivity was also dependent on the concentration of unsaturated additives as hydrogen acceptor. As shown in Fig. 2, addition of benzylideneacetone to the reaction system resulted in an enhancement of enantio-selectivity and appreciably suppressed PEE formation. In the absence of the additive, PEE predominantly formed, and consequently the enantio-selectivity became lower through the consumption of 1 without enantio-selection. Although the olefin suppressed PEE formation through hydrogen transfer from 1 to the olefin, PEE formation still

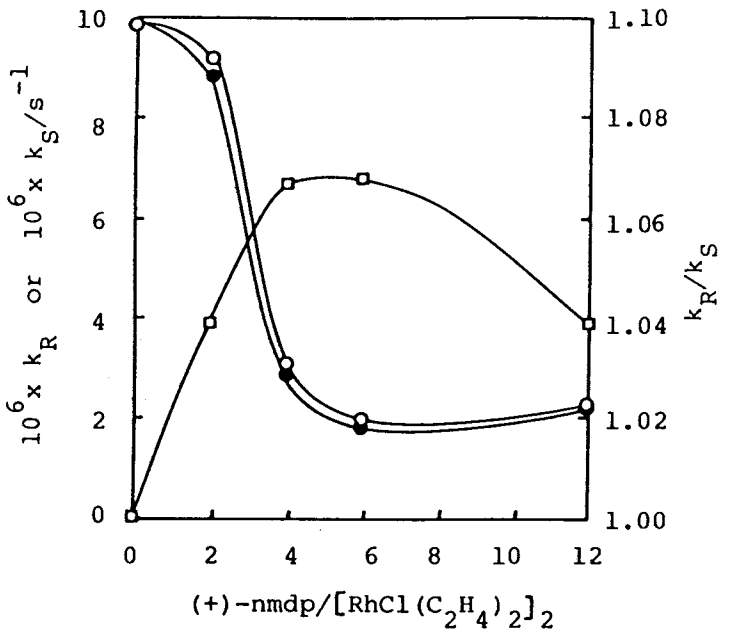


Fig. 1. Effects of mole ratio of (+)-nmdp/$[RhCl(C_2H_4)_2]_2$ on reaction rate (k_R, ○; k_S, ●) and on enantio-selectivity (k_R/k_S, □) in the dehydrogenation of 1 (83.5 mmol) by Rh(I)-(+)-nmdp complex with benzylideneacetone (68.5 mmol) at 180°C. $[RhCl(C_2H_4)_2]_2$, 5 mmol dm^{-3}.

occurred even in an excess concentration of the olefin. Thus, the reaction includes competitive processes of AP and PEE formations, as shown in a proposed mechanism in Scheme 1, where (Ru) denotes active chiral rhodium(I) species. Intermediates of 2 and 3, which possess newly formed asymmetric center, contribute to an enhancement of the enantio-selection of 1 during Reaction (3b). The deprotonation and protonation processes, Reaction (3b) and (3d) respectively, have been reported in the transfer hydrogenation of benzylideneacetophenone by deuterated 1 with $RuCl_2(PPh_3)_3$,[10] where the abstraction of α-carbon-bound hydrogen by the complex is the rate-determining step.[10]

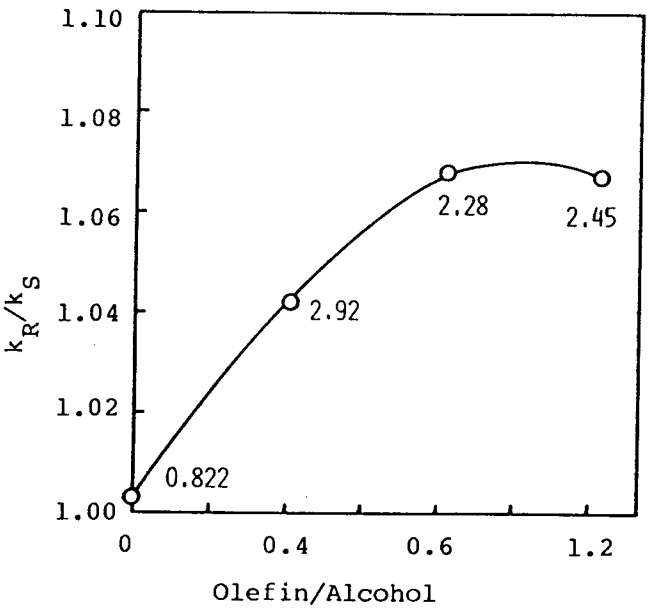


Fig. 2. Effects of mole ratio of benzylideneacetone/1 on enantio-selectivity in the dehydrogenation of 1 by Rh(I)-(+)-nmdp complex at 180°C.
Concentrations of the catalyst and 1 were the same as in Table 1. Values are the mole ratio of AP/PEE in the products.

Change in the structure of unsaturated additives varied the magnitude of enantio-selectivity (Table 2). This indicates that olefins as hydrogen acceptors play an important role in enhancement of the selectivity by suppression of PEE formation and by the creation of asymmetric center through coordination to the chiral rhodium(I) complex.[12,13]

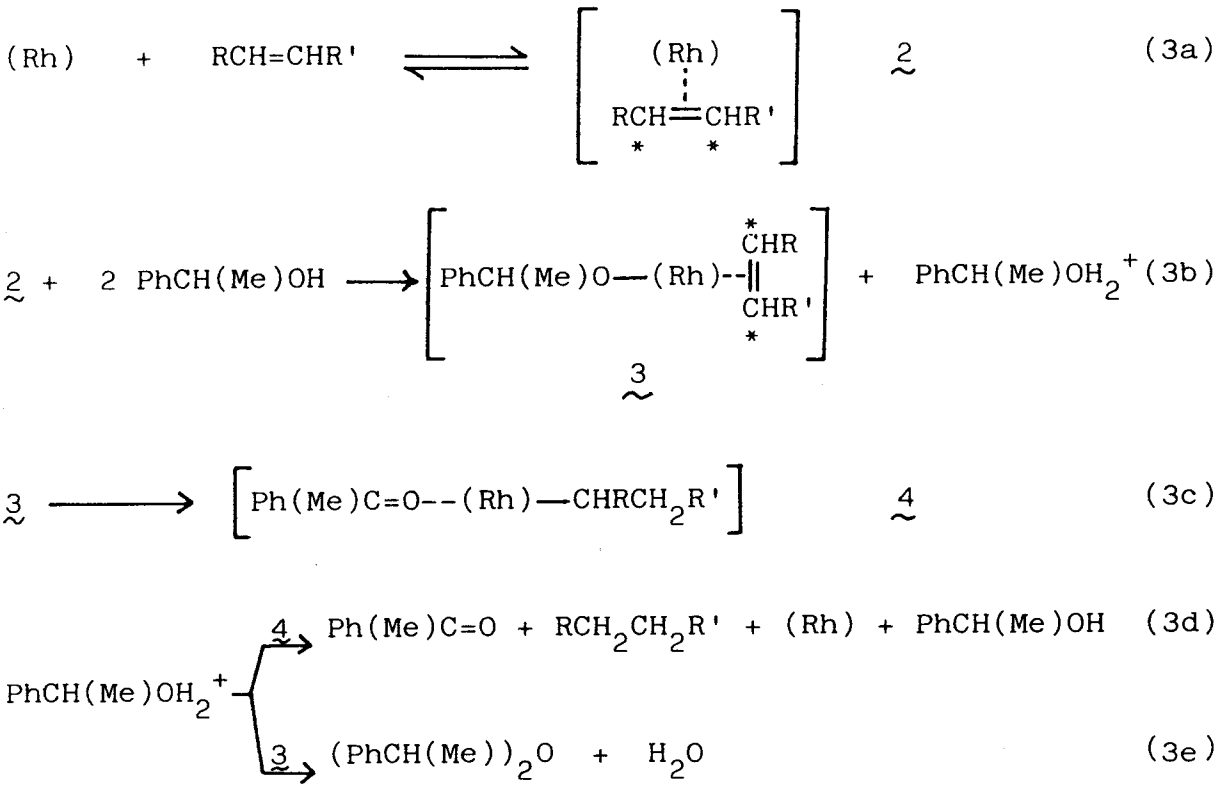
The effect of olefin to be tested at 180°C on increasing of the selectivity is the following order: benzylideneacetophenone> benzylideneacetone>*trans*-stilbene>ethyl cinnamate>hexyl methacrylate. Such an order of the effect of additives on the selectivity elevation was just the same as in the dehydrogenation of 1

Table 2. Effect of Hydrogen Acceptors on Enantio-selectivity in the Dehydrogenation of 1 by Rhodium(I)-(+)-nmdp Complex[a)]

No.	Hydrogen acceptor	Temp °C	Time h	Conv %	O.P. %	k_R/k_S
1	Benzylideneacetone	160	36	7.9	0.512	1.14
		170	30	10.9	0.613	1.11
		180	30	18.5	0.743	1.08
		190	20	22.5	0.827	1.07
2	Benzylideneaceto-phenone	170	38	11.1	0.521	1.09
		180	30	12.4	0.631	1.10
		195	30	41.6	1.084	1.04
3	*trans*-Stilbene	170	48	5.0	0.231	1.09
		180	30	6.4	0.147	1.05
		195	30	19.1	0.200	1.02
4	Ethyl cinnamate	170	48	9.5	0.098	1.02
		180	30	11.0	0.066	1.01
		195	23	28.8	0.082	1.01
5	Hexyl methacrylate	170	43	8.9	0.072	1.02
		180	30	23.2	0.059	1.01
		195	26	70.6	0.000	1.00
6	Benzylideneacetone[b)]	140	24	27.2	0.033	1.00_2
		160	24	38.9	0.291	1.00_8
		170	24	41.1	0.041	1.00_2
7	None	170	30	12.1	0.133	1.02
		180	30	29.4	0.048	1.00_3
		190	22	45.1	0.091	1.00_3

a) Reaction conditions were the same as in Table 1.

b) RhH((-)-diop) was used instead of the Rh(I)-(+)-nmdp complex.



Scheme 1.

catalyzed by the Ru(II)-(+)-nmdp complex in the presence of the same olfins.[24] The bulky substituent of olefins seems to be more effective for the selectivity elevation, and it is also taken into consideration that remarkable effect of the unsaturated ketones on enantio-selectivity is due to the formation of a bulky chiral ligand of phosphobetaine ($R'_3\overset{+}{P}CH(Ph)CH=C(R)O^-$) from the ketone and chiral ligand (R'_3P).[14] The phosphobetaine is capable of behaving as an asymmetrically effective ligand instead of (+)-nmdp.

Effects of Added Base.

Inorganic bases accelerate hydrogen transfer from alcohol to unsaturated species,[31] and this basicity effect has already been observed in the transfer hydrogenation of

Table 3. Basicity Effect of 2,5-Xylidine on Enantio-selectivity in the Dehydrogenation of 1 by Rh(I)-(+)-nmdp and Rh(I)-(-)-diop Complexes at 180°C[a)]

Complex	2,5-Xylidine	Conv	O.P.	$10^6 k_R$	$10^6 k_S$	k_R/k_S	AP	PEE
	mmol	%	%	s^{-1}	s^{-1}		mmol	mmol
Rh(I)-(+)-nmdp	0	18.4	0.67	1.95	1.82	1.06	7.82	3.43
	50	40.7	0.67	4.98	4.77	1.02	32.9	trace
Rh(I)-(-)-diop	0	73.3	0.05	12.2	12.2	1.00	26.1	32.2
	25	36.0	0.04	4.13	4.13	1.00	29.5	trace
	50	48.7	0.69	6.23	6.10	1.02	35.8	3.79
	100	39.4	0.26	4.65	4.60	1.01	32.0	trace

a) Reaction period was 30 h and other conditions were the same as in Table 1. The Rh(I)-(-)-diop complex was prepared *in situ* from $[RhCl(C_2H_4)_2]_2$ (5 mmol dm^{-3}) and (-)-diop (15 mmol dm^{-3}). Benzylideneacetone was used as an unsaturated additive.

benzylideneacetophenone with $PhCH(Me)O^{-}Na^{+}$ catalyzed by $RuCl_2(PPh_3)_3$.[10] In the present reaction, effect of 2,5-xylidine on enantio-selectivity in the dehydrogenation of 1 by Rh(I)-(+)-nmdp and Rh(I)-(-)-diop complexes with benzylideneacetone was investigated. 2,5-Xylidine caused AP to dominate PEE completely, changing the reaction rate and the selectivity (Table 3). However, the rate and the selectivity did not vary consistently with the 2,5-xylidine concentration, so that such a basicity effect is not simple; the base is capable of participating in both protonation and deprotonation steps, and in changing the catalytic activity of the chiral rhodium(I) complex. At any rate, the basicity effect was observed in present asymmetric catalysis of the chiral rhodium(I) complexes.

Activation-parameter Relationships.

The enantio-selectivity decreased with elevating temperature in spite of increasing of conversion of 1 (Table 2).

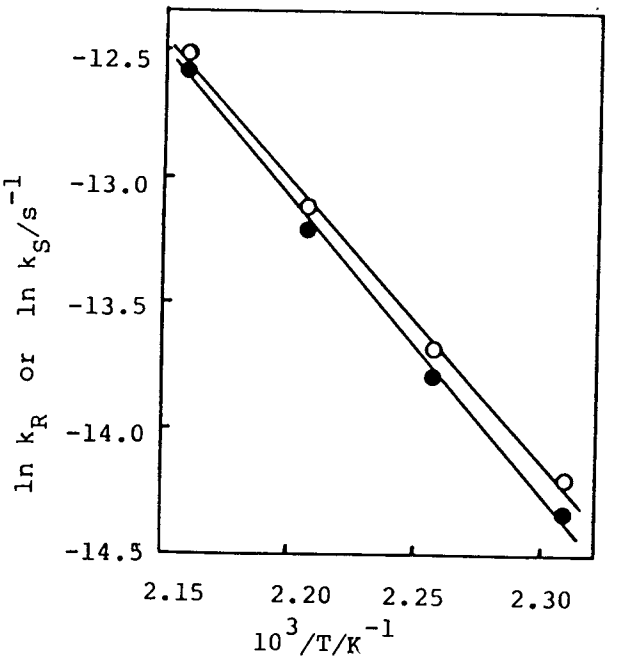


Fig. 3. Typical Arrhenius plots in the dehydrogenation of 1 by Rh(I)-(+)-nmdp complex. Hydrogen acceptor was benzylideneacetone and other conditions were the same as in Table 2. k_R, ○; k_S, ●.

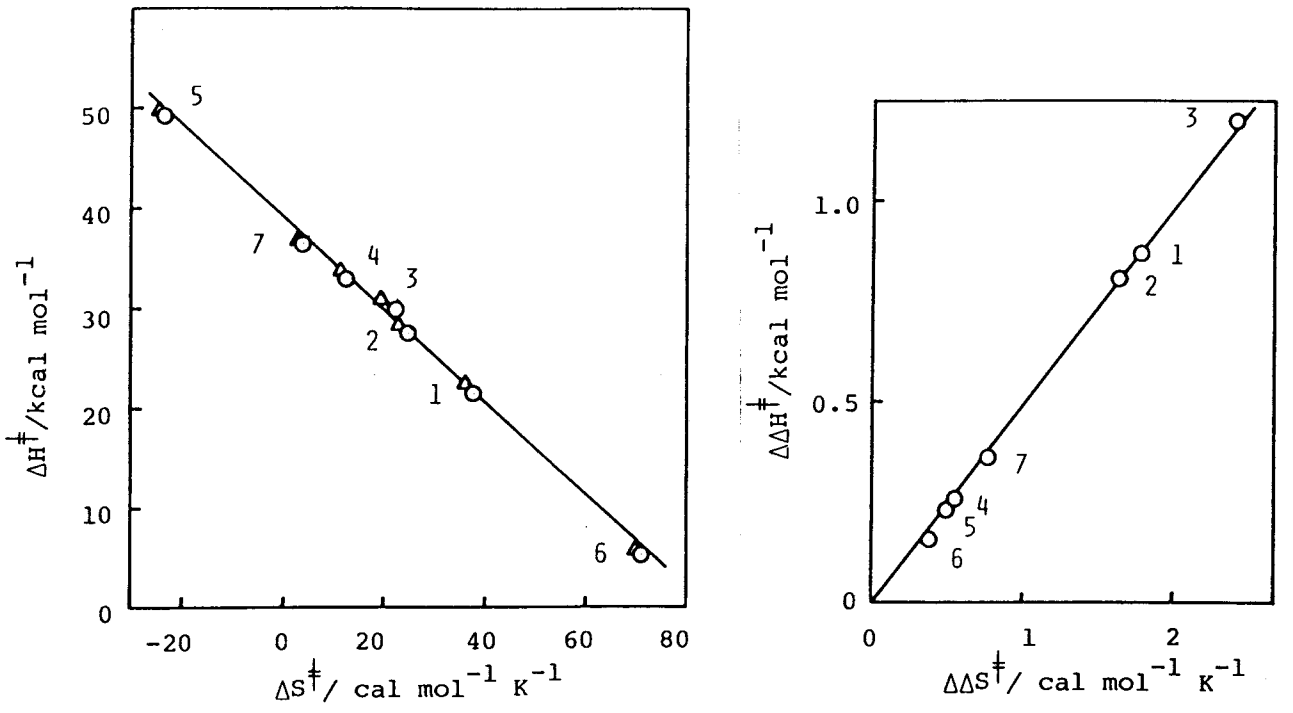


Fig. 4. Isokinetic relationship. Numbers are the same as in Table 2. R, ○; S, △.

Fig. 5. Correlation between $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. Numbers are the same as in Table 2.

Presumably, higher temperature lowers the magnitude of induced asymmetry in the intermediate 2 owing to epimerization,[12,13] and makes the interaction between the catalyst and the reactants less strong so as to diminish enantio-selectivity.

Each rate constnat (k_R or k_S) satisfied the Arrhenius relationship in the range of 170-195°C (Fig. 3), suggesting that the reaction course or mechanism remains unchanged in the temperature range.

It is noteworthy that an isokinetic relationship is observed between the activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, which reflect rate-determining step during the dehydrogenation of the alcohol

(Fig. 4). This implies that steric factor compensates for activation barrier in hydrogen transfer from the alcohol to the olefin by the rhodium(I) complex, that is, the shorter the coordination distance between α-carbon-bound oxygen and rhodium metal center in the intermediate 3 makes the easier the abstraction of α-carbon-bound hydrogen of the alkoxide-rhodium complex.

Further, it is found out that the difference, $\Delta\Delta H^{\ddagger}$, of activation enthalpy between enantiomers is linearly proportional to the difference, $\Delta\Delta S^{\ddagger}$, of activation entropy through that of the origin (Fig. 5). The enthalpy difference $\Delta\Delta H^{\ddagger}$ exhibits activation barrier between enantiomers during hydrogen transfer in the intermediate 3. Therefore, it is suggested that enantio-selection of 1 is controlled by coordination distance in the alkoxide-rhodium(I) complex (intermediate 3) for each enantiomer.

3-4 Summary

Asymmetric dehydrogenation of 1-phenylethanol by *in situ* prepared Rh(I)-(+)-nmdp and Rh(I)-(-)-diop complex was investigated with or without unsaturated additives. Enantio-selectivity was dependent on the concentration of chiral phosphine and unsaturated additives, on basicity of the reaction system, on the structure of unsaturated additives, and on reaction temperature. Isokinetic relationship was observed between activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, and it was found out that the difference, $\Delta\Delta H^{\ddagger}$, in activation enthalpies between (*R*) and (*S*)-alcohol was proportional to the corresponding entropy difference, $\Delta\Delta S^{\ddagger}$.

CHAPTER 4 ENANTIOMER-DIFFERENTIATING INTRAMOLECULAR HYDROGEN TRANSFER OF AN UNSATURATED ALCOHOL BY RUTHENIUM(II) AND RHODIUM(I) CHIRAL PHOSPHINE COMPLEXES

4-1 Introduction

Ruthenium(II) and rhodium(I) chiral phosphine complexes have been reported to be catalytically active for enantiomer-differentiating dehydrogenation of racemic secondary alcohols with intermolecular hydrogen transfer between alcohols and olefins.[11,33,34] There have, however, so far been no reports on kinetic resolution of alcohols by means of intramolecular hydrogen transfer with chiral transition metal complexes as catalysts. An unsaturated alcohol has both hydrogen donor and acceptor groups *per se*, so that the hydrogen transfer is expected to proceed easily and efficiently under mild condition.

This Chapter describes on enantiomer-differentiating intramolecular hydrogen transfer of an unsaturated alcohol, 1-buten-3-ol (1), by ruthenium(II) and rhodium(I) chiral phosphine complexes.

4-2 Experimental

Materials.

The alcohol (1) was distilled before use. The chiral phosphines of (+)-neomenthyldiphenylphosphine (nmdp),[3] (-)-2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)-2,3-butanediol (diop),[17] (+)-benzylmethylphenylphosphine (bmpp),[6] and (-)-*o*-methoxyphenylmethylphenylphosphine (*o*-ampp)[6] were synthesized

according to the literature methods, respectively. Preparation of $[RhCl(C_2H_4)_2]_2$ and $Ru_2Cl_4((-)\text{-diop})_3$ were done by Cramer's[29] and James'[18] methods, respectively. Complexes of $RuCl_2((+)\text{-bmpp})_3$ and $RuCl_2(o\text{-ampp})_2(PPh_3)$ were prepared by the phosphine exchange method.[7]

Reaction Procedure and Analyses.

A typical reaction was run as follows. A mixture of 1 (4.1 g, 58.3 mmol), $[RhCl(C_2H_4)_2]_2$ (8.0 mg, 2.4×10^{-2} mmol) and (-)-diop (20.1 mg, 4.2×10^{-2} mmol) was put into a flask (50 cm^3), purged with nitrogen prior to use. The flask was controlled at 70°C. After the given reaction period, unreacted 1 was separated by fractional distillation from the mixture, and the distillate was supplied for the measurement of optical rotation with a high sensitive digital polarimeter (Union PM-101). Reaction products were analyzed by a gas-chromatograph (Hitachi 063), using a 2-m column packed with Tween 80 on Celite 545 at 80°C.

4-3 Results and Discussion

When the intramolecular hydrogen transfer of 1 by *in situ* prepared Rh(I)-(-)-diop copmlex was carried out at 80°C, the optical purity (O.P.) of the unreacted 1 enriched with (*S*)-enantiomer increased with increasing in conversion of the alcohol (Table 1). It is obvious from Fig. 1 that the reaction obeys pseudo-first-order rate law, and the ratios of rate constants for enantiomers (k_R/k_S), which reflect the enantio-selectivity in the present reaction, are virtually constant; k_R and k_S values were calculated from the following equations.

Table 1. Dependence of Optical Purity on Conversion of 1[a)]

Time / h	Conv / %	$[\alpha]_D^{20}$ / °	O.P.[b)] / %
1.5	6.0	0.130	0.38
3.5	13.0	0.296	0.87
5.0	18.0	0.312	0.92
6.0	21.9	0.369	1.09

a) Catalyst, *in situ* prepared Rh(I)-(-)-diop complex from $[RhCl(C_2H_4)_2]_2$ (4 mmol dm^{-3}) and (-)-diop (8 mmol dm^{-3}); reaction temperature, 80°C.

b) Calculated from the specific rotation; $[\alpha]_D^{20}$ +33.9° (neat) for (*S*)-(+)-1.[35)]

$$k_R = \frac{1}{t} \ln[R]_0/[R] = -\frac{1}{t} \ln(1-C)(1-O.P.) \quad (1a)$$

$$k_S = \frac{1}{t} \ln[S]_0/[S] = -\frac{1}{t} \ln(1-C)(1+O.P.) \quad (1b)$$

Where [R] and [S] mean respective concentrations of (*R*) and (*S*)-enantiomer, subscript zero represents the initial state, C is the fraction of conversion of the racemate, and O.P. is %O.P./100.

In present reaction, the extent of intermolecular reaction, *viz.*, hydrogen transfer from 1 to 1, was found to be very small in comparison with the intramolecular one, and 2-butanone (more than 91 mol% in the products) was never produced through the reaction of 2-butanol with 1-buten-3-on under the present reaction condition.

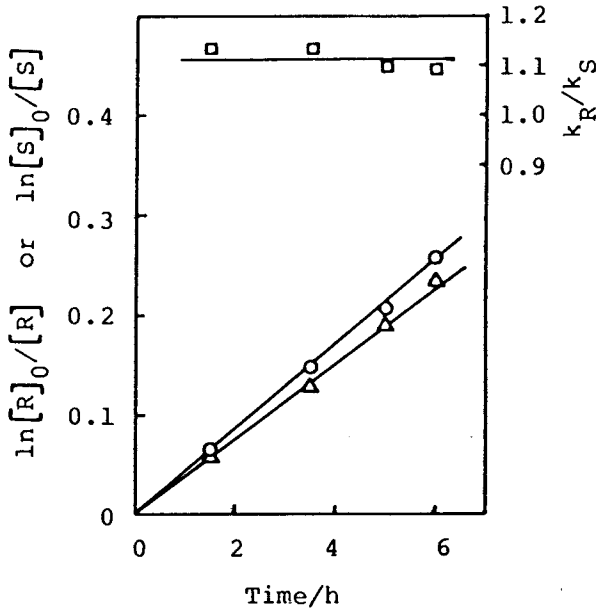
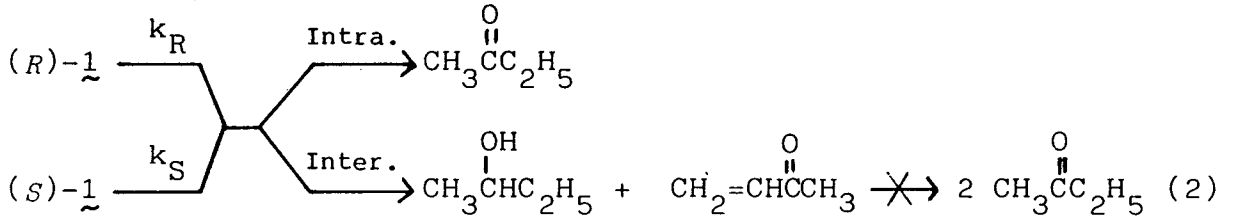


Fig. 1. Plots of reaction time *vs.* $\ln[R]_0/[R]$ (○) or $\ln[S]_0/[S]$ (△), and k_R/k_S values (□). Reaction conditions were the same as in Table 1.



In Table 2, the results of the intramolecular hydrogen transfer of 1 by various ruthenium(II) and rhodium(I) chiral phosphine complexes are listed. The ruthenium(II) complexes exhibited high catalytic activity as compared with the rhodium(I) complexes, as well as the ruthenium ones in the asymmetric hydrogen tansfer of racemic alcohols to olefins.[11,33,34] The highest enantio-selectivity (k_R/k_S=1.21) was brought about by Ru_2Cl_4((-)-diop)$_3$ at 70°C. The ruthenium(II) and rhodium(I) complexes with bulky chiral diphosphine of (-)-diop resulted in high enantio-selectivity more than those containing the chiral monophosphine. Probably, a bulky and rigid chelate structure of Ru(II)-(-)-diop or Rh(I)-(-)-diop complex is favolable for the enantio-selection through steric interaction during the hydrogen transfer.

Table 2. Asymmetric Intramolecular Hydrogen Transfer of 1 by Ru(II) and Rh(I) Chiral Phosphine Complexes[a)]

No.	Complex	Concn / mmol dm^{-3}	Temp / °C	Time / h	Conv / %	O.P. / %	k_R/k_S
1	Ru-(+)-nmdp	8	70	9.0	37.4	0.55	1.02
			80	5.0	48.6	0.16	1.02
			90	1.3	53.7	1.15	1.03
2	$RuCl_2$((+)-bmpp)$_3$	8	70	8.0	16.1	0.97	0.898
			80	4.0	15.0	0.59	0.930
			90	1.5	9.2	0.40	0.921
3	$RuCl_2$((-)-*o*-ampp)$_2$(PPh_3)	8	70	10.0	7.8	0.12	0.971
			80	5.0	9.8	0.13	0.975
			90	4.0	11.9	0.29	0.955
4	Ru_2Cl_4((-)-diop)$_3$	4	70	3.0	10.8	1.06	0.829
			80	3.0	20.6	1.09	0.910
			90	2.0	30.8	1.70	0.912
5	Rh-(+)-nmdp	10	70	30.0	8.9	0.18	1.04
			80	18.0	9.2	0.34	1.07
			90	10.0	7.7	0.17	1.04
6	Rh-(-)-diop	10	70	6.0	9.4	0.57	1.12
			80	4.0	14.7	1.28	1.18
			90	4.0	29.6	1.38	1.08

a) Ru-(+)-nmdp complex was prepared *in situ* from $RuCl_2(PPh_3)_3$ (8 mml dm^{-3}) and (+)-nmdp (48 mmol dm^{-3}), Rh-(+)-nmdp and Rh-(-)-diop complexes from $[RhCl(C_2H_4)_2]_2$ (5 mmol dm^{-3}) and (+)-nmdp (30 mmol dm^{-3}) and (-)-diop (10 mmol dm^{-3}), respectively.

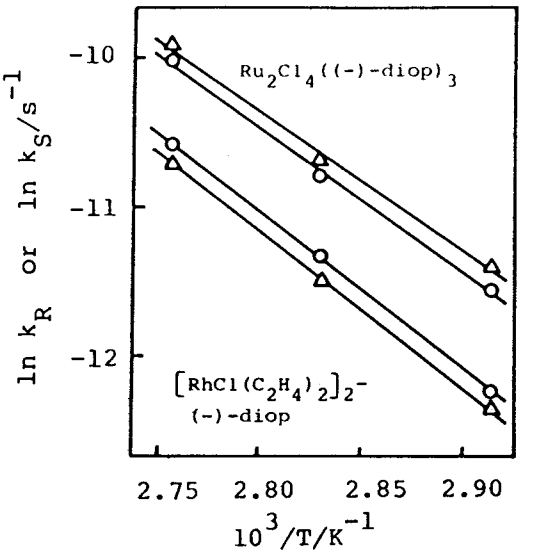


Fig. 2. Typical example of Arrhenius plots. k_R, O ; k_S, Δ.

Although the k_R/k_S ratio was also dependent on the reaction temperature, each rate constant, k_R or k_S, for the enantiomer satisfied linear Arrhenius relations (Fig. 2). Activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, obtained for each enantiomer of 1 bore an isokinetic relationship with the larger $\Delta H^{\ddagger}$ values always requiring negatively larger $\Delta S^{\ddagger}$ values. Similar isokinetic relationship has been observed for the intermolecular hydrogen transfer from racemic secondary alcohols to olefins, and interpreted by compensating effect of steric factors on electronic ones in the rate-determining step of an abstraction of the hydrogen bound to α-carbon atom in the ruthenium-alkoxide intermediate.[11,34] For the present reaction, therefore, the following mechanism can be acceptable for establishing isokinetic relationship;

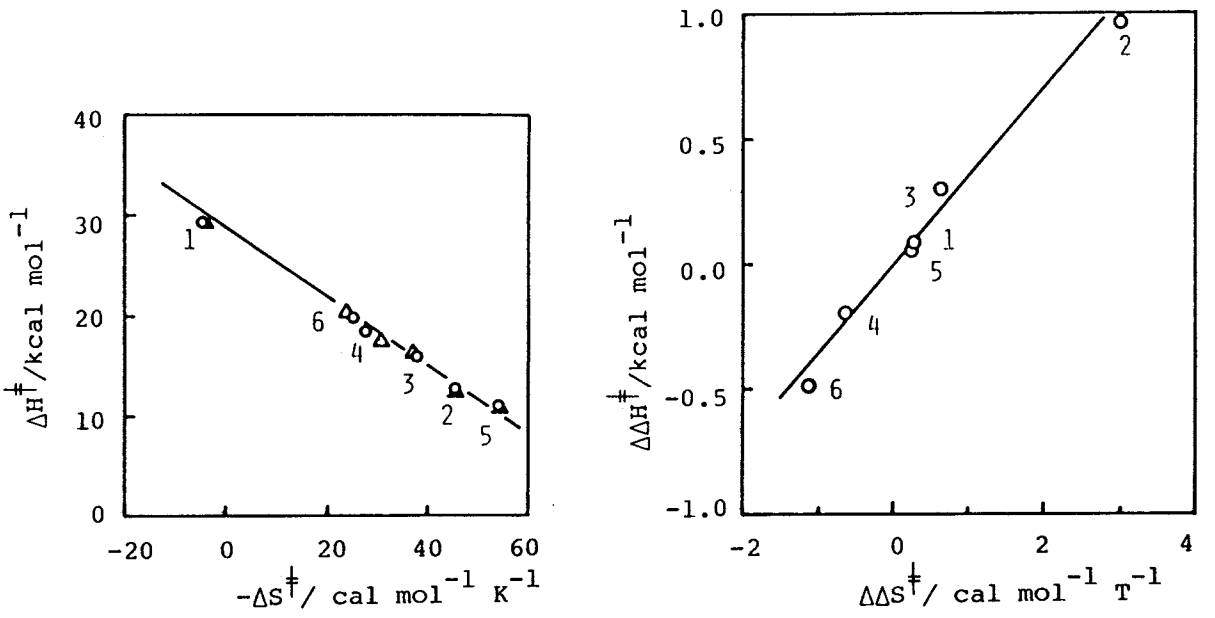
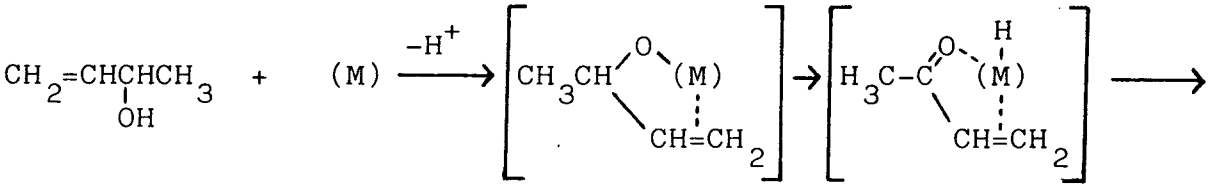


Fig. 3. Isokinetic relationship. Numbers are the same as in Table 2. R, ○; S, △.

Fig. 4. Correlationship between $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$. Numbers are the same as in Table 2.



where (M) denotes active species. The deprotonation and the protonation processes have been established for the case of intermolecular hydrogen transfer from alcohols to olefins by $RuCl_2(PPh_3)_3$.[10] Presumably, the difference in the coordination distance of each enantiomer to the chiral complex is reflected in those in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values of the enantiomers.

Furthermore, it is noteworthy that the differences of

the activation parameters ($\Delta\Delta H^{\ddagger}=\Delta H_R^{\ddagger} - \Delta H_S^{\ddagger}$ and $\Delta\Delta S^{\ddagger}=\Delta S_R^{\ddagger} - \Delta S_S^{\ddagger}$) between enantiomers show a linear correlation through the origin without any appreciable difference between the ruthenium(II) and rhodium(I) complexes (Fig. 4). Such a correlation suggests that enantio-differentiating process is controlled by steric factor (*viz.*, the coordination distance in the alkoxide complex intermediate), to compensate electronic one.

4-4 Summary

Asymmetric intramolecular hydrogen transfer of racemic 1-buten-3-ol by ruthenium(II) and rhodium(I) chiral phosphine complexes was studied. The enantio-selectivity was affected by the structure of chiral phosphine. The highest selectivity (k_R/k_S= 1.21) was obtained in the Ru_2Cl_4((-)-diop)$_3$-catalyzed reaction at 70°C. The activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) exhibited an isokinetic relationship, and the difference in the parameters for each enantiomer ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) showed a satisfactory linear correlation between them.

CHAPTER 5 ENANTIOMER-DIFFERENTIATING DEHYDRATION OF A 1,3-DIOL BY RHODIUM(III) CHIRAL PHOSPHINE COMPLEXES

5-1 Introduction

While the dehydration of 1,3-diols with sulfuric acid has been reported to give the unsaturated alcohols or aldehydes, or ethers,[36] a system of $RhCl_3$ and triphenylphosphine has been found to be an effective catalyst for the selective one-step conversion of 1,3-diols into monoketones.[37]

Therefore, the author has examined the application of the catalytic reaction to the enantiomer-differentiation of racemic 1,3-butanediol by the use of $RhCl_3$-chiral phosphine complexes.

5-2 Experimental

Materials.

Rhodium trichloride trihydrate ($RhCl_3 \cdot 3H_2O$) was commercially available. 1,3-Butanediol and phenol were distilled before use. (-)-2,3-*O*-Isopropylidene-1,4-bis(diphenylphosphino)-2,3-butanediol (diop)[17] and (+)-neomenthyldiphenylphosphine (nmdp)[3] were prepared according to the literature methods, respectively.

Reaction Procedure and Analyses.

A typical reaction was run as follows. A mixture of 6 g (66.7 mmol) of 1,3-butanediol, 0.132 g (0.50 mmol) of $RhCl_3 \cdot 3H_2O$ and 0.162 g (0.50 mmol) of (+)-nmdp was put into a flask (50 cm^3) purged with nitrogen previously. The flask was controlled at 70°C. After the desired reaction period, the unreacted diol was

separated by fractional distillation from the mixture, and supplied for the optical rotation measurement with a high sensitive digital polarimeter (Union PM-101). Reaction products were analyzed with Hitachi 063 gas-chromatograph, equipped with a 1-m column packed with Tween 80 on Celite 545.

5-3 Results and Discussion

Various ruthenium(II) and rhodium(I) chiral phosphine complexes were examined as a catalyst for the asymmetric dehydration of 1,3-butanediol in the presence of phenol, which was added in order to homogenize the reaction system. Complexes of $[RhCl(C_2H_4)_2]_2$-L*, $RhCl(PPh_3)_3$-L*, $RuCl_3$-L*, $RuCl_2(PPh_3)_3$-L*, and $Ru_2Cl_4((-)\text{-diop})_3$ (L*=chiral phosphine) showed markedly low or negligible activity at 80°C, but only $RhCl_3$-chiral phosphine complexes had remarkable catalytic activity.

When the reaction of the diol by the rhodium(III) complexes was carried out at 70-90°C, the unreacted diol was found to be optically active and enriched with (*R*)-(-)-enantiomer in the reaction by the Rh(III)-(+)-nmdp complex and with (*S*)-(+)-enantiomer in the reaction by Rh(III)-(-)-diop complex. The optical purity (O.P.) of the diol increased with increasing in conversion (Table 1). As indicated in Fig. 1, the reaction obeyed pseudo-first-order rate law, and rate constant ratios (k_R/k_S) for each enantiomer, reflecting enantio-selectivity in the present reaction, were constant virtually.

$$\begin{matrix}(R)\text{-}(-)\text{-}CH_3CH(OH)CH_2CH_2OH \xrightarrow{k_R} \\ (S)\text{-}(+)\text{-}CH_3CH(OH)CH_2CH_2OH \xrightarrow{k_S}\end{matrix} \rightarrow CH_3\overset{O}{\overset{\|}{C}}C_2H_5 + H_2O \qquad (1)$$

Table 1. Dependence of Optical Purity on Conversion of 1,3-Butanediol[a)]

Complex	Temp / °C	Time / h	Conv / %	$[\alpha]_D^{23}$ / °	O.P.[b)] / %
$RhCl_3$-(+)-nmdp	80	12	17.6	-0.170	0.90
	80	24	33.3	-0.179	0.95
	80	48	56.1	-0.350	1.86
$RhCl_3$-(-)-diop	90	10	12.8	+0.056	0.30
	90	18	20.9	+0.098	0.52
	90	30	33.4	+0.108	0.57

a) $RhCl_3$, 72 mmol dm^{-3}; mole ratio of the phosphine/$RhCl_3$, 1/1. the diol, 9.6 mol dm^{-3}.

b) Calculated from the specific rotation; $[\alpha]_D^{23}$ -18.8° (*c* 4, C_2H_5OH) for the (*R*)-(-)-diol.

2-Butanone was always formed in more than 98 mol% in the products, and k_R and k_S values were evaluated by the following equations.

$$k_R = \frac{1}{t}\ln[R]_0/[R] = -\frac{1}{t}\ln(1-C)(1-O.P.) \quad (2a)$$

$$k_S = \frac{1}{t}\ln[S]_0/[S] = -\frac{1}{t}\ln(1-C)(1+O.P.) \quad (2b)$$

Where [R] and [S] mean respective concentrations of (*R*) and (*S*)-enantiomer, the subscript zero represents the initial state, C is the fraction of conversion of the racemate, and O.P. is %O.P./100.

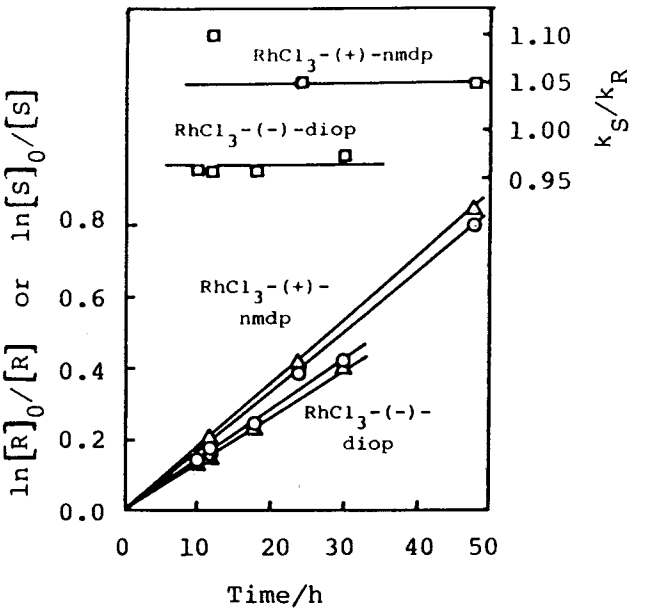


Fig. 1. Plots of reaction time *vs.* $\ln[R]_0/[R]$ (O) or $\ln[S]_0/[S]$ (Δ), and k_R/k_S ratio (□).
Reaction conditions were the same as in Table 1.

As Fig. 1 indicates, the monophosphine of (+)-nmdp was a more effective chiral ligand than the diphosphine of (-)-diop in the system of $RhCl_3$-L*, in terms of dehydration activity and enantio-selectivity. Mole ratio of the phosphine to $RhCl_3$ also affected the dehyration rate and the selectivity. In the case of Rh(III)-(+)-nmdp system, an increase in (+)-nmdp/$RhCl_3$ ratio accelerated the dehydration rate up to the ratio≃0.5, but remarkably diminished the rate with monotonous elevation of enantio-selectivity (Fig. 2). Probably, the rate drop in high (+)-nmdp concentration is attributable to neutralization of the positive charge of the rhodium metal center due to the coordination of the phosphine to the complex. In fact, the decrease in oxidation number of rhodium metal center in the complex resulted in

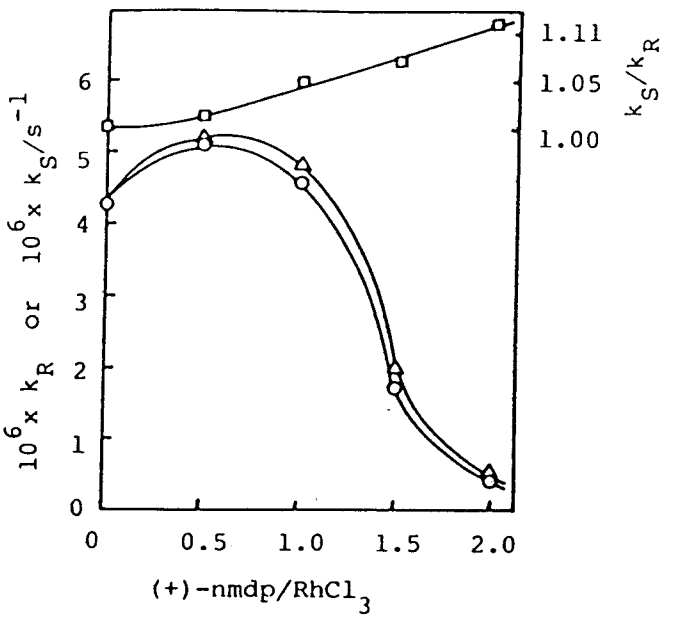


Fig. 2. Effects of (+)-nmdp/$RhCl_3$ mole ratio on dehydration rate (k_R, O; k_S, Δ) and on enantio-selectivity (k_S/k_R, □). Reaction conditions were the same as in Table 1.

Table 2. Dependence of Enantio-selectivity on the Concentration of $RhCl_3$-(+)-nmdp (1:1) Complex and Reaction Temperature[a)]

Concn / mmol dm^{-3}	Temp / °C	Time / h	Conv / %	O.P. / %	k_S/k_R
36	80	48	17.7	0.21	1.02
72	80	24	33.3	0.95	1.05
72	90	18	28.1	0.92	1.06
72	95	16	27.2	0.57	1.04
144	80	24	63.0	4.53	1.10

a) The diol , 9.6 mol dm^{-3}.

lowering the catalytic activity remarkably; the system of $[RhCl(C_2H_4)_2]_2$-L* or $RhCl(PPh_3)_3$-L* showed negligibly low activity.

In relation to above phenomena, it is also noteworthy that an increase in amount of $RhCl_3$-(+)-nmdp (1:1) accelerated the dehydration rate monotonously with increasing enantio-selectivity (Table 2). Therefore, magnitude of the selectivity is not directly related to the dehydration rate. On the other hand, elevation of reaction temperature from 70°C to 95°C increased the dehydration rate, but did not change the selectivity so markedly (Table 2).

5-4 Summary

Asymmetric dehydration of racemic 1,3-butanediol to 2-butanone by $RhCl_3$-chiral phosphine complexes was studied. Catalytic activity and enantio-selectivity were affected by the mole ratio of chiral phosphine to $RhCl_3$, by the concentration of the catalyst, and by reaction temperature. The maximum enantio-selectivity of k_R/k_S=1.11 was obtained.

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PART 2

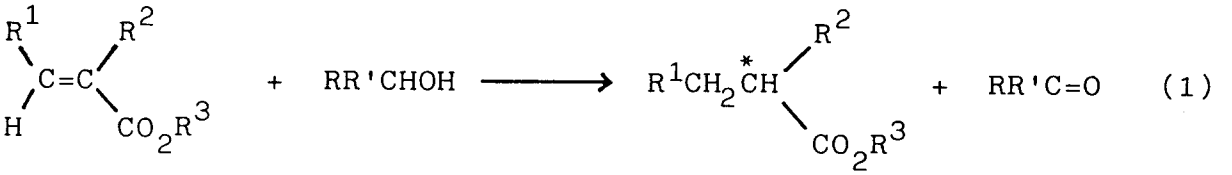
ASYMMETRIC HYDROGENATION

BY CHIRAL TRANSITION METAL COMPLEXES

CHAPTER 6 ASYMMETRIC TRANSFER HYDROGENATION OF UNSATURATED ACIDS AND ESTERS BY ALCOHOLS WITH BINUCLEAR RUTHENIUM(II) CHIRAL DIPHOSPHINE COMPLEXES

6-1 Introduction

Since ruthenium(II) chiral phosphine complexes have been effective catalysts for enantiomer-differentiating dehydrogenation of racemic secondary alcohols in the presence of unsaturated compounds,[1,2] the author has investigated the catalytic efficiency of the chiral ruthenium complexes for transfer hydrogenation of prochiral olefins by alcohols, to examine the asymmetric hydrogenation without molecular hydrogen.



(1)

This Chapter describes effects of chirality and bulkiness of substituent groups in reactants on the extent of asymmetric induction in the transfer hydrogenation of prochiral unsaturated acids and esters by alcohols with $RuCl_2(PPh_3)_3$ or Ru_2Cl_4((+)- or (-)-diop)$_3$ (diop=2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)-2,3-butanediol).

6-2 Experimental

Materials.

(+) or (-)-Diop and Ru_2Cl_4((+) or (-)-diop)$_3$ were prepared by Kagan's[3] and James'[4] methods, respectively. 1,2-*O*-Iso-

propylidene-, 1,2;5,6-*O*-diisopropylidene-, 1,2-*O*-cyclohexylidene- and 1,2;5,6-*O*-dicyclohexylidene-α-D-glucofuranose were synthesized by the methods reported.[5,6] Several α-methylcrotonates (1-phenylethyl, α-(ethoxycarbonyl)benzyl, (1*R*,2*R*)-1,2-bis(ethoxycarbonyl)-2-hydroxyethyl, and *l*-menthyl esters) were prepared *via* the reaction of α-methylcrotonoyl chloride with corresponding hydroxy compounds (1-phenylethanol, ethyl mandelate, diethyl (2*R*,3*R*)-tartrate, and *l*-menthol, respectively). Alcohols, prochiral acids, and esters were distilled or recrystallized before use.

Transfer Hydrogenation.

A mixture of prochiral olefin and alcohol was allowed to react in the presence of the chiral ruthenium complex in a test tube at the given temperature under nitrogen atmosphere. The reaction mixture was refluxed in a 10% NaOH-methanol solution, and the insoluble catalyst was separated from the solution by filtration. The filtrate was washed with water, acidified with dilute HCl solution in the range of pH 3-4, and extracted with ether. The etherial phase was washed with water, dried over magnesium sulfate, and then evaporated to dryness. The unreacted prochiral olefin and hydrogenated product were identified by gas-chromatographic analysis (Yanagimoto G-180) at 170°C using a 1-m column packed with 15% EGA on Uniport B or ^{1}H NMR (100 MHz, JEOL MH-100) method. The optical rotation of the hydrogenated products was measured with a high sensitive Union PM-101 digital polarimeter.

6-3 Results and Discussion

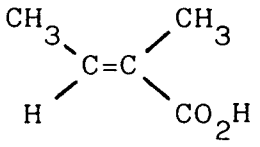
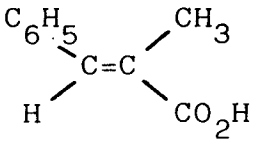
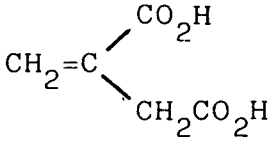
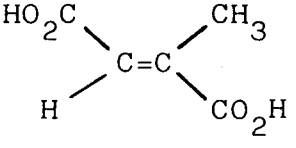
Hydrogenation of Unsaturated Carboxylic Acids and Esters.

Asymmetric reduction of the carbon-carbon double bond in prochiral α,β-unsaturated mono- and di-carboxylic acids by benzyl alcohol or *p*-methoxybenzyl alcohol was first carried out with $Ru_2Cl_4((-)\text{-diop})_3$. The results are summarized in Table 1. The optical purities of hydrogenated products for the unsaturated mono-carboxylic acids were relatively high as compared with those for the unsaturated di-carboxylic acids. The carboxyl groups might hinder asymmetrically favorable coordination of the carbon-carbon double bond in the substrate to the chiral ruthenium(II) complex in the step of asymmetric induction.

It is also noteworthy that optical purities of saturated products derived from α-methylcrotonic acid or α-methylcinnamic acid (16.4 and 15.4%, respectively) are higher than the reported values (maxima 6.9 and 1.5%, respectively) for the transfer hydrogenation of the same species with $H_4Ru_4(CO)_8((-)\text{-diop})_8$ at 120°C by 2-propanol, indoline, and dioxane.[7)]

Asymmetric transfer hydrogenation of a series of esters of α-methylcrotonic acid by benzyl alcohol or 1-phenylethanol was carried out with the Ru(II)-(-)-diop complex. The results are shown in Table 2. The ester derivatives of α-methylcrotonic acid, as compared with α-methylcrotonic acid itself, were easily hydrogenated to give the corresponding hydrogenated products with very low optical purities, which decreased with increasing bulkiness of the ester groups. The bulky ester moiety might decrease the extent of asymmetric induction considerably by suppressing approach of the ester to the chiral catalyst during

Table 1. Asymmetric Transfer Hydrogenation of Prochiral Unsaturated Carboxylic Acids by Benzyl Alcohol with $Ru_2Cl_4((-)\text{-diop})_3$ at 180°C[a)]

Substrate	Time / h	Yield / %	$[\alpha]_D$ / °	O.P.[b)] / %
	6	10	-1.99	16.4
	6	36	-3.29	15.9
	6	31	-0.86	6.1
	9	9	-0.59	3.4

a) Catalyst, 4 mmol dm^{-3}; olefin, 40 mmol; alcohol, 80 mmol.

b) Calculated with respect to the following values of optically pure acids: $[\alpha]_D^{23}$ +12.17° (*c* 5, C_2H_5OH) for (*S*)-(+)-$CH_3CH_2CH(CH_3)CO_2H$;[8)] $[\alpha]_D^{25}$ +20.68° (neat) for (*S*)-(+)-$C_6H_5CH_2CH(CH_3)CO_2H$;[9)] $[\alpha]_D^{20}$ +16.88° (*c* 2.16, C_2H_5OH) for (*R*)-(+)-$CH_3CH(CO_2H)CH_2CO_2H$;[10)] $[\alpha]_D^{20}$ -17.27° (*c* 5, C_2H_5OH) for (*S*)-(-)-$HO_2CCH_2CH(CH_3)CO_2H$.[11)]

Table 4. Asymmetric Transfer Hydrogenation of α-Methylcrotonic Acid and Its Esters by Achiral and Racemic Alcohols with $Ru_2Cl_4((-)\text{-diop})_3$ at 190°C[a)]

Alcohol	$CH_3CH=C(CH_3)CO_2R$ R	Time h	Yield %	$[\alpha]_D^{23}$ °	O.P.[b)] %	Confn
$C_6H_5CH_2OH$	H	8	10	-1.39	11.4	R
	CH_3	4	35	+0.22	1.8	S
	C_2H_5	5	53	+0.28	2.3	S
	C_4H_9	5	47	+0.28	2.3	S
	$C_6H_5CH_2$	5	41	+0.20	1.7	S
$C_6H_5CH(CH_3)OH$	H	10	13	-3.21	26.4	R
	H[c)]	4	10	-2.21	18.2	R
	CH_3	3	85	-1.21	10.0	R
	C_2H_5	22	59	-1.19	9.8	R
	C_4H_9	4	94	-0.90	7.4	R
	$C_6H_5CH_2$	5	75	-1.02	8.4	R
p-$CH_3OC_6H_4CH_2OH$	H	8	9	-1.35	11.1	R
	H[d)]	8	8	+1.25	10.3	S

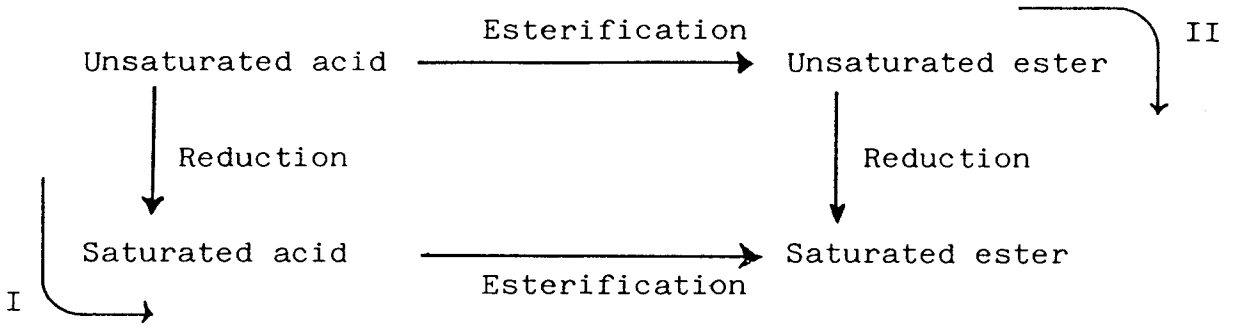
a) $Ru_2Cl_4((-)\text{-diop})_3$, 4 mmol dm^{-3}; alcohol, 67 mmol; olefin, 33 mmol. b) Optical purities of saturated esters calculated for α-methylbutyric acid obtained from the esters by base hydrolysis. C) Reaction temperature, 170°C. d) $Ru_2Cl_4((+)\text{-diop})_3$ was used.

enantio-differentiating process.

The extent of asymmetric induction is also affected by the structure of hydrogen donor. Such an achiral alcohol as benzyl alcohol resulted in a low magnitude of asymmetric induction than 1-phenylethanol in the hydrogenation of α-methylcrotonic acid. Although benzyl alcohol gave saturated esters enriched with (*S*)-enantiomer, racemic 1-phenylethanol afforded products enriched with the antipode with higher optical purity.

When a hydrogen transfer is effected with the Ru(II)-(-)-diop complex from alcohol to such an unsaturated acid as α-methylcrotonic acid, the reaction is considered to proceed *via* two courses I and II specified in Scheme 1. In Course I, a partial esterification of the saturated acid is followed by reduction of the carbon-carbon double bond of the unsaturated acid, and in Course II, an unsaturated ester is formed before the corresponding acid is hydrogenated by alcohol in the presence of the Ru(II) complex. In order to elucidate which course is predominant in the asymmetric transfer hydrogenation of unsaturated acid, the time dependences of chemical yields of products in the Ru(II)-(-)-diop complex catalyzed transfer hydrogenation of α-methylcrotonic acid and 1-phenylethyl α-methylcrotonate by 1-phenylethanol were determined.

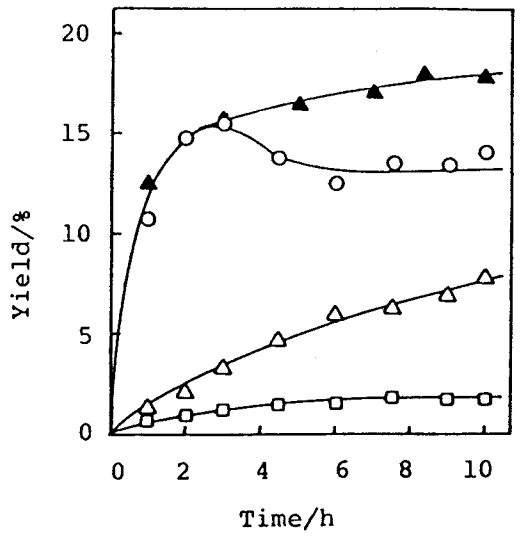
As shown in Fig. 1, α-methylcrotonic acid was hydrogenated smoothly by 1-phenylethanol with a small extent of esterification of the unsaturated acid, and the rates of hydrogen transfer from 1-phenylethanol to α-methylcrotonoic acid and to 1-phenylethyl α-methylcrotonate did not differ distinctly from each other. Strictly speaking, the hydrogenation of α-methylcrotonic



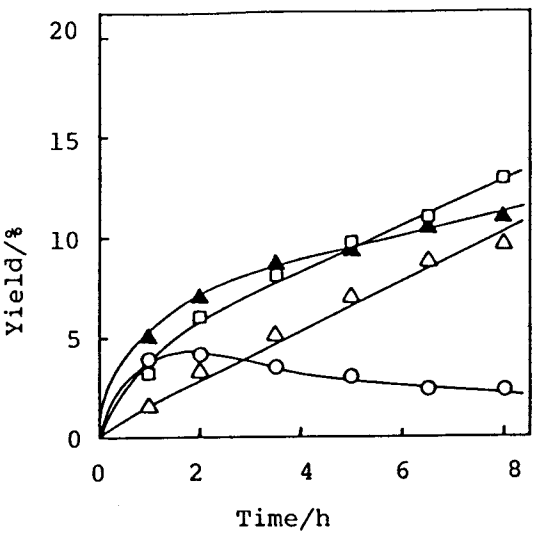
Scheme 1.

acid was accompanied by a rate drop due to the slow esterification of the acid. Thus, the chiral Ru(II) complex-catalyzed reaction of α-methylcrotonic acid with 1-phenylethanol proceeds mainly *via* Course I with formation of α-methylbutyric acid as a main product.

On the other hand, esterification of α-methylcrotonic acid by benzyl alcohol was relatively rapid, and benzyl α-methylcrotonate was easily reduced to benzyl α-methylbutyrate. From the gradual decrease in yield of α-methylbutyric acid after the reaction period of 2 h (Fig. 2), it is evident that the saturated ester is produced from α-methylbutyric acid *via* Course I, and that benzyl α-methylbutyrate is formed from α-methylcrotonic acid and benzyl alcohol *via* both Courses I and II; the latter path seems predominant. it should be stressed that in the transfer hydrogenation of α-methylcrotonate with benzyl alcohol or 1-phenylethanol, no hydrolysis of unsaturated or saturated esters was observed. Thus, the difference in reactivity between the hydrogen donors affected the transfer hydrogenation process, allowing 1-phenylethanol to give higher optical purity (18.2%) than that (11.4%) obtained with benzyl alcohol in the



(Fig. 1)



(Fig. 2)

Fig. 1. Changes of product yields with time in the transfer hydrogenation of α-methylcrotonic acid (3.0 mol dm^{-3}) by 1-phenylethanol (5.8 mol dm^{-3}) with $Ru_2Cl_4((-)\text{-diop})_3$ (4.0 mmol dm^{-3}) at 190°C.

Product: α-methylbutyric acid (○), 1-phenylethyl α-methylbutyrate (△), 1-phenylethyl α-methylcrotonate (□); 1-phenylethyl α-methylbutyrate (▲) obtained with 1-phenylethyl α-methylcrotonate (2.3 mol dm^{-3}) and 1-phenylethanol (4.7 mol dm^{-3}) at 190°C.

Fig. 2. Changes of product yields with time in the transfer hydrogenation of α-methylcrotonic acid (2.9 mol dm^{-3}) by benzyl alcohol (7.0 mol dm^{-3}) with $Ru_2Cl_4((-)\text{-diop})_3$ (4.0 mmol dm^{-3}) at 190°C.

Product: α-methylbutyric acid (○), benzyl α-methylbutyrate (△), benzyl α-methylcrotonate (□); benzyl α-methylbutyrate (▲) obtained with benzyl α-methylcrotonate (1.5 mol dm^{-3}) and benzyl alcohol (6.8 mol dm^{-3}) at 190°C.

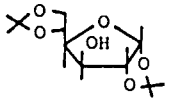
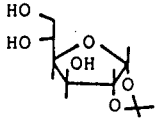
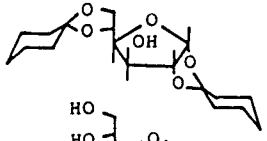
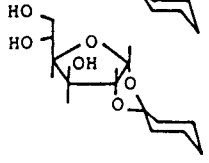
hydrogenation of α-methylcrotonic acid (Table 2). Since the saturated product from benzyl α-methylcrotonate had considerably low optical purity (1.7%) and contained the prevailing (*S*)-enantiomer, opposite to the predominant enantiomer found in the reaction of α-methylcrotonic acid with benzyl alcohol, the easy esterification of α-methylcrotonic acid by benzyl alcohol is taken to be responsible for the decrease in optical purity of the saturated product.

For the present reaction the effective asymmetric induction by racemic 1-phenylethanol was actually observed, and this is attributable to chiral circumstances enriched with one specific enantiomer of the unreacted alcohol. In fact, in the transfer hydrogenation of α-methylcrotonic acid or its esters by racemic 1-phenylethanol, enantiomer-differentiation of the alcohol was observed, and the optically active unreacted alcohol (maximum e.e. 4.2%) could be separated; the prevailing enantiomer was (*S*)-isomer in the case of the Ru(II)-(-)-diop complex and (*R*)-isomer in the case of the Ru(II)-(+)-diop complex. One of the enantiomers of 1-phenylethanol might contribute to the asymmetric induction through coordination to the chiral Ru(II) complex.

Hydrogenation of α-Methylcrotonic Acid by Chiral Alcohols.

Since the chirality of hydrogen donors was expected to affect the extent of asymmetric induction in the transfer hydrogenation of unsaturated species with the chiral Ru(II) complex, a reaction of α-methylcrotonic acid with chiral alcohol was carried out as follows; (1) an asymmetric transfer hydrogenation using α-D-glucofuranose derivatives as chiral alcohols with

Table 3. Asymmetric Transfer Hydrogenation of α-Methylcrotonic Acid by Chiral Alcohols with $RuCl_2(PPh_3)_3$ and Ru_2Cl_4((+) or (-)-diop)$_3$ at 160°C[a)]

Alcohol[b)]	Catalyst	Yield / %	$-[\alpha]_D^{23}$ / °	O.P. / %
	$RuCl_2(PPh_3)_3$	7	0.81	6.7
	Ru_2Cl_4((-)-diop)$_3$	7	1.57	12.9
	Ru_2Cl_4((+)-diop)$_3$	6	0.77	6.4
	$RuCl_2(PPh_3)_3$	18	1.08	8.9
	Ru_2Cl_4((-)-diop)$_3$	14	2.74	22.4
	Ru_2Cl_4((+)-diop)$_3$	13	-0.47	3.9
	$RuCl_2(PPh_3)_3$	5	0.37	3.1
	Ru_2Cl_4((-)-diop)$_3$	2	0.90	7.4
	Ru_2Cl_4((+)-diop)$_3$	7	0.15	1.2
	$RuCl_2(PPh_3)_3$	19	0.04	0.3
	Ru_2Cl_4((-)-diop)$_3$	3	0.23	1.9

a) $RuCl_2(PPh_3)_3$, 2.5 mmol dm^{-3}; Ru_2Cl_4((+) or (-)-diop)$_3$, 1.25 mmol dm^{-3}; olefin, 40 mmol; alcohol, 40 mmol in diphenyl ether (300 cm^3); reaction time, 12 h.

b) Products derived from the glucofuranose derivatives were not investigated.

an achiral catalyst $RuCl_2(PPh_3)_3$, and (2) a double asymmetric transfer hydrogenation by the chiral hydrogen donors with a chiral catalyst Ru_2Cl_4((+) or (-)-diop)$_3$. Results are listed in Table 3.

In the case of the transfer hydrogenation of α-methylcrotonic acid with a chiral alcohol and $RuCl_2(PPh_3)_3$, optically active α-methylbutyric acid (0.3-8.9% e.e.) was produced with the prevailing (*R*)-enantiomer, and the use of 1,2;5,6-*O*-diisopropylidene- and 1,2-*O*-isopropylidene-α-D-glucofuranose gave rise to higher optical purities (6.7-8.9%) than those (0.3-3.1%) obtained with 1,2;5,6-*O*-dicyclohexylidene- and 1,2-*O*-cyclohexylidene-α-D-glucofuranose.

In the double asymmetric reaction with the chiral alcohol and Ru_2Cl_4((-)-diop)$_3$, the Ru(II) complex substantially increased the optical purity of α-methylbutyric acid enriched with (*R*)-enantiomer with a maximum optical purity of 22.5% in the case of 1,2-*O*-isopropylidene-α-D-glucofuranose. However, the Ru(II)-(+)-diop complex gave a lower optical purity of the saturated product than that obtained with $RuCl_2(PPh_3)_3$, and changed prevailing enantiomer in the product from (*R*)-isomer to (*S*)-isomer in the case of 1,2-*O*-isopropylidene-α-D-glucofuranose.

At any rate, the chiral alcohols (α-D-glucofuranose derivatives) contributed to enhancing the extent of asymmetric induction, even though the maximum optical purity of 22.5% is lower than that (26.4%) attained with 1-phenylethanol.

Hydrogenation of α-Methylcrotonate Including Racemic or Chiral Ester Groups.

In the present transfer hydrogenation, double asymmetric

Table 4. Asymmetric Transfer Hydrogenation of α-Methylcrotonates Including Racemic or Chiral Ester Groups by 1-Phenylethanol with $Ru_2Cl_4((-)\text{-diop})_3$ at 190°C[a)]

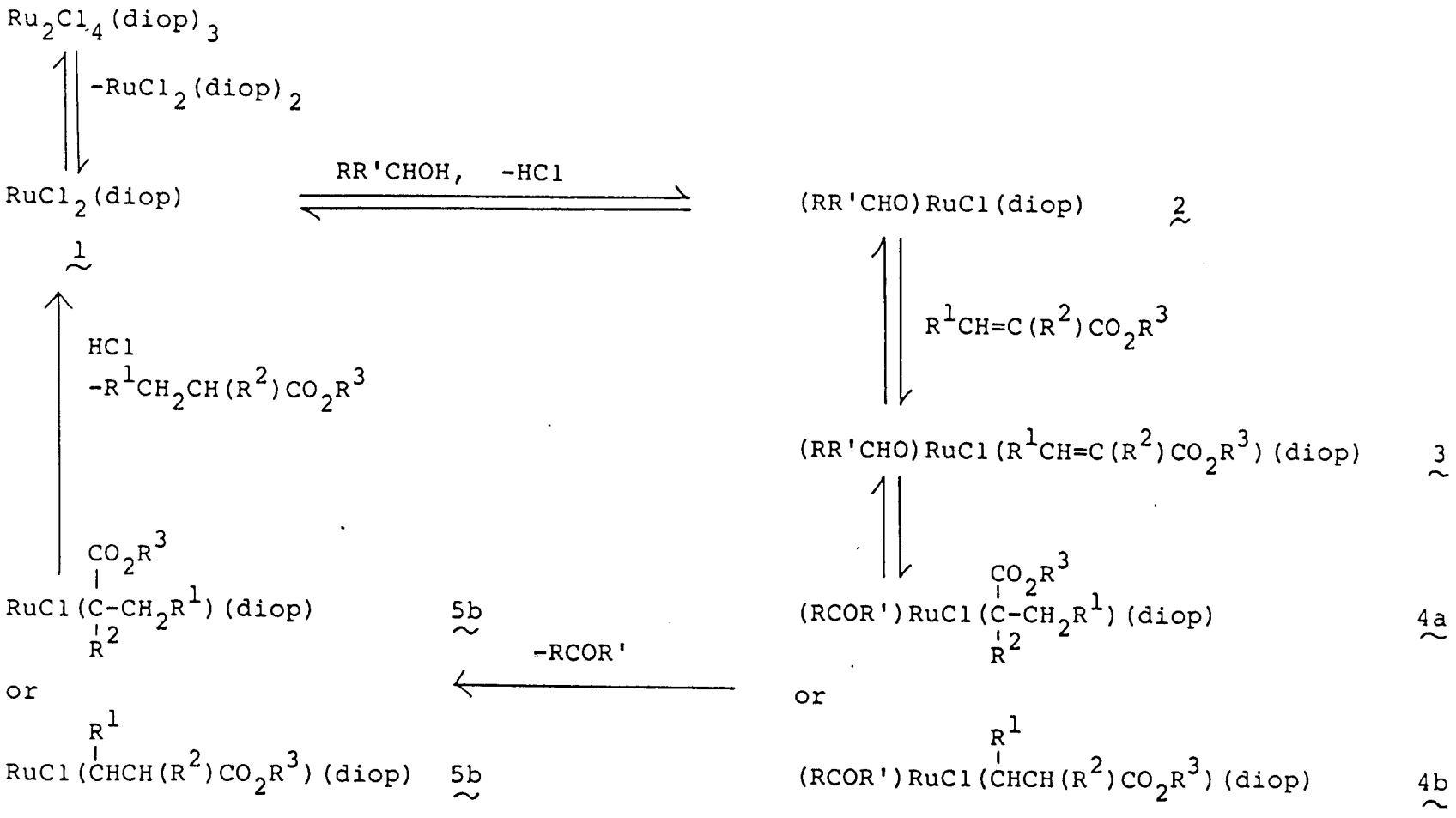
$CH_3CH=C(CH_3)CO_2R$ R	Time / h	Yield / %	$[\alpha]_D^{23}$ / °	O.P. / %
1-Phenylethyl	10	71	+0.10	0.8
α-(Ethoxycarbonyl) benzyl	9	93	-1.88	15.4
(1*R*,2*R*)-1,2-bis(ethoxycarbonyl)-2-hydroxyethyl	4	80	-0.41	1.1
l-menthyl	9	34	-0.23	1.9
	12[b)]	43	+0.06	0.6

a) Catalyst, 4 mmol dm^{-3}; alcohol, 67 mmol; ester, 33 mmol.

b) $Ru_2Cl_4((+)\text{-diop})_3$ was used.

induction, including diastereo-face differentiation of unsaturated esters by a chiral catalsyt, can also be expected by the use of the esters containing chiral carbon atoms in the ester moiety, chiral alcohol, and the Ru(II) complex.

When an asymmetric transfer hydrogenation of racemic or optically active α-methylcrotonate by 1-phenylethanol was effected with the Ru(II)-(-)-diop complex, no effective double asymmetric induction was realized (Table 4); optical purities of hydrogenated products were low (maximum e.e. 15.4%). Presumably, steric bulkiness of the ester group in the substrates decreases enantio-differentiating ability of the chiral Ru(II) complex through inhibition of the substrate coordination to the complex.



Scheme 2. The sign of the optical rotation of diop is omitted.

Reaction Mechanism.

It is obvious that the present asymmetric hydrogen transfer from an alcohol to unsaturated substrate is effected by the coordination of both the reactants to the Ru(II) complex. From the fact that chirality of the alcohol sustantially affects the extent of asymmetric induction by the Ru(II)-(+) or (-)-diop catalyst, the asymmetric induction can be expected in the process of coordination of an olefin to the unisolable ruthenium-alkoxide complex (*viz.*, the steric approach control over enantioface differentiation),[12] which has previously been formed from the active ruthenium species and the alcohol.

As for the catalytically active species, $RuCl_2$((+) or (-)-diop) (1) has been suggested as the plausible species by ^{31}P NMR analysis of Ru_2Cl_4((-)-diop)$_3$;[13] $RuCl_2$((-)-diop)$_2$ simultaneously formed seems inactive for the present reaction due to the lack of active sites.

Therefore, the present transfer hydrogenation is considered to proceed along the catalytic cycle in Scheme 2, where the participation of HCl in the step of coordination of the alcohol to the species 1 and of the elimination of the hydrogenated product has been proposed by Sasson[14] in the transfer hydrogenation of unsaturated ketones by alcohols with $RuCl_2(PPh_3)_3$. Ruthenium-alkyl complexes 4a and 5a are more plausible than complexes 4b and 5b in the light of the contribution of d-π conjugation between the ruthenium metal and carbonyl group to stabilization.[15]

6-4 Summary

Asymmetric transfer hydrogenation of prochiral unsaturated

acids and esters by alcohols was carried out with $RuCl_2(PPh_3)_3$ or Ru_2Cl_4((+) or (-)-diop)$_3$ at 160-190°C. The optical purity (3.4-16.4%) of the hydrogenated acids obtained with $PhCH_2OH$ and Ru_2Cl_4((-)-diop)$_3$ was in the order: $MeCH=C(Me)CO_2H$>$PhCH=C(Me)CO_2H$> $CH_2=C(CH_2CO_2H)CO_2H$>$HO_2CH=C(Me)CO_2H$. In the transfer hydrogenation of $MeCH=C(Me)CO_2R$ by $PhCH_2OH$ or (*RS*)-PhCH(Me)OH at 190°C, the extent of asymmetric induction of Ru_2Cl_4((-)-diop)$_4$ (1.7-11.4% e.e. with $PhCH_2OH$ and 7.4-18.2% e.e. with (*RS*)-PhCH(Me)OH) decreased with increasing bulkiness of group R and was not enhanced by the introduction of any groups R containing chiral carbon atoms into esters (maximum e.e. 15.4%). The change of hydrogen donors from $PhCH_2OH$ to (*RS*)-PhCH(Me)OH appreciably increased the optical purity of the hydrogenated acids and esters, and the chiral α-D-glucofuranose derivatives afforded optically active products, even with achiral $RuCl_2(PPh_3)_3$.

CHAPTER 7 KINETIC STUDY ON ASYMMETRIC TRANSFER HYDROGENATION OF UNSATURATED ACIDS AND ESTERS BY ALCOHOLS WITH A BINUCLEAR RUTHENIUM(II) CHIRAL DIPHOSPHINE COMPLEX

7-1 Introduction

Ruthenium chiral phosphine complexes have hitherto been the object of only limited investigation in asymmetric reaction, although some examples of asymmetric hydrogenation of olefins by ruthenium(II) chiral phosphine complexes have been documented.[4,16]

In this respect, as described in previous Chapters, a binuclear ruthenium(II) chiral diphosphine complex, Ru_2Cl_4((+) or (-)-diop)$_3$ (diop=2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)-2,3-butanediol), has been an efficient catalyst for enantiomer-differentiating dehydrogenation of racemic secondary alcohols[1] and for asymmetric transfer hydrogenation of prochiral olefins.[17] However, the mechanism of asymmetric transfer hydrogenation has not been elucidated, even though there are some kinetic studies on the transfer hydrogenation of olefins or aldehydes by hydrogen donors (alcohols, indole, or dioxane) with $RhCl(PPh_3)_3$,[18] $RuCl_2(PPh_3)_3$,[14] or $RuH_2(PPh_3)_3$.[19]

Therefore, the author has investigated the mechanism of Ru_2Cl_4((-)-diop)$_3$-catalyzed asymmetric transfer hydrogenation of unsaturated acids and esters by alcohols.

7-2 Experimental

Materials.

The binuclear ruthenium(II) complex of Ru_2Cl_4((-)-diop)$_3$

was prepared according to the literature method.[4] 1-Phenylethyl α-methylcrotonate was obtained by the reaction of 1-phenylethanol with α-methylcrotonoyl chloride, and deuterated benzyl alcohols ($C_6H_5CD_2OD$, $C_6H_5CD_2OH$, and $C_6H_5CH_2OD$) were prepared by the reported method.[20] Other commercially available organic materials were fractionally distilled or recystallized before use.

Kinetic Run.

A typical example of transfer hydrogenation was run as following procedure. A mixture of the ruthenium complex (5 mg, 2.7×10^{-3} mmol), 1-phenylethanol (1.57 g, 12.9 mmol) and α-methylcrotonic acid (0.20 g, 2.0 mmol) was put into each of five test tubes in nitrogen atmosphere, and total volume was made by diphenyl ether to 2.5 cm^3. These tubes was sealed and heated in a silicon bath controlled at 150±1°C for 10, 20, 30, 40 and 60 min, respectively. The amounts of unreacted substrate and hydrogenated product were determined by gas-chromatographic analysis using a 1-m column packed with 15% EGA on Uniport B (Yanagimoto G-180) or 100 MHz ^1H NMR (JEOL MH-100) analysis.

Transfer Hydrogenation by Deuterated Benzyl Alcohol.

A typical example of the reaction was run as follows. A mixture of α-methylcrotonic acid (0.54 g, 5.4 mmol), $C_6H_5CD_2OH$ (1.61 g, 14.6 mmol) and the ruthenium complex (19.8 mg, 10.7 mmol) was put into a test tube in nitrogen atmosphere, and this tube was sealed and heated for 12 h at 190°C. The deuterium distribution of reduced products was determined by means of ^1H NMR (100 MHz).

^{31}P NMR Spectrum.

^{31}P NMR spectrum of $Ru_2Cl_4((-)\text{-diop})_3$ in *p*-dichlorobenzene was recorded on JEOL FX-100 in 10 mm-tube at 40.32 MHz with the external standard of 85% H_3PO_4 in D_2O.

7-3 Results and Discussion

Rate Dependence on the Concentration of Catalyst, Alcohol, and Unsaturated Substrate.

As indicated by typical time-yield curves for the present $Ru_2Cl_4((-)\text{-diop})_3$-catalyzed transfer hydrogenation in Fig. 1, conversion of the unsaturated substrate to the hydrogenated product is linear with time during initial stage. When α-methylcrotonic acid was used as a hydrogen acceptor, the reaction proceeded stoichiometrically up to more than 20% conversion at temperature below 190°C, but thereafter some of the hydrogen donor was consumed by esterification reaction with the saturated acid; the extent of esterification between such an alcohol as 1-phenylethanol and the unsaturated acid was negligibly small, especially during the initial stage. Initial reaction rate (r_i), derived from linear part of the time-yield curve, was directly proportional to the concentration of the ruthenium(II) complex and to that of the hydrogen donor (Fig. 2 and 3). The first-order dependence of the reaction rate on the concentration of $Ru_2Cl_4((-)\text{-diop})_3$ and that of the hydrogen donor suggests that $Ru_2Cl_4((-)\text{-diop})_3$ itself changes into a catalytically active species, to which one molecule of hydrogen donor coordinates for reaction.

Although a linear dependence of reaction rate on the

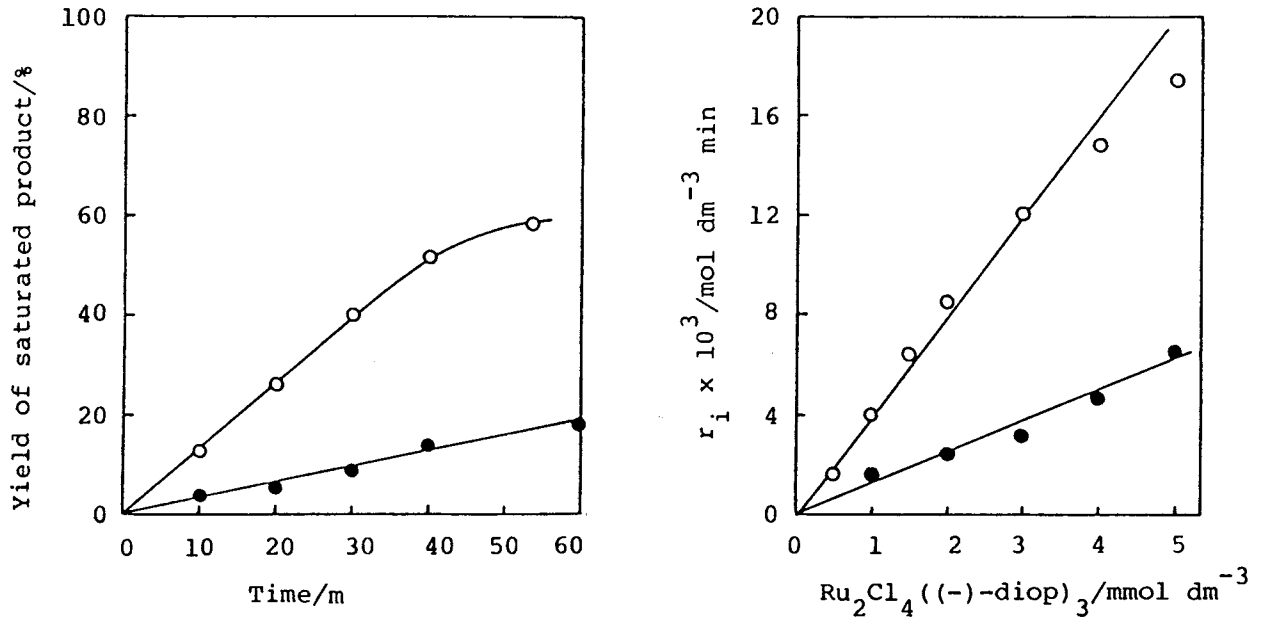


Fig. 1. Typical time-yield curves for $Ru_2Cl_4((-)\text{-diop})_3$ (1.0 mmol dm^{-3}) catalyzed transfer hydrogenation of α-methylcrotonic acid (0.63 mol dm^{-3}) (O) at 150°C, and 1-phenylethyl α-methylcrotonate (0.5 mol dm^{-3}) (●) at 165°C by 1-phenylethanol (7.0 mol dm^{-3}) in Ph_2O.

Fig. 2. Dependence of initial rate (r_i) on the concentration of $Ru_2Cl_4((-)\text{-diop})_3$ in the transfer hydrogenation of α-methylcrotonic acid (0.80 mol dm^{-3}) by 1-phenylethanol (7.5 mol dm^{-3}) at 150°C, and of 1-phenylethyl α-methylcrotonate (0.5 mol dm^{-3}) at 165°C by 1-phenylethanol (6.5 mol dm^{-3}) in Ph_2O.
Symbols are the same as in Fig. 1.

concentration of hydrogen acceptor was observed in the case of an unsaturated ester, 1-phenylethyl α-methylcrotonate, the initial rate was reduced with increasing in concentration of the unsaturated acid, and a linear relationship between $1/r_i$ and the concentration of the unsaturated acid was established, with a

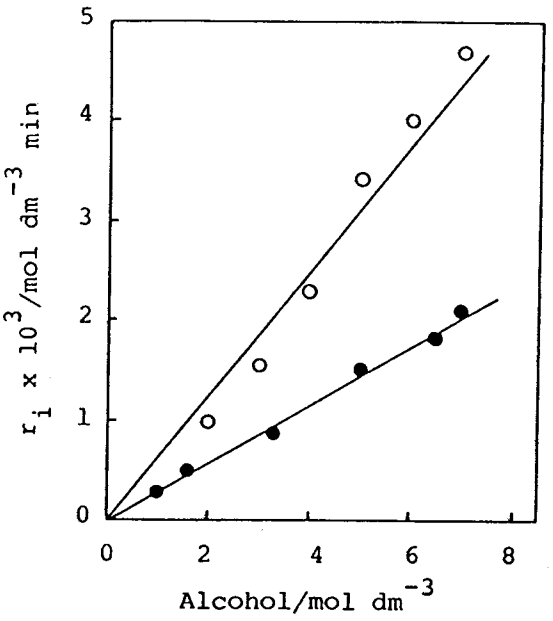


Fig. 3. Dependence of initial rate (r_i) on the concentration of 1-phenylethanol in $Ru_2Cl_4((-)\text{-diop})_4$ (1.0 mmol dm^{-3}) catalyzed transfer hydrogenation of α-methylcrotonic acid (0.8 mol dm^{-3}) at 150°C, and of 1-phenylethyl α-methylcrotonate (0.5 mol dm^{-3}) at 165°C in Ph_2O.
Symbols are the same as in Fig. 1.

positive intercept on the vertical axis (Fig. 4). The unsaturated acid coordinates to the ruthenium(II) complex easily and strongly, as compared with the unsaturated ester, which might retard the coordination of hydrogen donor *via* shielding of the active coordination site of the catalyst.

Rate Dependence of Added (-)-diop Concentration and Reaction Temperature.

Addition of (-)-diop to the reaction system lowered the initial rate, and the plots of $1/r_i$ *vs.* added (-)-diop

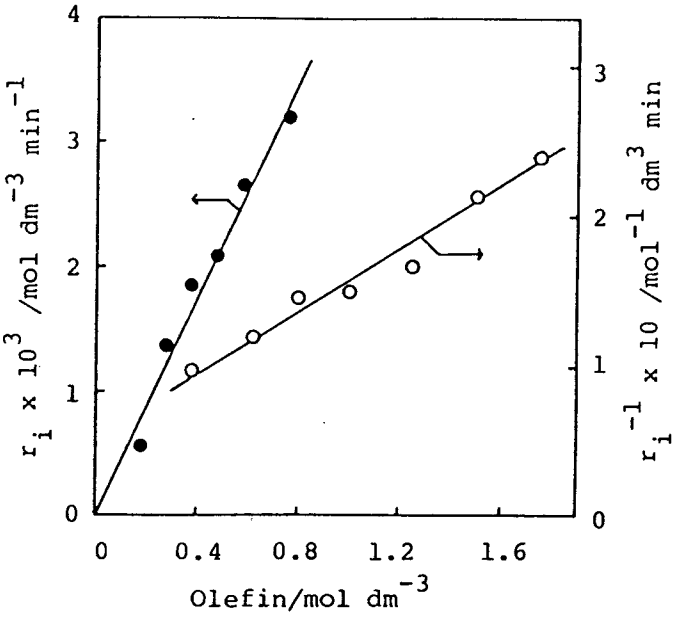


Fig. 4. Dependence of initial rate (r_i) on olefin concentration in $Ru_2Cl_4((-)\text{-diop})_3$ (1.0 mmol dm^{-3}) catalyzed transfer hydrogenation of α-methylcrotonic acid at 150°C, and of 1-phenylethyl α-methylcrotonate at 165°C by 1-phenylethanol (7.0 mol dm^{-3}) in Ph_2O.
Symbols are the same as in Fig. 1.

concentration tend towards a straight line with a positive intercept (Fig. 5). The coordination of added (-)-diop to catalytically active species, which will be discussed later, makes the catalyst inactive, but coordination strength of (-)-diop is not very much larger than that of hydrogen donor or acceptor, as can be seen from the rate decrease on addition of (-)-diop (Fig. 4). The initial rate was also influenced by reaction temperature (140-200°C), and the plots of $\ln(r_i)$ *vs.* 1/T gave linear Arrhenius relationships for the hydrogenation of the unsaturated acid and ester (Fig. 6). Therefore, the reaction proceeds

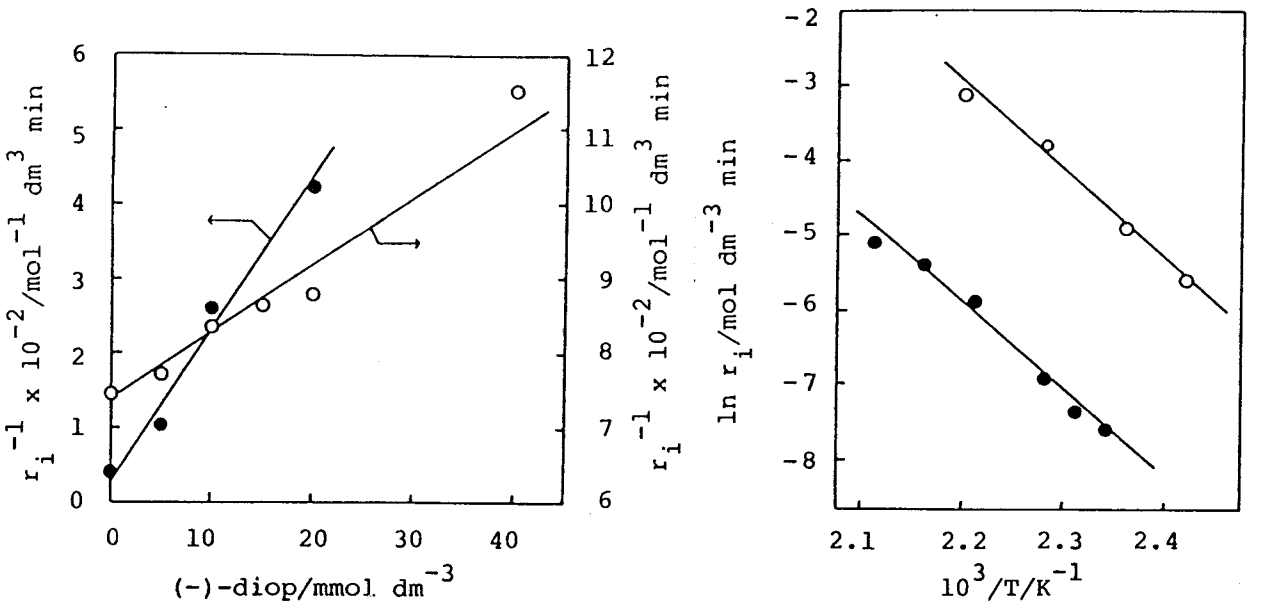
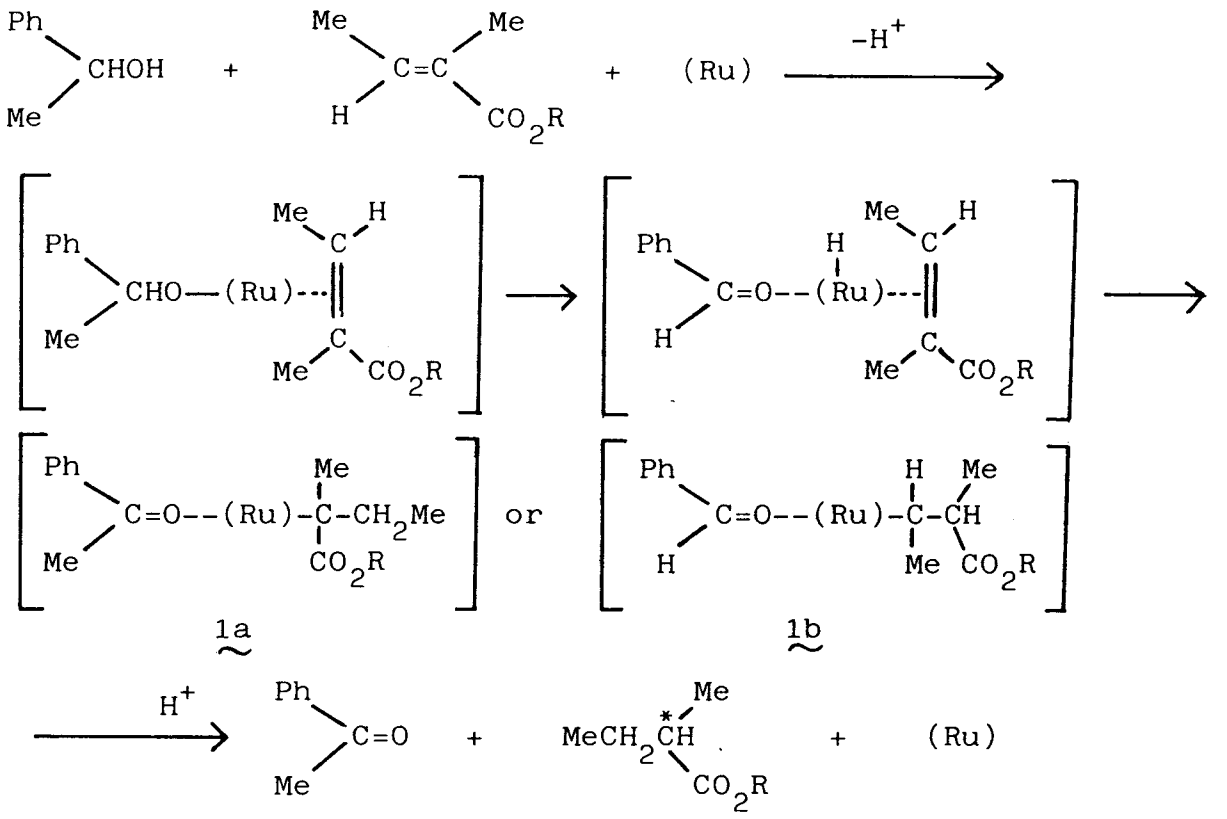


Fig. 5. Dependence of initial rate (r_i) on the concentration of added (-)-diop in the $Ru_2Cl_4((-)\text{-diop})_3$ (1.0 mmol dm^{-3}) catalyzed transfer hydrogenation of α-methylcrotonic acid (0.8 mol dm^{-3}) at 150°C, and of 1-phenylethyl α-methylcrotonate (0.5 mol dm^{-3}) at 190°C by 1-phenylethanol (7.5 mol dm^{-3}) in Ph_2O.
Symbols are the same as in Fig. 1.

Fig. 6. Plots of ln r_i *vs.* 1/T for the $Ru_2Cl_4((-)\text{-diop})_3$ (1.0 mmol dm^{-3}) catalyzed transfer hydrogenation of α-methylcrotonic acid, and of 1-phenylethyl α-methylcrotonate by 1-phenylethanol (7.4 mol dm^{-3}) in Ph_2O.
Symbols are the same as in Fig. 1.

the same mechanism in the temperature range of 140-200°C without structure change in catalytically active species. With regard to activation parameters, the activation energy $E^{\ddagger}$, enthalpy of activation $\Delta H^{\ddagger}$, and entropy of activation $\Delta S^{\ddagger}$ were evaluated as 22.8 (23.9) kcal mol^{-1}, 22.0 (23.1) kcal mol^{-1}, and -13.7 (-18.9)



Scheme 1.

cal mol^{-1} K^{-1} for the $Ru_2Cl_4((-)\text{-diop})_3$-catalyzed transfer hydrogenation of α-methylcrotonic acid (1-phenylethyl α-methylcrotonate) by 1-phenylethanol. Although the transfer hydrogenation of bulky unsaturated ester required a slightly larger activation energy as compared with that of the unsaturated acid, the reaction is considered to proceed *via* the process shown in Scheme 1, where (Ru) denotes a catalytically active species; the participation of H^+ in the reaction process has been confirmed by Sasson.[14)]

Generation of Catalytically Active Species.

It is necessary here to discuss the catalytically active species formed from the binuclear ruthenium(II) diphosphine

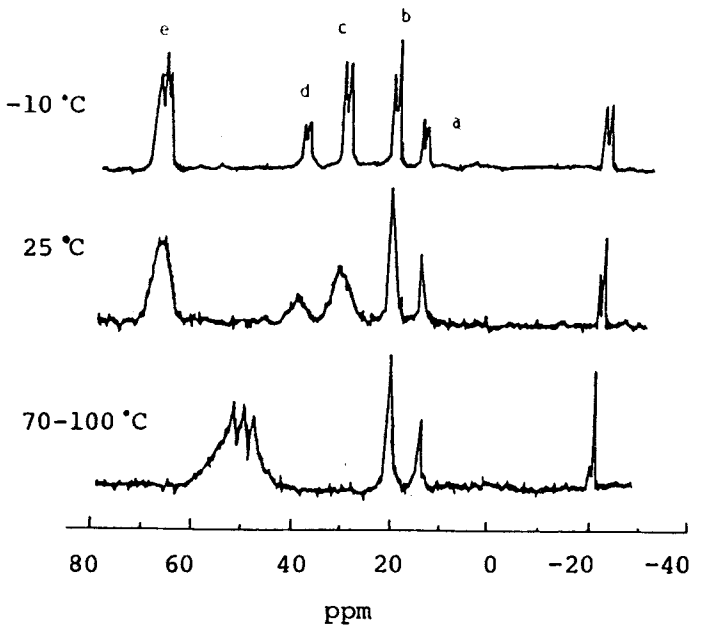
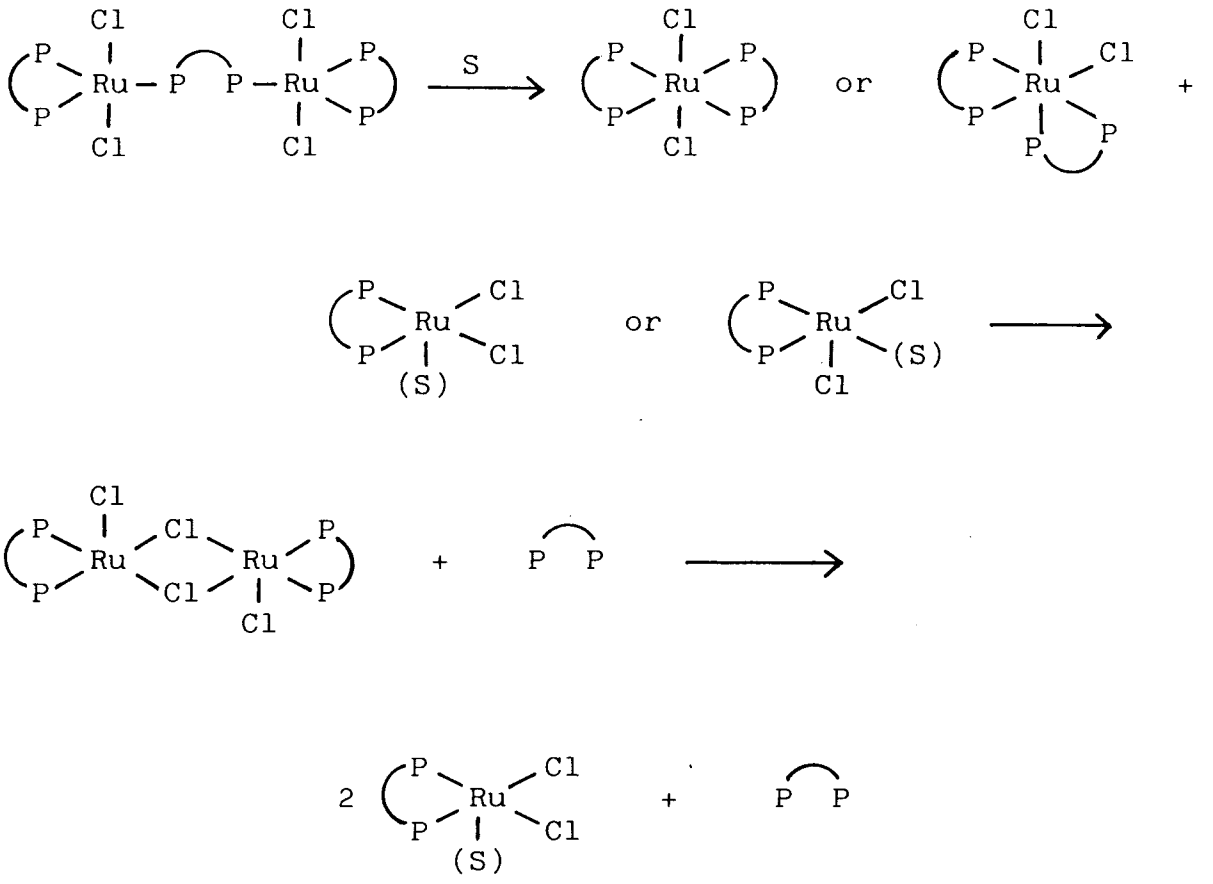


Fig. 7. ^{31}P NMR spectrum of $Ru_2Cl_4((-)\text{-diop})_3$.

complex, $Ru_2Cl_4((-)\text{-diop})_3$. The ^{31}P NMR spectrum of $Ru_2Cl_4((-)\text{-diop})_3$ at -10°C showed six different peaks, one due to free (-)-diop (-24.6 ppm) and five others denoted by a (13.4 ppm, doublet J_{PP}=28.1 Hz), b (21.0 ppm, doublet, J_{PP}=28.1 Hz), c (29.7 ppm, doublet, J_{PP}=35.4 Hz), d (37.4 ppm, doublet, J_{PP}=35.4 Hz), and e (67.6 ppm, triplet, J_{PP}=33.9 Hz), in the ratio of 1.5:1:3:3:1:4, as shown in Fig. 7.

Since the remarkable difference in the chemical shifts (a-b 306 Hz, b-c 351 Hz, and c-d 310 Hz) does not correspond to the usual P-P coupling (J_{PP}=25-40 Hz);[21-23] there is no Ru-P coupling. The chemical shifts indicate the mixture of relative stable five or six-coordinate ruthenium(II) complexes generated from $Ru_2Cl_4((-)\text{-diop})_3$ *via* the equiliblium reaction shown in Scheme 2, where the coordination of one solvent molecule to



Scheme 2. P⌒P: (-)-diop; S: solvent.

the five coordinated ruthenium(II) complexes is assumed. Since peaks c, d, and e change into broad signal (51.0 ppm) on raising temperature from -10 to 70°C, they can be assigned to (-)-diop in $Ru_2Cl_4((-)\text{-diop})_2$, bridged (-)-diop in $Ru_2Cl_4((-)\text{-diop})_3$, and terminal (-)-diop in $Ru_2Cl_4((-)\text{-diop})_3$, respectively, and peaks a and b could well be those of (-)-diop in two stable isomers of $RuCl_2((-)\text{-diop})$ (tetrahedral or square planar).

Thus, three different ruthenium(II) complexes, $RuCl_2((-)\text{-diop})$, $RuCl_2((-)\text{-diop})_2$, and $Ru_2Cl_4((-)\text{-diop})_2$, can be produced from $Ru_2Cl_4((-)\text{-diop})_4$ as shown in Reactions (1a-1c).

$$Ru_2Cl_4((-)\text{-diop})_3 \rightleftharpoons 2\ RuCl_2((-)\text{-diop}) + (-)\text{-diop} \quad (1a)$$

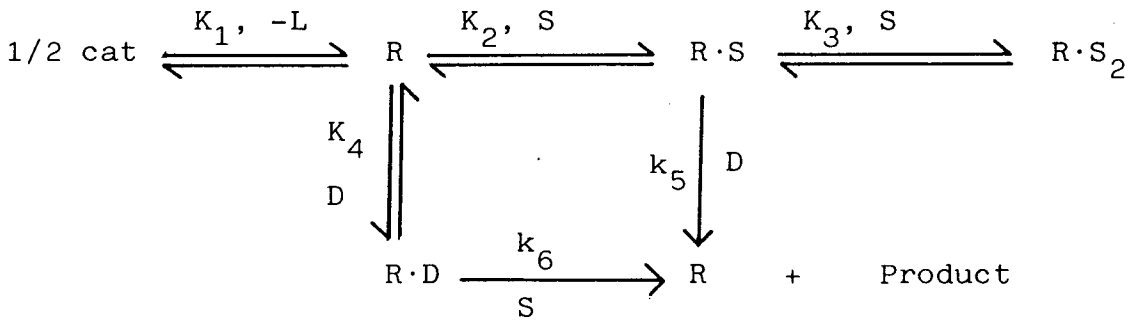
$$Ru_2Cl_4((-)\text{-diop})_3 \rightleftharpoons Ru_2Cl_4((-)\text{-diop})_2 + (-)\text{-diop} \quad (1b)$$

$$Ru_2Cl_4((-)\text{-diop})_3 \rightleftharpoons RuCl_2((-)\text{-diop})_2 + RuCl_2((-)\text{-diop}) \quad (1c)$$

The unstable four-coordinate complexes might include solvent as ligand. The catalytically active species $RuCl_2((-)\text{-diop})$ is then generated *via* Reaction (1a) or (1c).

Reaction Mechanism.

If catalytically active $RuCl_2((-)\text{-diop})$ complex is generated *via* Reaction (1a), the mechanism shown in Scheme 3 can be considered, where cat=$Ru_2Cl_4((-)\text{-diop})_3$, L=(-)-diop, R=catalytically active $RuCl_2((-)\text{-diop})$, S=unsaturated substrate, and D=alcohol. From the material balance: $[cat]_0=([cat] + [R] + [R\cdot S] +$



Scheme 3.

$$r=k_5[R\cdot S][D] + k_6[R\cdot D][S]=(k_5K_2 + k_6K_4)(K_1[cat]/[L])^{\frac{1}{2}}[D][S] \quad (2a)$$

$[R\cdot D] + [R\cdot S_2])/2=[cat] + [cat]^{\frac{1}{2}}(1 + K_2[S] + K_4[D] + K_2K_3[S]^2)x$ $(K_1/4[L])^{\frac{1}{2}}$, the rate equation (2a) can be rewritten in two different ways. The case $[cat]<<[cat]^{\frac{1}{2}}(1 + K_2[S] + K_4[D] +$

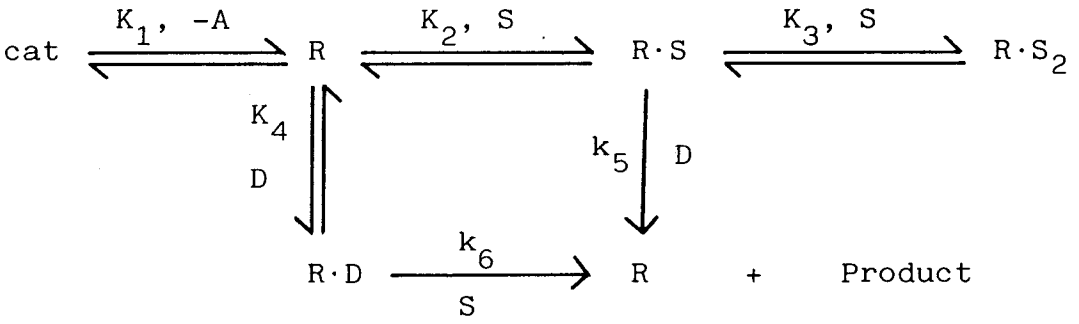
$K_2K_3[S]^2)(K_1/4[L])^{\frac{1}{2}}$ (*i.e.*,($[R] + [R\cdot S] + [R\cdot D] + [R\cdot S_2]$)/2>> [cat]) gives the equation (2b), and the case [cat]>>$[cat]^{\frac{1}{2}}$(1 +

$$r=2(k_5K_2 + k_6K_4)[cat]_0[S][D]/(1 + K_2[S] + K_4[D] + K_2K_3[S]^2) \quad (2b)$$

$K_2[S] + K_4[D] + K_2K_3[S]^2)(K_1/4[L])^{\frac{1}{2}}$ (*i.e.*, ($[R] + [R\cdot S] + [R\cdot D]+$ $[R\cdot S_2]$)/2<<[cat]) gives the equation(2c). Although the first order dependence of r_i on $[cat]_0$ is explained not by equations (2a) and (2c) but (2b), linear relation between $1/r_i$ and [L] is not recognized from any equations (2a-2c). Therefore, Scheme 3 can be discarded as unacceptable.

$$r=(k_5K_2 + k_6K_4)[S][D](K_1[cat]_0/[L])^{\frac{1}{2}} \quad (2c)$$

If catalytically active $RuCl_2$((-)-diop) complex is formed in Reaction (1c), the mechanism can be expressed as in Scheme 4, where cat=Ru_2Cl_4((-)-diop)$_3$, A=$RuCl_2$((-)-diop)$_2$, R=$RuCl_2$((-)-diop), S=unsaturated substrate, and D=alcohol.



Scheme 4.

The rate equation derived from stationary-state assumption applied to [R·S] and [R·D] is (3a). From the relation of

$$r=k_5[R\cdot S][D] + k_6[R\cdot D][S]$$
$$=K_1(k_5K_2 + k_6K_4)[cat][S][D]/[A] \quad (3a)$$

$[cat]_0=[cat] + [R] + [R\cdot S] + [R\cdot D] + [R\cdot S] =([A] + K_1 + K_1K_2[S] + K_1K_4[D] + K_1K_2K_3[S]^2)[cat]/[A]$, the rate equation can be rewritten as (3b). When the substrate S is unsaturated acid such

$$r=(k_5K_2 + k_6K_4)[cat]_0[S][D]/([A]/K_1 + 1 + K_2[S] + K_4[D] + K_2K_3[S]^2) \quad (3b)$$

as α-methylcrotonic acid, the linear relationship between $1/r_i$ and $[S]$ requires $[A]/K_1 + 1 + K_4[D] \ll K_2[S] + K_2K_3[S]^2$ (*i.e.*, $[cat] + [R] + [R\cdot D] \ll [R\cdot S] + [R\cdot S_2]$), so that the rate equation is (3c), where $k'=(k_5K_2 + k_6K_4)/K_2$.

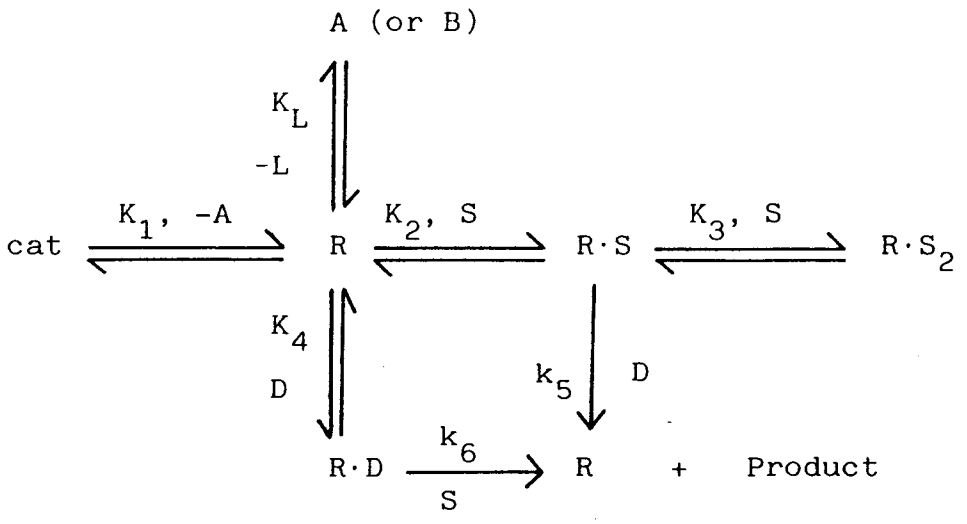
$$r=k'[cat]_0[D]/(1 + K_3[S]) \quad (3c)$$

Where the substrate is an unsaturated ester such as 1-phenylethyl α-methylcrotonate, the linear relation between r_i and $[S]$ requires $[A]/K_1 + 1 \gg K_2[S] + K_4[D] + K_2K_3[S]^2$ (*i.e.*, $[cat] + [R] \gg [R\cdot S] + [R\cdot D] + [R\cdot S_2]$), so that the rate equation can be expressed as (3d), where $k''=k_5K_2 + k_6K_4$. Both rate equations (3c and 3d) reflect linear relations of r_i *vs.* $[cat]_0$ and r_i *vs.* $[D]$.

$$r=k''[cat]_0[S][D]/([A]/K_1 + 1) \quad (3d)$$

In order to discuss the effect of addition of (-)-diop on the reaction rate, it is necessary to rewrite Scheme 4 as Scheme 5, where L=(-)-diop, A=$RuCl_2$((-)-diop)$_2$, and B=$RuCl_2$((-)-diop)$_2$ but with different structure from A.

The rate equation of Scheme 5 is given as (4). Since this satisfies the linear relation between $1/r_i$ and $[L]$ in addition to other linear relations mentioned above, the mechanism of the present reaction can be expressed by Scheme 5.



Scheme 5.

$$r=(k_5K_2 + k_6K_4)[cat]_0[S][D]/([A]/K_1 + K_L[L] + K_2[S] + K_4[D] + K_2K_3[S]^2) \quad (4)$$

Isotope Effects.

In order to define the reaction mechanism more precisely, $Ru_2Cl_4((-)\text{-diop})_3$-catalyzed transfer hydrogenation of α-methylcrotonic acid by a deuterated benzyl alcohol ($PhCD_2OD$) was examined at 190°C. The reaction rate r_i^D is lower than that (r_i^H) in the same reaction with $PhCH_2OH$, and the value of r_i^D/r_i^H (2.4) indicated the occurrence of rate-determining abstraction of the hydrogen bound to α-carbon of the hydrogen donodr by the ruthenium(II) complex catalyst, as suggested previously.[14] Such an isotope effect was also observed in the transfer hydrogenation of α-methylcrotonic and α-methylcinnamic acids and/or their esters (Table 1). It is noteworthy that the deuterated hydrogen donor $PhCD_2OH$ resulted in a predominance of deuterium distribution in $MeCDHCH(Me)CO_2R$ or $PhCDHCH(Me)CO_2R$ (R=H or Et) rather than in $MeCH_2CD(Me)CO_2R$ or $PhCH_2CD(Me)CO_2R$. This suggests the

Table 1. Transfer Hydrogenation of Unsaturated Acids and Esters by Deuterated Benzyl Alcohols with $Ru_2Cl_4((-)\text{-diop})_3$ at 190°C[a)]

Unsaturated species	Alcohol[b)]	Time / h	Yield / %	Deuterium distribution/mol%	
				Methine(CD)	Methylene(CDH)
$MeCH=C(Me)CO_2H$	$PhCH_2OD$	12	75	6	25
	$PhCD_2OH$	12	37	18	52
$MeCH=C(Me)CO_2Et$	$PhCH_2OD$	3	89	11	20
	$PhCD_2OH$	4	54	10	84
$PhCH=C(Me)CO_2H$	$PhCH_2OH$	24	47	0	0
	$PhCH_2OD$	24	32	7	18
	$PhCD_2OH$	24	25	43	91
	$PhCD_2OD$	24	23	43	96
$PhCH=C(Me)CO_2Et$	$PhCH_2OD$	12	27	14	27

a) $Ru_2Cl_4((-)\text{-diop})_3$, 5.0 mmol dm^{-3}; unsaturated species, 2.5 mol dm^{-3} in the alcohol.

b) Deuterium contents of alcohols were $PhCH_2OD$ (98%), $PhCD_2OH$ (81%), and $PhCD_2OH$ (81% in CD_2).

preferential formation of [PhCDO-(Ru)-C(Me)-(CO_2R)CDHR'] (R=Me or Ph) as intermediate (*cf.* 1a in Scheme 1), which might be stabilized by π-conjugation of (Ru)-CO_2R bond.[15] On the other hand, deuterated products MeCDHCH(Me)CO_2R and PhCDHCH(Me)CO_2R were also observed to the extent of 18-27%, even in the case when $PhCH_2OD$ was used. This is attributable to irreversible formation of PhCDHOH from $PhCH_2OD$ *via* Ru_2Cl_4((-)-diop)$_3$-catalyzed intramolecular hydrogen-deuterium exchange in the deuterium source. When $PhCH_2OD$ was heated at 190°C for 6 h in the presence of Ru_2Cl_4((-)-diop)$_3$ (5.7 mol dm^{-3}), 29% of the deuterium was exchanged, with the formation of benzaldehyde and dibenzyl ether.

With regard to the enantio-differentiating process in the present reaction, there are two possible steps, *viz.*, (a) selection of one face or the other during the coordination of a prochiral unsaturated substrate to the ruthenium(II) complex, and (b) enantio-selective product development during the protonation of a σ-type Ru(II)-substrate complex (1a in Scheme 1). If the former process is acceptable, the bulky substituent of the ester group in the substrate would hinder the approach of the substrate to the Ru(II) complex so as to decrease the extent of asymmetric induction. In the Ru_2Cl_4((-)-diop)$_3$-catalyzed transfer hydrogenation of MeCH=C(Me)CO_2R (R=H, Me, Et, Bu, $PhCH_2$, and PhCH(Me)) by 1-phenylethanol at 190°C, the enantiomeric excess of the saturated product decreased in the order R=H>Me>Et≒Bu> $PhCH_2$>PhCH(Me) (Table 2 in Chapter 6). Therefore, selection of enantio-face plays a predominant role in the asymmetric induction process of the present reaction.

7-4 Summary

Kinetic investigation of $Ru_2Cl_4((-)\text{-diop})_3$-catalyzed transfer hydrogenation of unsaturated acids and esters by alcohols indicated that the catalytically active $RuCl_2((-)\text{-diop}$ complex generated from the $Ru_2Cl_4((-)\text{-diop})_3 \rightleftharpoons RuCl_2((-)\text{-diop}) + RuCl_2((-)\text{-diop})_2$ reaction offered optically active hydrogenated products *via* the reaction of hydrogen acceptor and $RuCl_2((-)\text{-diop})$(hydrogen donor) complex, and hydrogen donor and $RuCl_2((-)\text{-diop})$(hydrogen acceptor) complex. ^{31}P NMR analysis of $Ru_2Cl_4((-)\text{-diop})_3$ in solution also suggested the possibility of $RuCl_2((-)\text{-diop})$ formation. The enantio-differentiating process was also discussed on the basis of isotopic effects observed in the $Ru_2Cl_4((-)\text{-diop})_3$-catalyzed reaction between deuterated benzyl alcohol and unsaturated species.

CHAPTER 8 ASYMMETRIC HYDROGENATION OF KETONES BY HOMOGENEOUS AND HETEROGENEOUS RHODIUM(I) CHIRAL PHOSPHINE CATALYTIC SYSTEMS

8-1 Introduction

The most effective method for obtaining optically active alcohols, instead of the kinetic resolution of racemic alcohols as described in previous Chapters, is the asymmetric hydrogenation of prochiral ketones with chiral catalyst. However, high enantio-selection has not been attained in the asymmetric reaction by cationic[25-29] and neutral[30-34] rhodium chiral phosphine complexes. Exceptionally, Markó[34] has reported that the addition of triethylamine to $[RhCl(norbornadiene)]_2$-(+)-2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)-2,3-butanediol (diop) catalytic system has brought about the increment of the enantiomeric excess (54-84%) of products. It has also been suggested by Tani[35,36] that diop-type chiral tetraalkyldiphosphines, being strong electron donating ligand, are excellent chiral ones in the rhodium complex catalyzed hydrogenation of ketones.

On the other hand, there are only limited reports on the heterogeneous asymmetric hydrogenation of carbonyl compounds by the use of modified-Raney nickel catalyst with chiral compounds,[37,38] and alkaloid-Pt/Al_2O_3 catalyst.[39,40]

On the practical viewpoint, the author has investigated the homogeneous and heterogeneous asymmetric hydrogenation of ketones by rhodium(I) chiral phosphine complexes, prepared *in situ* from $[RhCl(C_2H_4)_2]_2$ and (-)-diop, or (+)-1,2-bis(diphenyl-

phosphino)propane (prophos), and by polystyrene-supported rhodium(I)-diop complex. It is discussed how to effect on catalytic activity and enantio-selectivity for the mole ratio of rhodium to chiral phosphine in the homogeneous system, and the pore size and the structure of polystyrene carrier in the heterogeneous system.

8-2 Experimental

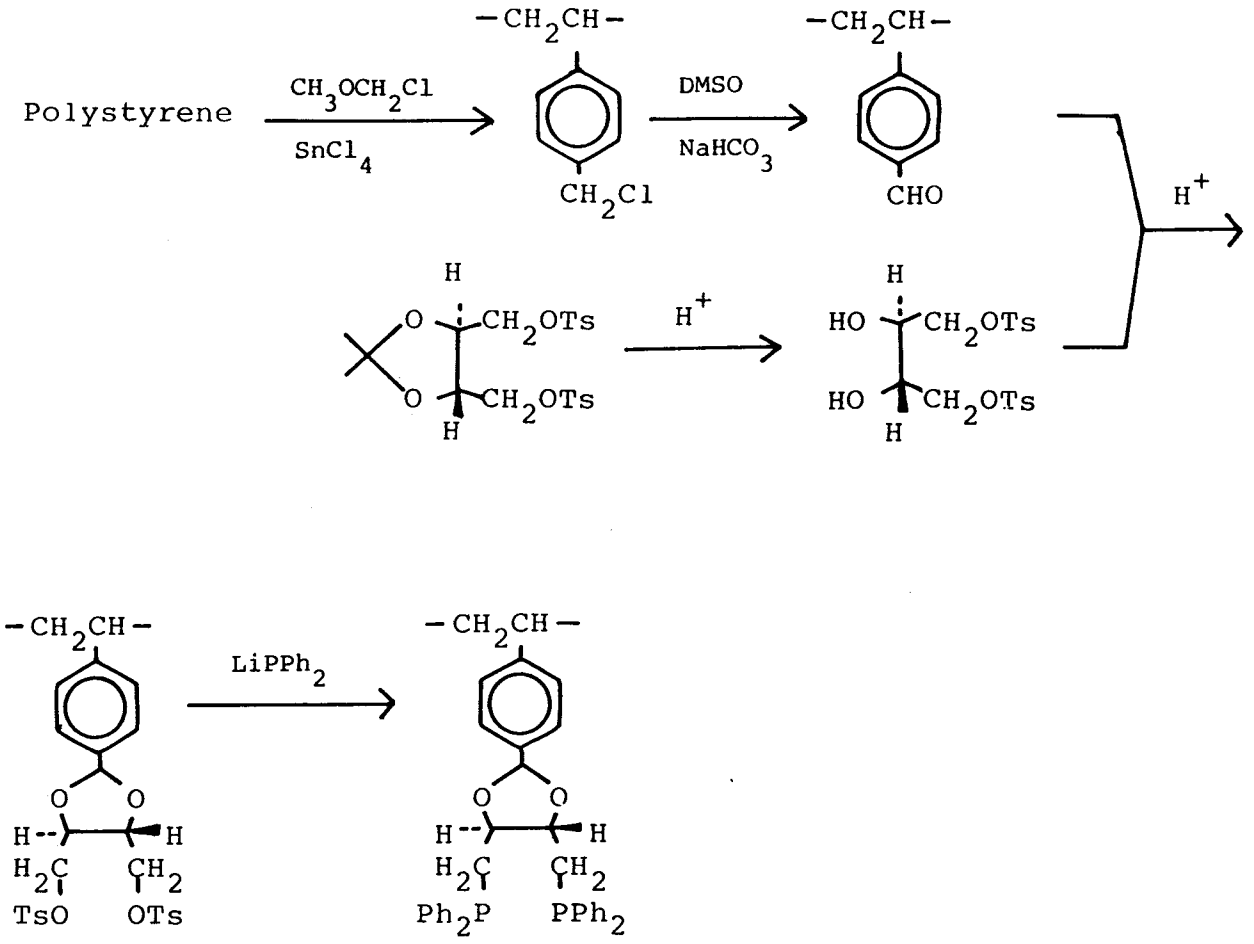
Materials.

Prochiral ketones were distilled before use. Styrene-divinylbenzene polymers to be used were Amberlite XAD-2 (ABL-1) and Amberlite XAD-4 (ABL-2) of Oruganǫ Co. Ltd.; pore sizes of them were 90 Å and 50 Å, respectively.

Chiral phosphines, (-)-diop and (+)-prophos, were synthesized by Kagan's[3] and Fryzuk's[41] methods, respectively. $[RhCl(C_2H_4)_2]_2$ was prepared by the method of the literature.[42]

Catalyst Preparation.

ABL-1-supported Rh(I)-(-)-diop (Rh-diop/ABL-1). Chiral diphosphine ((-)-diop) moiety was introduced to ABL-1 according to the procedure of Kagan,[43] as shown in Scheme 1. Rh-diop/ABL-1 was prepared by stirring of the phosphinated ABL-1 and $[RhCl(C_2H_4)_2]_2$ in benzene at room temperature for 24 h under nitrogen atmosphere, and then separated by filtration, followed by washing with benzene thoroughly and drying *in vacuo*. The amount of supported-rhodium was 0.47 mg-atom/g-resin, evaluated by the difference in the quantity between the charged $[RhCl(C_2H_4)_2]_2$ and dissolved one in the filtrate, which were determined by



Scheme 1.

a spectroscopic method at 500nm (ε=4850).

ABL-2-supported Rh(I)-(-)-diop (Rh-diop/ABL-2). This polymer complex was prepared by the same method as Rh-diop/ABL-1. The amount of the supported rhodium was 0.38 mg-atom/g-resin.

Noncross-linked polystyrene-supported Rh(I)-(-)-diop (Rh-diop/PST). A mixture of freshly distilled styrene (30 cm^3), azobis(isobutyronitrile) (0.55 g), and 1,1,2,2-tetrachloroethane (100 cm^3) was vigorously stirred at 80°C for 2 h under nitrogen stream. The solution poured into methanol to precipitate the polystyrene. The resulting solid was filtered, washed with

methanol, and dried *in vacuo*. Number average molecular weight by vapour pressure method was 3300. Introdution of chiral phosphine moiety to the polymer, and successive coordination to rhodium complex were undergone by the same method as described above. The amount of the supported rhodium was 0.54 mg-atom/g-resin.

Hydrogenation Procedure and Analyses.

In the case of atmospheric hydrogenation, $[RhCl(C_2H_4)_2]_2$ and the chiral phosphine were put into a two-neck flask (50 cm^3) in an oil bath. The flask was purged with nitrogen thoroughly, a mixture of the substrate (3 cm^3) and ethanol (2 cm^3) was charged in it. The reaction was run under bubling of hydrogen presaturated with ethanol. The reaction product was analyzed by gas-chromatography, using a 1-m column packed with Tween 80 on Uniport B. The optical purity of the product was determined from the optical rotation measured with a high sensitive digital polarimeter (Union PM-101).

Hydrogenation under applied hydrogen pressure was carried out in a pressure glass tube (50 cm^3), or in an autoclave.

8-3 Results and discussion

Homogeneous Hydrogenation.

It has been known that the enantio-selection decreases with elevating hydrogen pressure to be applied in asymmetric hydrogenation of prochiral olefins, such as (α-acylamino)cinnamic acid derivatives, by rhodium chiral diphosphine complexes, in spite of acceleration of the hydrogenation rate.[44] Thus, the asymmetric hydrogenation of acetophenone was carried out under an

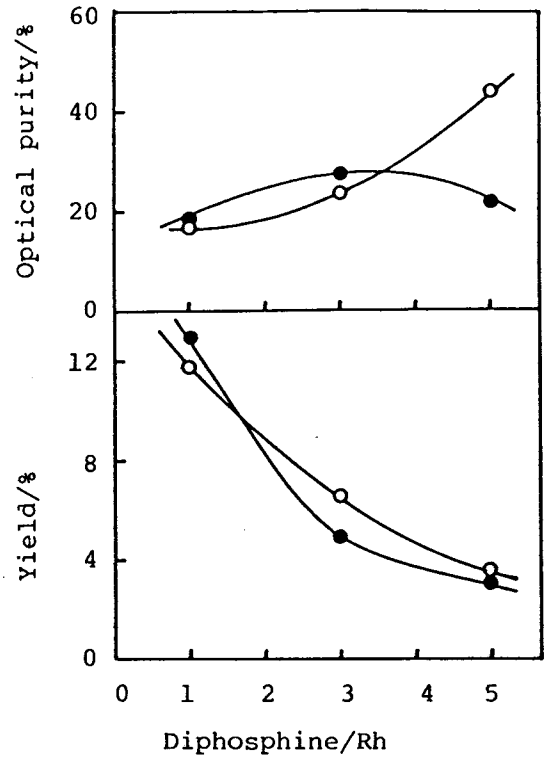


Fig. 1. Effects of chiral diphosphine/rhodium mole ratio on yield and optical purity of the product in the hydrogenation of acetophenone by Rh(I)-(+)-prophos (○) and Rh(I)-(-)-diop (●) complexes (0.09 mmol) at 50°C for 100 h in ethanol.
The optical purity was calculated with respect to the rotation of pure (*S*)-(-)-1-phenylethanol; $[\alpha]_D^{23}$ -52.5° (*c* 2.27, CH_2Cl_2).[45)]

atmospheric hydrogen pressure at 50°C by *in situ* prepared Rh(I)-(+)-prophos and Rh(I)-(-)-diop complexes from $[RhCl(C_2H_4)_2]_2$ and the respective phosphine. Results are shown in Fig.1.

In both reaction systems, the product was 1-phenylethanol only, enriched with (*S*)-(-)-enantiomer, and hydrogenation rates decreased with increasing in the diphosphine/rhodium ratio, whereas optical purity of the alcohol was also dependent on the mole ratio. In Rh(I)-(-)-diop complex catalyzed reaction, the

rhodium complex of (-)-diop/Rh=3/1 gave the alcohol with maximum optical purity of 28%. In the Rh(I)-(+)-prophos complex catalyzed reaction, the optical purity of the alcohol monotonously increased with the (+)-prophos/Rh ratio to attain the highest value of 44% with the mole ratio of 5/1. Although such an enhancement of the asymmetric induction due to added phosphine to the reaction system has also been observed by Markó[33] in the asymmetric hydrogenation of acetophenone with *in situ* prepared $[RhCl(norbornadiene)]_2$-(*S*)-(-)-benzylmethylphenylphosphine complex, the reason for this enhancement has been not clarified yet.

The chiral diphosphine of (+)-prophos, forming the rigid five-membered chelate rhodium complex, is a more excellent ligand than (+) or (-)-diop in terms of the enantio-selection in rhodium(I) complex catalyzed asymmetric hydrogenation of prochiral enamide.[41,46,47] For this reason, the difference in the enantio-selection has been attributable to the difference in conformational rigidity and in the P-Rh-P bond angle of the complex formed, and in the steric interaction between the substrate and the diphosphine.[48,49] Furthermore, as for the catalytically active species in the rhodium diphosphine complex catalyzed hydrogenation, RhCl(diphosphine) has proposed in the system of $[RhCl(monoolefin)_2]_2$ and diphosphine;[50] $[RhCl((+)\text{-diop})]^+Cl^-$ from $[RhCl(C_2H_4)_2]_2$ and (+)-diop.[51] In the present reaction, however, the difference in effects of added phosphine between (-)-diop and (+)-prophos can not be related to structural difference in plausible catalytically active species, RhCl(diphosphine) or $[Rh(diphosphine)]^+Cl^-$, between them. Presumably, this difference is caused by chiral circumstance due to the presence

Table 1. Asymmetric Hydrogenation of Ketones by Rh(I)-(-)-diop and Rh(I)-(+)-prophos Complexes at 50°C under Atmospheric Hydrogen Pressure[a)]

Ketone	Ligand	Time / h	Yield / %	O.P.[b)] / %
$C_6H_5COCH_3$	(+)-prophos	100	6.7	24.3
	(-)-diop	100	5.1	27.5
$C_6H_5COC_2H_5$	(+)-prophos	105	3.3	9.4
	(-)-diop	104	3.4	9.5
$C_6H_5COCH(CH_3)_2$	(+)-prophos	153	n.d.	
	(-)-diop	153	n.d.	
$C_6H_{13}COCH_3$	(-)-diop	102	4.3	5.7

a) $[RhCl(C_2H_4)_2]_2$, 0.09 mmol; ketone, 3 cm^3; ethanol, 2 cm^3; diphosphine/Rh=3/1 (mol/mol).

b) Calculated with respect to the following values of optical pure alcohol; $[\alpha]_D^{17-20}$ +40.0° (*c* 5, C_6H_6) for (*R*)-(+)-1-phenyl-1-propanol[29)] and $[\alpha]_D^{20}$ +11.9° (*c* 6, C_2H_5OH) for (*S*)-(-)-2-octanol.[30)]

of excess chiral phosphine in the coordination sphere of the active species.

The enantio-selectivity was also dependent on the structure of ketone, and decreased with increasing in bulkiness of alkyl group; phenyl isopropyl ketone was not hydrogenated in detectable extent (Table 1). However, ketones containing a phenyl group brought about higher enantio-selectivity than the alkyl ketone (2-octanone), suggesting that phenyl group plays

important role for the enantio-face differentiation of prochiral ketone by the rhodium(I) complex. Probably, the steric interaction involving electron-repulsion among phenyl groups of the substrate and of the chiral phosphine is favorable for asymmetric induction during the enantio-differentiating coordination to the chiral rhodium complex.

Heterogeneous Hydrogenation.

Since the hydrogenation of acetophenone by polystyrene-supported chiral rhodium complexes, Rh-diop/PST, Rh-diop/ABL-1, and Rh-diop/ABL-2, scarcely proceeded under an atmospheric hydrogen pressure, the reaction was carried out at the pressure of 4 kg/cm^2. Results are shown in Table 2.

Hydrogenation activities of these catalysts decreased in the following order; Rh-diop/ABL-1>Rh-diop/PST>Rh-diop/ABL-2. The order is not consisted with that of amount of rhodium supported, but the catalytic activity is dependent on pore size and frame work of the polystyrene. Markedly low activity of Rh-diop/ABL-2 can be ascribed to limiting diffusion of the substrate in small pore (average 50 Å) of the catalyst.

In this reaction system, polymer-supported complexes gave 1-phenylethanol only, enriched with (*S*)-enantiomer, and enantioselectivities of the catalysts also varied with the structure of the polymer, decreasing in the order of Rh-diop/PST>Rh-diop/ABL-1>Rh-diop/ABL-2. Noncross-linked structure of the polystyrene showed the effective asymmetric induction for the hydrogenation of ketone.

At any rate, both catalytic activities and enantio-

Table 2. Asymmetric Hydrogenation of Acetophenone by Polystyrene-supported Rh(I)-diop Complexes[a)]

Catalyst	Solvent	Temp °C	Yield %	O.P. %
Rh-diop/PST	C_6H_6	25	11	7.7
Rh-diop/ABL-1	C_6H_6	25	50	3.7
(reusing)	C_6H_6	25	34	2.2
Rh-diop/ABL-2	C_6H_6	25	3	1.2
	C_6H_6	50	44	1.2
	C_2H_5OH	50	37	6.1
	$(CH_3)_2CHOH$	50	35	2.2
(+0.5 (-)-diop)	C_2H_5OH	50	2	n.d.
(+3 (-)-diop)	C_6H_6	50	9	1.8

a) Catalyst, 0.2 g; acetophenone, 3 cm^3; solvent, 2 cm^3; initial H_2 pressure, 4 kg/cm^2; reaction time, 27 h.

selectivities of supported rhodium complexes were markedly lower than those of *in situ* prepared Rh(I)-(-)-diop and Rh(I)-(+)-prophos complexes. Such a decrease in catalytic activity and selectivity due to the immobilization of rhodium chiral complex on polymer has also observed in the asymmetric hydrogenation of α-methylstyrene and 2-ethyl-1-hexene,[43)] and of the asymmetric hydrofomylation of styrene.[54)] However, the use of copolymer of 2-hydroxyethyl methacrylate and styrene, or the polystyrene incorporated chiral secondary alcohol moiety has scarcely lowered not only the catalytic activity, but the enantio-selectivity for the asymmetric hydrogenation of prochiral enamides;[55,56)]

Table 3. Asymmetric Hydrogenation of Ketones by Polystyrene-supported Rh(I)-diop Complexes[a)]

Ketone	Catalyst	Yield / %	O.P.[b)] / %
$C_6H_5COCH_3$	Rh-diop/ABL-2	98	1.9
		(42)	(1.2)
$C_6H_5COC_2H_5$		73	2.5
$CH_3COC_2H_5$		(0.4)	(n.d.)
$CH_3COC_3H_7$		48	5.2
		(1.5)	(n.d.)
$CH_3COC_4H_9$		55	6.2
		(3.9)	(n.d.)
$CH_3COC_6H_{13}$		66	6.5
	Rh-diop/ABL-1	56	6.8
	Rh-(-)-diop[c)]	47	9.1

a) Catalyst, 0.2 g; ketone, 3 cm^3; ethanol, 2 cm^3; initial H_2 pressure, 60 kg/cm^2; temperature, 50°C. Values in parentheses are those obtained under initial pressure 4 kg/cm^2.

b) Calculated with respect to the following values of optically pure alcohols; $[\alpha]_D^{20}$ +13.83° (neat) for (*S*)-(+)-2-butanol;[8)] $[\alpha]_D$ +13.9° (neat) for (*S*)-(+)-2-pentanol;[35)] $[\alpha]_D$ +10.7° (neat) for (*S*)-(+)-2-hexanol.[36)]

c) The homogeneous catalyst *in situ* prepared from $[RhCl(C_2H_4)_2]_2$ (0.5 mmol) and (-)-diop (1.0 mmol).

details on these catalytic behaviors are unknown yet.

The reuse of Rh-diop/ABL-1, which was separated from the reaction mixture by filtration, washed with benzene, and dried *in vacuo*, resulted in the lowering of about 40% in the yield and optical purity of the product (Table 2).

(-)-Diop addition of only one-half equivalent to the supported rhodium suppressed the hydrogenation of acetophenone considerably (Table 2), as compared with those in the case of homogeneous reactions. Excess (-)-diop close to the coordination sphere of the supported-rhodium complex is seemed to prevent the substrate from approaching to the complex.

In the hydrogenation of ketones by Rh-diop/ABL-2, the rate decreased in the following order: $C_6H_5COCH_3 > C_6H_5COC_2H_5 > CH_3COC_6H_{13} > CH_3COC_4H_9 > CH_3COC_3H_7 > CH_3COC_2H_5$. The order is the same as that in the homogeneous reaction; ketones possessing a phenyl group or a long alkyl group is easily reduced. The ordering in the magnitude of enantio-selection is $CH_3COC_6H_{13} > CH_3COC_4H_9 > CH_3COC_3H_7 > C_6H_5COC_2H_5 > C_6H_5COCH_3$, which is in the reverse one in the homogeneous reaction. These results suggests that the manner of the interaction between the substrate and the rhodium metal center in the supported-complex differs from that in the homogeneous system, even though alcohols produced enriched with (*S*)-enantiomer in both systems. The rate in the hydrogenation of 2-octanone with Rh-diop/ABL-1 under higher hydrogen pressure (60 kg/cm^2) was comparable to that with Rh-diop/ABL-2, indicating that the hydrogenation rate was independent on the pore size of the polymer. This implies that the hydrogen pressure changes the magnitude or the manner of the interaction between the substrate and

the catalyst in the heterogeneous reaction.

8-4 Summary

Asymmetric hydrogenation of prochiral ketones was carried out by the use of homogeneous rhodium chiral diphosphine complexes (*in situ* prepared from $[RhCl(C_2H_4)_2]_2$ and (-)-diop, and (+)-prophos) and heterogeneous polystyrene-supported rhodium-(-)-diop complex. The homogeneous catalytic system containing excess chiral phosphine showed high enantio-selectivity, and the maximum optical purity of 44% was observed in the hydrogenation of acetophenone by the rhodium-(+)-prophos system ((+)-prophos/Rh=5/1). The activity and the selectivity of the heterogeneous catalyst, which were appreciably affected by the pore size and the framework of polymer support, were lower than those of homogeneous catalyst. The contribution of catalytically active species to the present hydrogenation was found to be different in the homogeneous and heterogeneous catalytic system, probably because of the difference in the asymmetric circumstances between two catalytic systems.

CHAPTER 9 ASYMMETRIC HYDROGENATION OF UNSATURATED ESTERS BY COBALT(II) AND NICKEL(II) CHIRAL DIPHOSPHINE COMPLEXES

9-1 Introduction

Successful development in asymmetric homogeneous hydrogenation of olefins catalyzed by chiral rhodium(I) complexes has made possible to give excellent enantio-selectivity. Nevertheless, chiral first-row transition metal complexes, which have been the object of only limited investigation in the asymmetric hydrogenation,[59,60] are also required in a viewpoit of practical asymmetric synthesis of optically active compounds.

In this chapter, the author describes the catalytic features of cobalt(II) and nickel(II) chiral diphosphine complexes for the asymmetric hydrogenation of prochiral unsaturated esters.

9-2 Experimental

Materials.

Prochiral esters were distilled before use. The chiral diphoshine of (-)-2,3-*O*-isopropylidene-1,4-bis(diphenylphosphino)-2,3-butanediol (diop) was synthesized by Kagan's method.[3] The isolable cobalt complex, $CoCl_2$((-)-diop), was prepared by refluxing the ethanolic solution (30 cm^3) of $CoCl_2$ (2 g) and (-)-diop (1.5 g) for 2 h in a nitrogen atmosphere; the blue crystal separated on cooling at 0°C: mp 207-213°C; IR (CsI): 308 and 345 cm^{-1} (CoCl)). Found: C, 59.05; H, 5.14%; M^+, 627. Calcd for $C_{31}H_{32}Cl_2O_2P_2Co$: C, 59.25; H, 5.14%; M, 627. The nickel complex,

$NiCl_2$((-)-diop), was prepared in a similar manner, noncrystallizing from the solution on cooling, the ethanol solution was evaporated to dryness. The resulting solid was washed with ether, and dissolved in benzene. The solution was filtered, and evaporated to give pale yellow crystals: mp 165-173°C (decomp); IR (CsI): 308 cm^{-1}(broad, NiCl). Found: C, 57.63; H, 5.66%; a molecular ion was undetectable in mass-spectroscopy. Calcd for $C_{31}H_{32}Cl_2O_2P_2Ni$; C, 59.27; H, 5.15%; M, 626.

Reaction Procedure and Analyses.

The hydrogenation of prochiral esters (2 cm^3) by cobalt(II)-(-)-diop or nickel(II)-(-)-diop complex (0.16 mmol) was carried out in an autoclave under initial hydrogen pressure of 50 kg/cm^2. The reaction mixture was hydrolyzed by refluxing in 10% NaOH-methanol solution to obtain the saturated acid, which was supplied to the optical rotation measurement. The product was identified and determined by ^1H NMR (100 MHz, JEOL MH-100) and by gas-chromatography (using a 3-m column packed with NPGS + H_3PO_4 on Uniport B).

9-3 Results and Discussion

The cobalt(II)-(-)-diop and nickel(II)-(-)-diop complexes isolated or prepared *in situ* were able to catalyze the hydrogenation of unsaturated esters such as methyl or ethyl α-methylcrotonate at 80-100°C slowly, but did not exhibit catalytic ability for the reduction of bulky unsaturated acids and esters such as α-(acethylamino)cinnamic acid derivatives.

In Table 1, results in the hydrogenation of ethyl α-methylcrotonate by Co(II)-(-)-diop and Ni(II)-(-)-diop complexes with or without amine at 80-100°C are summarized. Although the rates were extremely low in both catalytic reactions, addition of triethylamine to the reaction systems resulted in enhancement of the hydrogenation rate and the optical purity (O.P.) of the product. The maximum O.P. was obtained in the reaction by the catalytic system of *in situ* prepared Co(II)-(-)-diop complex and Et_3N ($Co/Et_3N=1/2$). It has been reported that the addition of a small amount of triethylamine to the reaction system has increased the enantio-selectivity in the asymmetric hydrogenation of olefinic acids such as α-(acylamino)cinnamic acid by rhodium(I) chiral phosphine complexes.[63] This enhancement has been proposed to be attributable to favorable alternation in the predominant reaction pathway for the effective asymmetric induction due to the generation of the carboxylate anion from the substrate by the added amine. However, no effects of added amine for the ester of methyl α-(acetylamino)cinnamate have been observed.[63] Therefore, the observed effects of added triethylamine on the rate and the selectivity in the present reaction may be due to improvement of the stereochemistry requirement in the coordination sphere of the chiral complex. Presumably, the addition of triethylamine induces the formation of catalytically active species, expressed as $HMCl((-)\text{-diop})(Et_3N)$ (M=Co or Ni);

$$MCl_2((-)\text{-diop}) + Et_3N + H_2 \longrightarrow HMCl((-)\text{-diop}) + Et_3NHCl$$
$$HMCl((-)\text{-diop}) + Et_3N \longrightarrow HMCl((-)\text{-diop})(Et_3N)$$

where M indicates Co(II) or Ni(II). The putative complex of

Table 1. Asymmetric Hydrogenation of Ethyl α-Methylcrotonate by Transition Metal-(-)-diop Complexes with or without Amine[a)]

Catalytic system	Temp °C	Time h	Yield %	O. P.[b)] %
$CoCl_2$/(-)-diop	100	96	20	3.6(R)
$CoCl_2$/(-)-diop	80	22	trace	n.d.
$CoCl_2$/(-)-diop + Et_3N	80	22	5	7.4(R)
$CoCl_2$/(-)-diop + 2 Et_3N	80	22	17	11.7(R)
$CoCl_2$/(-)-diop + 4 Et_3N	80	22	9	0.8(R)
$CoCl_2$/(-)-diop + 2 (+)-PhCH(Me)NH_2	80	22	6	9.3(S)
$CoCl_2$((-)-diop) + 2 Et_3N	80	22	6	11.5(R)
$NiCl_2$/(-)-diop	80	22	trace	n.d.
$NiCl_2$/(-)-diop + 2 Et_3N	80	22	12	8.4(R)
$NiCl_2$((-)-diop) + 2 Et_3N	80	22	7	10.0(R)
$[RhCl(C_2H_4)_2]_2$/(-)-diop	25	72	38	1.7(R)
Ru_2Cl_4((-)-diop)$_3$	50	32	20	2.7(R)
Ru_2Cl_4((-)-diop)$_3$ + Et_3N	50	22	39	2.6(R)
Ru_2Cl_4((-)-diop)$_3$ + 2 Et_3N	50	22	29	7.5(R)

a) The catalytic system expressed as MCl_2/(-)-diop + n Et_3N (M= Co or Ni) involves a mixture of *in situ* prepared Co(II) or Ni(II)-(-)-diop complex (MCl_2=(-)-diop=0.16 mmol) and Et_3N (n x 0.16 mmol).

b) Calculated with regard to α-methylcrotonic acid; $[\alpha]_D^{24}$ +12.17° (*c* 5.12, C_2H_5OH) for the (*S*)-acid;[62)] configuration of the product in parentheses.

$HMCl((-)\text{-diop})(Et_3N)$ probably exhibits the enantio-face selection of the prochiral substrate more efficiently than $MCl_2((-)$-diop) *per se* during π-complex formation from $HMCl((-)\text{-diop})(Et_3N)$ and the substrate. In this regard, the use of a bulky chiral amine, $(+)\text{-}C_6H_5CH(CH_3)NH_2$, instead of triethylamine decreased the rate and the selectivity, but resulted in the change of the prevailing configuration of the product from (*R*)-enantiomer to the antipode, indicating that the chirality of the adduct affected the asymmetric induction of the catalyst. However, the excess of triethylamine ($Et_3N/MCl_2>2$) decreased the rate and the selectivity considerably.

It is also noteworthy that enantio-selectivites of Co(II)-(-)-diop and Ni(II)-(-)-diop complexes are higher than those of Rh(I)-(-)-diop complex prepared *in situ* and $Ru_2Cl_4((-)\text{-diop})_3$ with or without triethylamine, in spite of low hydrogenation activities.

From Table 2, it is obvious that the enantio-selectivity of *in situ* prepared Co(II)-(-)-diop complex is affected by the bulkiness of the ester moiety in the substrate. The bulky substituent decreased the hydrogenation rate, but the order of the selectivity was not in accordance with that of the bulkiness of the ester moiety. The small methyl substituent brought about the change of the predominant enantiomer in the product from (*R*)-isomer to (*S*)-one, and *l*-menthyl substituent clearly exhibited its chirality effect for the asymmetric induction of the $Co(II)\text{-}(-)\text{-diop-}Et_3N$ system, even in uneasy complexation between the catalytic system and the bulky substrate.

Table 2. Asymmetric Hydrogenation of α-Methylcrotonates by *in situ* Prepared Co(II)-(-)-diop Complex at 80°C in the Presence of Triethylamine[a)]

$MeCH=C(Me)CO_2R$ R	Time h	Yield %	O.P.[b)] %
Me	22	21	4.5(S)
Et	22	17	11.7(R)
Bu	22	6	6.3(R)
l-Menthyl	36	5	11.4(R)

a) $CoCl_2$=(-)-diop=0.16 mmol and Et_3N=0.32 mmol.

b) Configuration of the products in parentheses.

9-4 Summary

Catalytic efficiency of chiral cobalt(II) and nickel(II) complexes containing (-)-diop for asymmetric hydrogenation of unsaturated esters was studied. Addition of amine to the reaction system resulted in the enhancement of hydrogenation rate and enantio-selectivity, which were also affected by bulkiness of ester moiety. The maximum optical purity was 11.7% in the hydrogenation of ethyl α-methylcrotonate by the catalytic system of $CoCl_2$-(-)-diop-Et_3N (Co/amine=1/2).

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CONCLUSION

The purposes of this research are to study effective kinetic resolution with chiral catalyst to obtain optically active alcohols, and to develop practical procedures and effective chiral catalysts in asymmetric hydrogenation.

In Part 1 the kinetic resolution of racemic secondary alcohols with chiral ruthenium and rhodium complexes is described. Ruthenium(II) and rhodium(I) chiral phosphine complexes catalyzed the enantiomer-differentiating dehydrogenation of secondary alcohols, and their enantio-selectivities were dependent on concentration and structure of the phosphines and unsaturated hydrogen acceptors. The complexes also exhibited catalytic ability for the enantiomer-differentiating intramolecular hydrogen transfer of racemic 1-buten-3-ol to 2-butanone. Furthermore, the system of $RhCl_3$ and a chiral phosphine was able to catalyze the enantiomer-differentiating dehydration of racemic 1,3-butanediol to 2-butanone. Enantio-selectivities in the reactions were relatively low. Probably, moderately high reaction temperature (70-200°C) results in low selectivity, and therefore kinetic resolution of a racemate with low-temperature catalytic process is expected to become a more effective procedure.

In Part 2 catalytic asymmetric hydrogenation is described. Ruthenium(II) chiral phosphine complexes efficiently catalyzed asymmetric transfer hydrogenation of olefinic acids and esters by alcohols; the maximum enantiomeric excess was found to be 26%. Kinetic study on the reaction showed that the asymmetry was induced by enantio-face selection during the coordination of

the olefin to the chiral ruthenium complex. Optically active alcohols (maximum enantiomeric excess of 44%) was obtained in the asymmetric hydrogenation of ketones by homogeneous or heterogeneous (polystyrene-supported) rhodium(I) chiral diphosphine complexes. Furthermore, cobalt(II) and nickel(II) chiral phosphine complexes catalyzed the asymmetric hydrogenation of olefinic esters; the maximum enantiomeric excess of 12% was obtained. The author hopes further study to bring forth more efficient catalysts in the asymmetric hydrogenation, especially by using first-row transition metal complexes, for practical application.

The author expects that the results obtained in this thesis would develop further works for practical production of optically active compounds utilizing chiral catalysts.

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