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New Type of Aldol Condensations Catalyzed by Metal(II) Complexes of α-Amino Acid Esters and that with Cyclodextrin System

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The aldol condensations of *p*-nitrobenzaldehyde with acetone catalyzed by metal complexes of α-amino acid esters proceeded under mild and neutral conditions to afford an enantiomeric excess aldol-type product, 4-hydroxy-4-(4-nitrophenyl)-2-butanone, along with some dehydrated products without any by-product. The most effective catalyst system was a zinc(II) complex of the tyrosine ethyl ester, Zn^{II}–$(TyrOEt)_2$ in MeOH. Complexes of the second-row transition metals were inadequate for the reactions. Reactions at 30—40 °C for 24 h were favorable regarding the asymmetric induction. An H_2O solvent was the best for aldol-type product formations without asymmetric induction. An assistant effect of cyclodextrins(especially, β-CD) on the catalysis of the Zn^{II}–TyrOEt complex were thought to be observed.

Aldol-condensation reactions are generally catalyzed using bases and acids. Accordingly, some side reactions are apt to occur, and it is not always easy to get only cross-aldol-reaction products. Recently, we found that the reactions are generelly catalyzed under neutral conditions by 2,2′-bipyridine complexes of the first-row transition metals[1] and also by cobalt(II) complexes of pyridine-containing copolymers.[2] The reactions of various aldehydes with ketones in the presence of these metal complex catalysts afford liberated condensation products in satisfactory yields without any by-products. However, the reaction products are always α,β-unsaturated ketones(2) derived through the dehydration of the aldol-type products, β-hydroxy ketones(1).

$$\mathrm{RCH(=O) + CH_3C(=O)R' \xrightarrow[\text{DMF., 80 °C}]{\text{M(II)-L}_n} \underset{\text{aldol-type product}}{\mathrm{RCH(OH)CH_2C(=O)R'}} \quad (1)}$$

$$\mathrm{\xrightarrow{-H_2O} RCH{=}CHC(=O)R' \quad (2)}$$
dehydrated product

We have developed a new investigative technique for the following three objectives regarding these complex-catalyzed aldol reactions:

1) To produce the aldol-type product(1) without the dehydrated product(2), or to depress any dehydration if it occurs.

2) To get an optically active aldol-type product(1) by use of a chiral metal-complex catalysts with optically active ligands.

3) To apply the inclusion effects of cyclodextrins to enhance the catalytic activity of the metal-complex system.

In order to realize these objectives, reactions of *p*-nitrobenzaldehyde with acetone were adopted as the standards due to their high reactivity and of a relative difficulty regarding the dehydration of the aldol-type product. Metal species of the employed complexes were the first- and second-row transition metal salts. The first-row efficiencies were investigated in one of our previous studies[1,2] and it was of interest to examine the second-row for the first time. As a result of various examinations involving chiral ligands of the complexes, we have found that esters of α-amino acids are fairly effective for the purpose of obtaining the aldol reactions with asymmetric induction. Among esters of the α-amino acids easily prepared, L-tyrosine ethyl ester (L-TyrOEt, mp 108 °C) and L-histidine methyl ester (L-HisOMe, mp 61 °C) were used, since they are crystals and can be easily handled and purified. Quinine and quinidine as ligands were also examined because pyridine and bipyridine *etc.* were the most effective ligands of the complex catalysts for the aldol condensations.[1,2]

Since the 1970's, many studies have been reported in regard to the aldol reactions utilizing organometallic compounds as an auxiliary reagent for diasteroselective additions through metal enolate intermediates.[3] Our studies since 1978 have been essentially different in that metal complexes were used as catalysts. Such studies as the asymmetric aldol reactions catalyzed by chiral metal complexes of an α-amino acid system under neutral conditions have not been reported yet.

Cyclodextrins(CD) possess hydrophobic cavities in which hydrophobic molecules are able to be selectively included. For this reason, many studies on the effect of the inclusion behavior on catalytic, regioselective, and enantioselective reactions by use of CDs have been reported.[4] Such inclusion effects are sometimes used to simulate an enzyme action. We have investigated assistant effects of CDs on complex-catalyzed aldol reactions. In this paper, the scope and limitations of these complex-catalyzed aldol reactions are reported in detail.

Results and Discussion

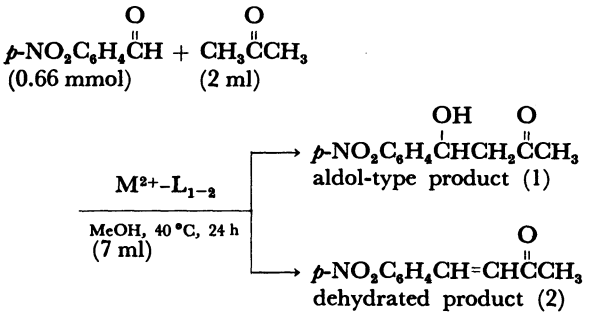
Effects of Metal Species and Ligands of the Complex Catalysts. Effects of metal species and ligands of

TABLE 1. ALDOL CONDENSATIONS OF *p*-NITROBENZALDEHYDE WITH ACETONE (1) (EFFECTS OF CHIRAL LIGANDS OF $Zn(NO_3)_2$ COMPLEXES[a])

Ligand	M : L	Yield of (1)/%[b] (isolated)	$[\alpha]_D$ (in EtOH)	Yield of (2)/%[c] (NMR)
L-TyrOEt	1 : 1	35	−6.4	13
L-TyrOEt	1 : 2	40	−11.2	42
D-TyrOEt	1 : 2	41	+11.9	
DL-TyrOEt	1 : 2	20	0	26
L-TyrOMe	1 : 2	39	−8.3	30
L-HisOMe[d]	1 : 2	14	−5.3	
L-HisOMe[e]	1 : 2	47	−1.9	Trace
L-AlaOEt	1 : 2	30	−2	4
Q[f]	1 : 1	40	+1	Trace
Q	1 : 1/2	54	0	
Q'[g]	1 : 2	13	0	0
Q+bpy[h]	1 : 1 : 1	72[i]	0	Trace
Q'+bpy[h]	1 : 1 : 1	75[i]	0	Trace
Q+L-TyrOEt	1 : 1 : 1	61	−1.3	10
L-TyrOEt+bpy	1 : 1 : 1	26.4	−8.8	+
L-TyrOEt+Im[j]	1 : 1 : 1	34.6	−1.6	+

a) Reaction conditions: aldehyde 0.66 mmol, acetone 2 ml(excess), catalyst 16 mol% of the aldehyde, solvent MeOH 7 ml, at 40 °C for 24 h. b) Aldol-type product. c) Dehydrated product, by NMR. d) Reaction for 48 h. e) $Zn(OAc)_2$ complex was used for 48 h. f) Quinine. g) Quinidine. h) Reaction at 30 °C. i) 100% by NMR. j) Imidazol.

complex catalysts on the reactions of *p*-nitrobenzaldehyde with acetone were examined for the first time. Tables 1 and 2 show that among the metal ions and ligands examined, an Zn^{2+}–L-TyrOEt system was the most adequate catalyst.



In order to prepare the complex catalysts, the metal salt and the ligand compound were mixed with dry methanol and stirred for a while; and, the complex solution was subsequently used without the isolation of the complex in its crystal form. The homogeneous reaction proceeded smoothly at 40 °C for 24 h and the aldol-type product(1), 4-hydroxy-4-(4-nitrophenyl)-2-butanone, was obtained from the reaction mixture by means of column chromatography with silica-gel. The reaction did not proceed without the catalyst and was extremely slow when only the metal salts were used without the ligand. As was expected, the reactions with an L-TyrOEt complex afforded an enantiomeric excess product(1) having a minus sign $[\alpha]_D$. A plus sign in the reaction with the D-TyrOEt complex, indicated that an asymmetric regulation occurred (Table 1). The Zn^{II}–$(TyrOEt)_2$ (1:2) complex was superior to the 1:1 complex with respect to the product yield and the asymmetric induction.

TABLE 2. ALDOL CONDENSATIONS OF *p*-NITROBENZALDEHYDE WITH ACETONE (2) (EFFECTS OF METAL SPECIES OF L-TyrOEt COMPLEXES(M : L = 1 : 2)[a])

Metal salts	Yield of (1)/%[b] (isolated)	$[\alpha]_D$ (in EtOH)	Yield of (2)/%[c] (NMR)
$Co(OAc)_2 \cdot 4H_2O$	33	−5.7	13
$Ni(OAc)_2 \cdot 4H_2O$	26	−8.2	11
$Ni(NO_3)_2 \cdot 6H_2O$[d]	63	−3.0	+
$Cu(OAc)_2 \cdot H_2O$	9	−2.7	4
$Zn(OAc)_2 \cdot 2H_2O$	22	−6.2	30
$Zn(NO_3)_2 \cdot 6H_2O$	40	−11.2	42
$ZnCl_2$	19	−4.9	48
$RuCl_3 \cdot 3H_2O$[e]	0		0
$RuCl_3 \cdot 3H_2O$[f]	14	+2.5	8
$Pd(OAc)_2$[g]	0		0
$RhCl_3 \cdot 3H_2O$	0		0

a) Reaction conditions were similar to those shown in Table 1. b) Aldol-type product. c) Dehydrated product. d) Reaction for 48 h. e) Formation of acetal (62%) with MeOH without any aldol condensation products. f) Reaction in 9 ml. acetone without MeOH. g) Deposition of Pd° during the reaction.

The reactions with quinine(Q) and quinidine(Q') complexes showed no asymmetric induction at all. Examinations with other Q-complexes were further

carried out using Co, Ni, and $Cu(OAc)_2$, $RuCl_3$, and $Pd(OAc, NO_3$, and $Cl)_2$ *etc.*; but, almost no reaction took place. It was found that mixed ligand complexes of Zn^{II}–Q (or Q′)–bpy (1:1:1) showed a high catalytic activity to give only product(1) quantitatively even at 30 °C (100%, by NMR) but without any asymmetric induction. The reaction with a $Zn(NO_3)_2$–bpy_2 complex gave product(1) (40 °C, 24 h, racemate) in a 60% yield (by NMR).

From the results in Table 2, it is evident that $Zn(NO_3)_2$ is a very effective metal species. On the contrary, the second-row transition metal salts were all inadequate for the reactions. Besides $Pd(OAc)_2$, $Pd(NO_3)_2$, and $PdCl_2$ were also examined but none of them showed any catalytic activity at all. In the presence of the $RuCl_3$–(L-TyrOEt)$_2$ complex, an acetal of the aldehyde with a MeOH solvent was formed in a 62% yield(NMR) and no aldol reaction took place at all (see experimental). Then, the reaction was carried out in acetone without MeOH, no notable result was obtained (product(1), 14%).

Now, the optical purity of the aldol-type product obtained in the reactions is still unknown since the specific rotation of the pure enantiomer is unknown. We tried to determine the enantiomeric excess of the aldol-type product(1) by means of ^{1}H-NMR spectroscopy with shift reagents (Eu(tbc)$_3$ and Eu(tfc)$_3$) or by some other methods. However, definite values were not obtained.

Examination of the Complex Formation. When the metal salts and the ligand compounds were added together in methanol, a color change was observed, indicating a complex formation. In order to further understand this formation, UV spectra of $Ni(OAc)_2 \cdot 4H_2O$, L-TyrOEt, and $Ni(OAc)_2$–(L-TyrOEt)$_{1-2}$ complexes were measured. Also, the pH of the solution (MeOH+H_2O) and their optical rotation (in EtOH) were measured (Table 3). The absorption maximum of the Ni^{2+} (670 nm) showed a blue shift after the addition of L-TyrOEt. The hyperchromic effect was observed, indicating a change of the electronic state of the Ni^{2+} ion by the coordination of the ligand. On the other hand, the pH of a TyrOEt solution itself (7.8) turned almost neutral (7.0—7.2) in a Ni^{II}–TyrOEt complex solution (M:L=1:1, 1:2) which was similar in pH to a $Ni(OAc)_2$ solution. This means that the NH_2 group of the ligand was masked by the coordination. With regard to the specific rotation, $[\alpha]_D$=+19.8° of the TyrOEt turned into −2.5°—−3.3°, indicating a chiral complex formation.

Examination of Catalysis of $Zn(NO_3)_2$–(L-TyrOEt)$_2$ Complex System. On the basis of the above examinations, the effects of the solvent, temperature, reaction time, and the amount of the catalyst were widly studied with regard to catalysis of the $Zn(NO_3)_2$–(TyrOEt)$_2$ complex. The results of reactions in various solvents are shown in Table 4. DMF, THF, and HMPA as solvents were also examined, but the reactions did not proceed well and isolation of the products was difficult. According to Table 4, a H_2O solvent was the best in view of the aldol-type product formation (100%, by NMR). However, almost no asymmetric induction was observed. On the other hand, MeOH was the best regarding asymmetric induction. Acetone might represent a special case, as it is the substrate for the reactions and the reactions were completed within 8 h.

It may be presumed that the aldol-type(1) and the dehydrated-type(2) were in equilibrium; hence, the reaction in pure H_2O did not afford (2) at all. The

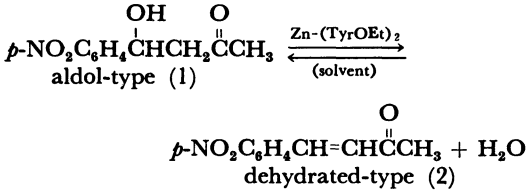


Table 3. Physical properties of Ni^{II}–L-TyrOEt complexes and the components

Compound[a]	pH	$[\alpha]_D$ (in EtOH)	UV λ_{max}	UV A
$Ni(OAc)_2 \cdot 4H_2O$	7.1	0	670	0.18
L-TyrOEt	7.8	+19.8		
Ni^{II}–L-TyrOEt	7.2	−3.3	656	0.29
Ni^{II}–(L-TyrOEt)$_2$	7.0	−2.5	644	0.39

a) 0.11 mmol each(except for Ni^{II}–(L-TyrOEt)$_2$) in MeOH(5 ml) + H_2O(2 ml) solvent.

Table 4. Aldol condensations with $Zn(NO_3)_2$–(L-TyrOEt)$_2$ complex (1)[a] (Effects of solvent)

Solvent (7 ml)	Yield of (1)/%[b] (isolated)	$[\alpha]_D$ (in EtOH)	Yield of (2)/%[c] (NMR)
MeOH	40	−11.2	42
EtOH	33	−8.0	53
Dioxane	32	−5.7	40
Acetone[d]	52	−11.3	40
H_2O[e]	83[f]	−1.4	0
MeOH + H_2O (ml)			
6 1	42	−12.2	9
5 2	45	−9.7	+
3 4	77	−3.2	+
1 6	81	−2.2	0

a) Reactions and the reaction conditions are similar to those shown in Table 2(40 °C, 24 h, catalyst: 16 mol% of the aldehyde). b) Aldol-type product. c) Dehydrated product. d) Acetone 9 ml. e) pH 7. f) 100% by ^{1}H-NMR, the reaction was completed within 20 h.

results of the reactions in MeOH–H_2O mixed solvents at various ratios support the above equilibrization. The low $[\alpha]_D$ value of the product(1) may be due to the reversible dehydration-hydration reactions which cause the racemization of (1). In order to ascertain this assumption, the aldol-type(1) showing $[\alpha]_D=-12°$ was treated with a catalyst in H_2O or MeOH under similar conditions to those shown in Table 4. Treating in H_2O (addition of a small amount of MeOH to make the system homogeneous), the racemization occurred ($[\alpha]_D$ decreased to $-5°$), but no racemization occurred in the MeOH solvent (Eq. 1).

$$\text{(1) } ([\alpha]_D=-12°) \xrightarrow{\text{cat}} \begin{cases} \xrightarrow{H_2O} \text{(2) } 11\%\cdots[\alpha]_D \rightarrow -5° \\ \xrightarrow{MeOH} \text{(2) } 38\%\cdots[\alpha]_D \rightarrow -12° \end{cases} \quad (1)$$

$$\text{(2)} \xrightarrow{\text{cat., } H_2O} \text{(1) } 18\% \quad (2)$$

On the other hand, the hydration of (2) in H_2O occurred in a 18% yield (Eq. 2). Thus, an equilibrium between (1) and (2) in connection with the racemization was confirmed.

The effects of the reaction temperature, time, and the amount of the catalyst are summarized in Table 5. Comparing Entries 1(20 °C), 2(30 °C), 6(40 °C), and 8(50 °C) with each other, the elevation of the temperature seems to affect the dehydration and racemization. In Entry 3(48 h), $[\alpha]_D$ value of (1) is low compared with 2(24 h) and the prolonged reaction time seems to unfavorably affect the results accompanying racemization and dehydration, even in the MeOH solvent.

When twice the amount of the catalyst was employed (Entry 4, 32 mol% of the aldehyde), the reaction proceeded quickly (conversion 100%, by NMR, 24 h), but the dehydration increased up to 52% (NMR). On the contrary, when half the amount of catalyst was used (Entry 5, 8 mol% of the aldehyde), the reaction was very slow (conversion 30%, by NMR, 24 h) and gave a small amount of (2). Thus, an amount of the catalyst affected both the reaction velocity and the dehydration rate, but not to the degree of the racemization in the MeOH solvent. Benzaldehyde and *p*-chlorobenzaldehyde were also reactive with this catalyst system, but a high degree of the dehydration was notable under these conditions. As a general conclusion, the factors controlling the reactions are solvent, reaction temperature, time, and the amount of the catalyst. The effect of the reaction temperature seems to be most serious for asymmetric induction.

Assistant Effects of Cyclodextrins on the Catalysis of Zn^{II}-L-TyrOEt Complex. It has been known that aromatic aldehydes such as *p*-nitrobenzaldehyde are included well in the cavity of the CD.[4,5] In this system, the coordination of the *sec.* hydroxyl group located on the edge of the CD to the Zn^{2+} ion of the complex coexisted will occur. Then, the coordination of the formyl group to the Zn^{2+} ion may be accelerated. As a result, an increase in the reactivity may be expected. Since the CDs were soluble in H_2O but not in MeOH, reactions with a CD–Zn^{II}–TyrOEt system (1:1:1) were carried out in H_2O (pH 6 and 7). The pH of the reaction mixture with CD–Zn^{II}–TyrOEt was 6, and a buffer KH_2PO_4/NaOH was employed to adjust the pH to 7. The results of the experiments are shown in Table 6.

The sole α- or β-CD did not show any catalytic activity under these conditions. Entry 1 gave the aldol-type product in not very high yield in contrast with the reaction with the 1:2 complex (Table 4, 83%[f]). Whereas, in Entry 2, the catalytic activity increased much (100% yield, by NMR) without any

TABLE 5. ALDOL CONDENSATIONS WITH $Zn(NO_3)_2$-(L-TyrOEt)$_2$ COMPLEX (2)[a]
(EFFECTS OF TEMPERATURE, TIME, AND CATALYST)

No.	Temp/°C	Time/h	Yield of (1)/%[b] (isolated)	$[\alpha]_D$ (in EtOH)	Yield of (2)/%[c] (NMR)
1	20	48	52	−15	+
2[d]	30	24	35	−19	20
3	30	48	34	−9.7	43
4[e]	30	24	40	−17	52
5[f]	30	24	21	−19.5	4
6	40	24	40	−11.2	42
7	40	16	34	−12.8	30
8	50	24	62	−4.4	+
9[g]	40	24	16[i]		76[j]
10[h]	40	24	22[i]		53

a) Reaction conditions are similar to those shown in Table 2. Reactions Nos. 1—8, *p*-nitrobenzaldehyde with acetone, No. 9, benzaldehyde with acetone, No. 10, *p*-chlorobenzaldehyde with acetone. b) Aldol-type product. c) Dehydrated product. d) In the case with Zn^{II}-TyrOEt(1 : 1) complex, the yield of (1) was 16%, $[\alpha]_D=-16.4°$. e) Catalyst: ×2(32 mol%). f) Catalyst: ×1/2(8 mol%). g) Reaction of benzaldehyde. h) Reaction of *p*-chlorobenzaldehyde. i) Yield by ^{1}H-NMR. j) Contaminated with acetal.

Table 6. Formation of the aldol-type product(1) with CD-$Zn(NO_3)_2$-L-TyrOEt catalyst systems[a] (Effects of cyclodextrins)

No.	Catalyst (1 : 1 : 1)	Yield of (1)/%[b]		Remarks
		pH 6	pH 7[c]	
1	Zn^{II}+TyrOEt (1 : 1)	53	68	No dehydration
2	α-CD+Zn^{II}+TyrOEt	58	100	
3	β-CD+Zn^{II}+TyrOEt	100	100	
4	β-CD+Zn^{II}+TyrOEt	67		For 16 h reaction
5	β-CD+Zn^{II}+TyrOEt	56		At 30 °C
6	α-CD+Zn^{II}+TyrOEt		55	(3 : 1 : 1) system
7	β-CD+$Zn(OAc)_2$+TyrOEt	69		Dehydration 19%
8	β-CD+Zn^{II}+TyrOEt	49		With C_6H_5CHO (dehydration 18%)
9	β-CD+Zn^{II}+TyrOEt	18		With p-ClC_6H_4CHO

a) Reactions of p-nitrobenzaldehyde with acetone, conditions: catalyst, 16 mol% of the aldehyde, 40 °C, 24 h in H_2O. b) By ^1H-NMR. c) Buffer, KH_2PO_4/NaOH, was used.

dehydration. The assistant effect of the CD was more remarkable with the β-CD, as shown in Entry 3. The yield of (1) increased up to 100% even in the pH 6 solution.

The retio of the added CD seemed to be adequate in CD-Zn^{II}-TyrOEt=1:1:1. When three times the amount of α-CD was used (Entry 6, 3:1:1), the yield of (1) decreased to 55%, even in the pH 7 solution (unreacted aldehyde 45%). This was lower than that for a reaction without the CD (Entry 1). In Entry 7, the yield of (1) was lower than that for reactions with the $Zn(NO_3)_2$ complex system. All the reactions in Table 6 were carried out in an H_2O solvent; therefore, it could be infered that almost no asymmetric induction was observed in the reactions. When mixed solvents were used (MeOH 4 ml+H_2O 3 ml) under similar conditions to those in Entry 2(pH 7), the yield of (1) was only 20% in contrast with 100% in Entry 2. Accordingly, it may be necessary to find an adequate solvent system or some other reaction methods for asymmetric induction.

Conclusion. An original and preliminary survey on the aldol reactions catalyzed by metal complexes bearing ligands of the α-amino acid ester have been achieved. The most adequate catalytic system to afford an enantiomeric excess of the aldol-type product was the $Zn(NO_3)_2$-(L-TyrOEt)$_2$ in MeOH. The assistant effects of α- and β-cyclodextrins, especially of the β-CD, on the catalysis of the Zn^{II}-TyrOEt complex in the aldol reactions were observed evidently.

Aldol reactions in biological systems have been known to be catalyzed by aldolase enzymes, Class-I and -II.[6] The latter is a metalloenzyme containing a Zn^{2+} ion at the active sites. However, the catalysis of the Class-II aldolase has not been sufficiently elucidated. Therefore, our reaction systems with Zn^{II}-L-TyrOEt and CD-Zn^{II}-L-TyrOEt may present novel possibilities for understanding a Zn^{2+} ion catalysis from the point of view of organic catalytic reactions.

Experimental

Instruments. The ^1H-NMR spectra were taken with a Hitachi Perkin-Elmer R-20A spectrophotometer (60 MHz). The UV and IR spectra were taken with a Hitachi 220A double-beam spectrophotometer and a Hitachi 260-10 Infrared spectrophotometer, respectively. The optical rotations were measured with a JASCO DIP-140 digital polarimeter (Nippon Bunko).

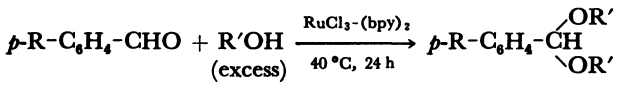
Materials. L-, D-, and DL-Tyrosine ethyl esters and the L-tyrosine methyl ester were prepared from their original amino acids with alcohols in the presence of small quantities of concd sulfuric acid, L-TyrOEt: mp 105 °C, $[\alpha]_D$=+19.5° (EtOH), (lit,[7] 108 °C, +20°), DL-TyrOEt: mp 99—102 °, L-TyrOMe: mp 128—131 °C, $[\alpha]_D$=+28.0° (EtOH) (lit,[8] 135 °C, +25.7°). L-Histidine methyl ester was obtained from L-HisOMe·2HCl, mp 60—61 °C, $[\alpha]_D$=+11.2° (MeOH), Anal ($C_7H_{11}O_2N_3$) C,H,N. Other ligand compounds were commercially available, quinine: mp 177 °C, $[\alpha]_D$=−117° (in $CHCl_3$), qunidine: mp 175 °C, $[\alpha]_D$=−230° (in $CHCl_3$), 2,2′-bipyridine: mp 69.7 °C (recrystallyzed from EtOH–H_2O). The solvents used were distilled before use, and the dry methanol was preserved with molecular sieves. α- and β-cyclodextrins were commercially available, α-CD: $[\alpha]_D$=+133°, β-CD: $[\alpha]_D$=+154° (in H_2O).

The Aldol Reactions with Chiral Metal Complexes. As a representative example, the reaction of p-nitrobenzaldehyde with acetone in the presence of $Zn(NO_3)_2$-(TyrOEt)$_2$ in MeOH is described. To a solution of $Zn(NO_3)_2 \cdot 6H_2O$ (33 mg, 0.11 mmol) in MeOH (3.5 ml), L-TyrOEt (46.mg, 0.22 mmol) in MeOH (3.5 ml) was added and the mixed solution was well stirred (M:L=1:2). A solution of the complex catalyst was added to a solution of p-nitrobenzaldehyde (100 mg, 0.66 mmol) in 2 ml of acetone in a 20-ml flask. The flask was plugged and the reaction mixture was stirred with a magnetic stirrer for 24 h at 40 °C. After the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer separated was dried over anhydrous magnesium sulfate and then evaporated under a reduced pressure at room temperature to give an oily mixture of unreacted aldehyde, aldol

type product, and its dehydrated product. The oily mixture was submitted to column chromatography on silica-gel (eluent: hexane and ethyl acetate, 1:1) to give the aldol-type product which was monitored by TLC on silica gel (R_f value: aldol-type 0.32, dehydrated-type 0.53, aldehyde 0.67). In the case of the determination of the ratio of these components, the ^{1}H-MNR spectra of the oily mixture was measured ($CDCl_3$, TMS 1%) before the chromatographic separation, and each percentage was calculated. The fractions of the aldol-type product were collected together and evaporated under reduced pressure. Thus, the aldol-type product, 4-hydroxy-4-(4-nitrophenyl)-2-butanone, was obtained. The enantimeric excess one was oily but the racemate was light-yellowish crystals of mp 63 °C.[9] Its optical rotation was measured in EtOH with D-line and the specific rotation was calculated.

The Aldol Reactions with Cyclodextrin(CD)-Zn^{II}-L-TyrOEt System. $Zn(NO_3)_2 \cdot 6H_2O$ (33 mg, 0.11 mmol) and β-CD (124 mg, 0.11 mmol) were dissolved together in H_2O (7 ml). To this solution, a solution of L-TyrOEt (23 mg, 0.11 mmol) in acetone (1 ml) was added and stirred. This was a water solution of the CD-Zn^{II}-L-TyrOEt (1:1:1) catalyst system. Then, a solution of *p*-nitrobenzaldehyde (100 mg, 0.66 mmol) in acetone (1 ml) was added to the catalyst solution and the pH of the reaction mixture was adjusted to 6 or 7. The amount of the catalyst system was 16 mol% of the aldehyde used. The flask was plugged and kept at 40 °C for 24 h (magnetic stirring). The procedures after the reaction were similar to that of the reactions without the CD. An extraction with ethyl acetate was also carried out.

The Acetal Formation with $RuCl_3$ Complexes. In a reaction with $RuCl_3$-$(TyrOEt)_2$ in MeOH (Table 2), only the *p*-nitrobenzaldehyde dimethyl acetal was obtained in a 62% yield without any aldol reaction product at all. The acetal was isolated by means of column chromatography as well as the aldol-type product. Thereupon, it was prepared separately from the aldehyde and methanol by the conventional method (HCl catalyst) for further identification. R_f value: 0.54 by silica-gel TLC, bp 64.7 °C ^{1}H-NMR ($CDCl_3$): δ=3.39 (3H, s, CH_3), 5.51 (1H, s, CH), 7.59—8.34 (q, aromatic proton). It was found that acetals were also formed with the $RuCl_3$-$(bpy)_2$ complex as follows.



R	R'OH	Catalyst (mol% of CHO)	Yield/% (NMR)
NO_2	MeOH	16	100
		1	100
	EtOH	1	80
	i-PrOH	1	41
H	MeOH	2	100
OMe		2	54

Reaction Products. 4-Hydroxy-4-(4-nitrophenyl)-2-butanone (racemate),[9] mp 63 °C, Found: C, 57.44; H, 5.30; N, 6.61%. Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70%. IR (cm^{-1}): 3400 (OH), 1710 (C=O), 1510, 1440 (NO_2). ^{1}H-NMR ($CDCl_3$): δ=2.19 (s, 3H), 2.88 (d, 2H), 4.10 (br.s, OH), 5.18 (t, 1H), 7.56—8.15 (q, aromatic proton). 4-(4-nitrophenyl)-3-buten-2-one(dehydrated product),[9] mp 114—116 °C, ^{1}H-NMR ($CDCl_3$): δ=2.42 (s, 3H), 6.68—6.96 (d, 1H), 7.30—7.46 (d, 1H), 7.64—8.37 (q, aromatic proton). 4-hydroxy-4-phenyl-2-butanone, oil, ^{1}H-NMR ($CDCl_3$): δ=2.14 (s, 3H), 2.73 (d, 2H), 5.19 (t, 1H), 7.36-8.03 (m, aromatic proton). 4-hydroxy-4-(4-chlorophenyl)-2-butanone, oil, ^{1}H-NMR ($CDCl_3$): δ=2.14 (s, 3H), 2.73 (d, 2H), 5.10 (t, 1H), 7.32—7.82 (q, aromatic proton).

References

1) K. Irie and K. Watanabe, *Bull. Chem. Soc. Jpn.*, **54**, 1195 (1981); **53**, 1366 (1980); *Chem. Lett.*, **1978**, 539.

2) K. Watanabe and A. Imazawa, *Bull. Chem. Soc. Jpn.*, **55**, 3208 (1982).

3) C. H. Heathcock,"Asymmetric Synthesis," ed by J. D. Morrison, Academic Press (1984), Vol. **3B**, p. 111; H. O. House, "Modern Synthetic Reactions," W. A. Benjamin Inc. (1972), p. 629.

4) M. L. Bender and M. Komiyama,"Cyclodextrin Chemistry," Springer (1978); H. Dugas and C. Penny,"Bioorganic Chemistry," Springer (1981), p. 290; I. Tabushi, *Acc. Chem. Res.*, **15**, 66 (1982).

5) F. Cramer, *Chem. Ber.*, **84**, 851 (1951); F. Cramer, W. Saenger, and H. Ch-Spatz, *J. Am. Chem. Soc.*, **89**, 14 (1967); R. L. VanEtten, J. F. Sebastian, G. A. Clowes, and M. L. Bender, *ibid.* **89**, 3243 (1967).

6) D. E. Morse and B. L. Horecker, *Adv. Enzymolo.*, **31**, 125 (1968); B. L. Horecker, O. Tasles, and C. Y. Lai, "The Enzymes," 3rd ed. Ed. by P. D. Boyer, Academic Press (1972), Vol. **7**, p. 213.

7) E. Fischer, *Ber.*, **34**, 451 (1901).

8) E. Fischer, *Ber.*, **41**, 855 (1908).

9) D. S. Noyce and W. L. Reed, *J. Am. Chem. Soc.*, **80**, 5539 (1958); R. E. Corbett and C. L. Davey, *J. Chem. Soc.*, **1955**, 296.