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SYMMETRIC BOROHYDRIDE REDUCTION OF KETONES BY UNSYMMETRICAL Co(II) CHIRAL SALEN COMPLEXES

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Abstract

New unsymmetrical chiral Co(II) salen complexes were synthesized and the efficiency of these catalysts was examined in the enantioselective reduction of aromatic ketones. The higher level of enantioselectivity was attainable over chiral Co(II) salen complexes prepared from salicylaldehyde and 2-formyl-4,6-di-*tert*-butylphenol derivatives.

Keywords : Unsymmetrical salen, enantioselective reduction, tetralone

Chiral salen Mn(III) complexes have been found to be highly enantioselective for the asymmetric epoxidation of conjugated *cis*-disubstituted and trisubstituted olefins [1-3]. Janssen *et al.* have already synthesized a dimeric form of Mn(III) salen ligand and retained this complex in the crosslinked polymer membrane to use as a catalyst for epoxidation [4]. In addition, chiral salen complexes of Co(III) were also shown by Tokunaga *et al.* to be efficient catalysts for the enantioselective ring opening of epoxides with water [5].

Recently Nagata *et al.* have also reported that a set of ketones were asymmetically reduced over conventional chiral salen Co(II) complexes of symmetrical type with high e.e% [6]. In this case, the modification of $NaBH_4$ with tetrahydrofurfuryl alcohol (THFA)-ethanol or THFA-methanol was applied to the reduction of acetophenones and tetralone.

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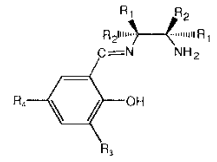
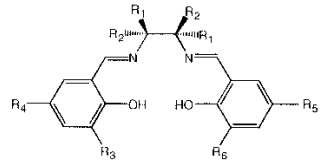
In most salen complexes studied to date, the two identical salicylaldehyde derivative moieties are connected to both sides of one diamine in the ligands [1-6]. Furthermore, Lopez *et al.* [7] have reported that a new class of unsymmetrical chiral salen Schiff base ligands can be synthesized efficiently by stepwise condensation method, each possessing two different salicylaldehyde derivatives, and each with different substituent groups. The synthesis of one chiral half unit of **1a, 1b** and **1c**, as shown in Scheme 1, is first needed [8]; this intermediate activates the construction of the desired compounds as the remaining free amine reacts with other salicylaldehyde derivatives [9].

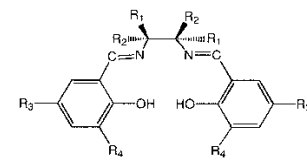


1a ; R_1=Ph, R_2=H, R_4=R_5=H
1b ; R_1=-$(CH_2)_4$-, R_2=H, R_4=R_5=H
1c ; R_1=-$(CH_2)_4$-, R_2=H, R_5=OCH_3, R_4=H



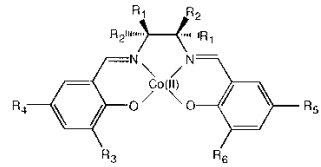
Unsymmetrical Salen

A ; R_1=-$(CH_2)_4$-, R_2=H, R_3= R_4=H, R_5= *t*-Bu, R_6= *t*-Bu
B ; R_1=Ph, R_2=H, R_4= R_5=H, R_5= *t*-Bu, R_6= *t*-Bu
C ; R_1=-$(CH_2)_4$-, R_2=H, R_3= OCH_3, R_4=H, R_5= *t*-Bu, R_6= *t*-Bu
D ; R_1=Ph, R_2=H, R_3= OCH_3, R_4=H, R_5= *t*-Bu, R_6= *t*-Bu
E ; R_1 =-$(CH_2)_4$-, R_2=H, R_3= R_4=H, R_5=H, R_6=OCH_3
F ; R_1 =Ph, R_2=H, R_3= R_4=H, R_5=H, R_6=OCH_3

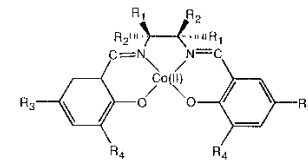


Symmetrical Salen

G ; R_1 =H, R_2=-$(CH_2)_4$-, R_3=*t*-Bu, R_4=*t*-Bu
H ; R_1=Ph, R_2=H, R_3=*t*-Bu, R_4=*t*-Bu
I ; R_1=Ph, R_2=H, R_3=H, R_4=OCH_3
J ; R_1=-$(CH_2)_4$-, R_2=H, R_3=H, R_4=H
K ; R_1=Ph, R_2=H, R_3=H, R_4=H



Co(II) - (A~F)



Co(II) - (G~K)

Scheme 1.

In this paper, we will describe how these new unsymmetrical chiral Schiff bases (**A ~ F**), synthesized from different chiral half units (**1a, 1b, 1c**), act as asymmetric catalysts in the borohydride reduction of aromatic ketones [8, 9]. In this study, conventional chiral salen ligands (**G ~ K**) were also used as catalysts to compare enantioselective catalytic activities. The unsymmetrical salen Co(II) catalysts were obtained by the reaction of $Co^{II}(OAc)\cdot 4H_2O$ with the corresponding chiral salen ligands in refluxed EtOH solution. The borohydride reduction of acetophenone and α-tetralone was carried out mainly at –20°C over chiral Co(II) salen catalysts to evaluate the relations between the structural features of new unsymmetric salen ligands and enantioselectivity.

Al containing MCM-41 was synthesized according to the literature method. Al-MCM-41 exhibited a very intense (100) peak in the X-ray diffractogram and the calculated d_{100}-spacing was 4.0 nm. The Si/Al ratio of the obtained sample was 35. This MCM-41 sample was used to immobilize the chiral salen complexes. First, to immobilize the chiral salen, Al-MCM-41 was ion exchanged with $Co(OAc)_2$ at 80°C for 24 h, before being filtered, washed with distilled water, and then vacuum dried. The calcined Co-ion exchanged Al-MCM-41 was then heated to reflux with a chiral salen ligand in ethanol for 24 h, cooled and washed with ethanol. This sample was later dried at 130°C for 6 h, resulting in the immobilization of 7 wt.% of the chiral salen complexes. The catalyst obtained by this ion exchange method is denoted as Co(II)-(**A~F**)-ion ex. In a second process, the chiral salen was supported on Al-MCM-41 by impregnation. 20 mg of the complex was dissolved in dichloromethane and then 500 mg of dried Al-MCM-41 was added to the solution. The mixture was heated to reflux for 24 h. The powder sample was then filtered and washed with dichloromethane. The resulting amount of chiral salen complex loaded was lower than in the previous process at 2.5 wt.%. The catalyst obtained by the impregnation method is denoted as Co(II)-(**A~F**)-imp.

The characterization of the samples was carried out using ^{1}H-NMR and ^{13}C-NMR. The NMR spectra showed that the synthesis of the chiral half unit of salen and the unsymmetrical salen had been achieved successfully. The chiral half-unit, the homogeneous unsymmetrical salen sample and the salen complex immobilized on MCM-41 were also characterized using the FT-IR spectroscopy. Figure 1 shows the FT-IR spectra of salicylaldehyde (**1a**), *o*-vanillin (**1b**), chiral half-units **3b** and **3d**, as well as the chiral salen complexes **C** and **E**. In the IR spectra, salicylaldehyde and *o*-vanillin show a characteristic C=O (aromatic aldehyde) band near 1680 cm^{-1}. This peak disappeared after condensation with optically pure diamines, synthesizing the chiral half-unit and the chiral salen complexes. At this point, the unsymmetrical salen complexes, as well as the conventional symmetrical chiral salen ligands, all exhibited a characteristic band at 1640 cm^{-1} after condensation. This peak can be seen as a result of the stretching vibration of the C=N bond in the salen ligands. The salen complexes immobilized over MCM-41 also exhibited this band in the IR spectra.

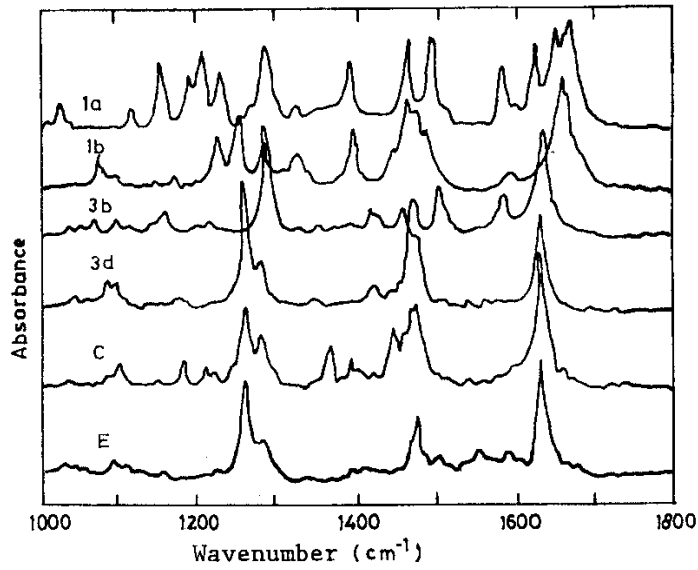


Fig. 1. FT-IR spectra of salicylaldehyde(**1a**), *o*-vanillin (**1b**), chiral half unit (**3b**, **3d**) and chiral salen complexes (**C** and **E**)

As can be seen in Table 1, the optically active Co(II) complexes of unsymmetrical salen catalyzed the reduction of aromatic ketones with sodium borohydride; the enantioselectivity was strongly controlled by the structure of the Schiff base ligand. The unsymmetrical salen catalyst Co(II)-(**A~F**) demonstrated an improved level of enantioselectivity in the asymmetric borohydride reduction of aromatic ketones over the conventional symmetrical salen catalysts Co(II)-(**G**) and -(**H**). Furthermore, a higher optical yield was obtained over the salen ligands synthesized using a 1,2-diaminocyclohexane derivative. The introduction of a methoxy group into the unsymmetrical salen ligands resulted in a decrease of enantioselectivity. The conventional salen ligands Co(II)-(**I**) and -(**K**) were efficient asymmetric catalysts for this reaction, having no bulky groups at para position to the salen oxygens. The introduction of a *tert*-butyl group para to the oxygens, as in Co(**II**)-(**G**) and -(**H**), resulted in a lower enantioselectivity. The presence of bulky groups, preventing the substrate approach, is also crucial to the enantioselectivity in a lower enantioselectivity. The presence of bulky groups, preventing the substrate approach, is also crucial to the enantioselectivity in the borohydride reduction

Table 1

Enantioselective borohydride reduction of ketone catalyzed by asymmetrical chiral Co(II) complexes

Entry[a]	Schiff base	Substrate	Alcohol	Conv. (%)	Ee (%)[b]
1	A	Acetophenone	THFA+EtOH	96	30(S)
2	A	α-Tetralone	None	<10	5(S)
3	A	α-Tetralone	EtOH	60	55(S)
4	A	α-Tetralone	THFA	85	58(S)
5	A	α-Tetralone	THFA+MeOH	97	66(S)
6	A	α-Tetralone	THFA+EtOH	95	65(S)
7	A[c]	α-Tetralone	THFA+EtOH	97	67(S)
8	A	2-Methylacetophenone	THFA+EtOH	50	48(S)
9	A	4-Methylacetophenone	THFA+EtOH	53	37(S)
10	A	Isobutylphenone	THFA+EtOH	63	11
11	B	Acetophenone	THFA+EtOH	95	15(S)
12	B	α-Tetralone	THFA+EtOH	96	22(S)
13	C	α-Tetralone	THFA+EtOH	95	46(S)
14	D	α-Tetralone	THFA+EtOH	94	20(S)
15	E	α-Tetralone	THFA+EtOH	97	58(S)
16	G	Acetophenone	THFA+EtOH	97	12(R)
17	G	α-Tetralone	THFA+EtOH	96	16(R)
18	G	2-Methylacetophenone	THFA+EtOH	41	12(R)
19	G	4-Methylacetophenone	THFA+EtOH	44	10
20	H	Acetophenone	THFA+EtOH	95	12(S)
21	H	α-Tetralone	THFA+EtOH	93	17(S)
22	I	Acetophenone	THFA+EtOH	96	31(S)
23	I	α-Tetralone	THFA+EtOH	94	60(S)
24	J	Acetophenone	THFA+EtOH	97	32(S)
25	J	α-Tetralone	THFA+EtOH	98	46(S)
26	J	4-Methylacetophenone	THFA+EtOH	96	30(S)
27	K	Acetophenone	THFA+EtOH	98	30(S)
28	K	α-Tetralone	THFA+EtOH	97	42(S)
29	K	2-Methylacetophenone	THFA+EtOH	98	26(S)
30	K	4-Methylacetophenone	THFA+EtOH	74	24(S)

[a]Reaction conditions; substrate 0.25 mmol, Co(II) catalyst 0.0175 mmol, $NaBH_4$ 0.75 mmol, EtOH(or MeOH) 0.75 mol, THFA 5.15 mmol; $NaBH_4$, tetrahydrofurfuryl alcohol(THFA) and ethanol (or methanol) were stirred for 3 h at 0°C in 5.0 mL $CHCl_3$ solvent before reaction. H_2 was released during the mixing. The catalyst and the substrate were added to this pre-modified borodydride solution at –20°C. Reaction time = 3 h.

[b]The ee% values for respect reactions were determined by capillary GC using chiral columns (CHIRALDEX™, Gamma-cyclodextrin trifluoroacetyl, 40mx0.25mm i.d.(Astec)).

[c]20 mol% of catalyst. Reaction time = 2 h

of ketone. The catalysts having bulky groups near the both salen oxygens resulted in a lower enantioselectivity. It should be noted that the proper selection of alcohol in the combination of THFA influenced the enantioselectivity. A higher optical purity of 66 ee% was obtained when the mixed solution of THFA and ethanol was used in the reduction of α-tetralone. In addition, the conversion and the enantioselectivity was very low when the reaction was carried out without the addition of alcohol.

Table 2

Enantioselective borohydride reduction of ketones catalyzed by homogeneous chiral salen and immobilized Co(II) complexes

Entry	Catalyst	Substrate	Conv. (%)	Ee (%)
1	Co(II)-(A)	α-Tetralone	95	65(S)
2	Co(II)-(A)-ion ex.	α-Tetralone	82	43(S)
3	Co(II)-(A)-imp.	α-Tetralone	83	63(S)
4	Co(II)-(A)	Acetophenone	96	30(S)
5	Co(II)-(A)-ion ex.	Acetophenone	86	15(S)
6	Co(II)-(A)-imp.	Acetophenone	88	30(S)
7	Co(II)-(E)	α-Tetralone	97	58(S)
8	Co(II)-(E)-ion ex.	α-Tetralone	84	40(S)
9	Co(II)-(E)-imp.	α-Tetralone	86	59(S)
10	Co(II)-(G)	α-Tetralone	96	16(R)
11	Co(II)-(G)-ion ex.	α-Tetralone	79	10(R)
12	Co(II)-(G)-imp.	α-Tetralone	82	15(R)
13	Co(II)-(I)	α-Tetralone	94	60(S)
14	Co(II)-(I)-ion ex.	α-Tetralone	80	37(S)
15	Co(II)-(I)-imp.	α-Tetralone	84	58(S)

Catalytic testing for the salen complexes immobilizd on Al-MCM-41 was compared with those for the homogeneous complexes, and the results are given in Table 2. In the case of **Co(II)-(A~F)-imp.** Catalyst, the enantioselective process was fully maintained. However, the modification of the Co-ion exchanged Al-MCM-41 with the chiral salen **(Co(II)-(A~F)-ion ex.)** generally leaded to a decrease in reactivity and enantioselectivity. The conversion and ee% obtained over the heterogenized chiral salen catalysts were found to be lower than those for the homogeneous catalysts. The homogeneous chiral Co (salen) complexes, as well as the solid samples, were a dark red color. After using Co (salen) complexes immobilized on MCM-41 as catalysts, the resulting solution exhibited no color, and no Co was detected in the product solution. This means that Co(salen) complexes immobilized on mesoporous materials remain stable during the reaction process and continue to exist in the pore system without any extraction. Finally, after reusing three times, the catalytic

activity and selectivity of the immobilized Co(salen) complexes have remained substantially unchanged.

In summary, new unsymmetrical chiral salen Co(II) complexes have been synthesized and an asymmetric reduction of ketones was performed to examine the structural features of these salen ligands. For this reaction, unsymmetrical (salen) complexes showed comparatively high enantioselectivity as compared to the conventional symmetrical salen complexes, prepared from salicylaldehyde and 2-formyl-4,6-di-*tert*-butylphenol derivative.

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8. 10 mmol salicylaldehyde (or *o*-vanilline) in 50 mL chloroform was added dropwise to a stirred solution of 30 mmol (1S,2S)-(+)-1,2-diaminocyclohexane (or (1S,2S)-(-)-1,2-diphenylethylenediamine) in 100 mL chloroform containing molecular sieve 4Å at 0°C. The addition of salicylaldehyde (or *o*-vanilline) took 5 h. A pale-yellow creamy solid was obtained after solvent evaporation under vacuum and washing with water to remove the unreacted diamines.
   1b: IR(CCl_4); 3400, 3091, 2930, 2870, 1630, 1580, 1497, 1461, 1448, 1414, 1281, 1211, 1150, 1118, 1091, 1064, 1045, 942, ^{1}H-NMR ($CDCl_3$/TMS); 1.18~1.49(m, 4H), 1.62~1.78(m, 3H), 1.78~1.90(m, 2H), 2.84(q, 1H), 3.27~3.29(m, 1H), 6.73(t, 1H), 7.10(d, 1H), 7.11~7.26(m, 1H), 8.17(s, 0.7H), 8.41(s, 0.3H), 13.31(s, 1H).
   1c: IR (CCl_4); 3404, 3060, 2931, 2868, 1631, 1582, 1464, 1417, 1345, 1275, 1256, 1092, 1082, 1042, 973, 907, ^{1}H-NMR ($CDCl_3$/TMS); 1.19~1.44(m, 4H), 1.61~1.79(m, 3H), 1.79~1.88(m, 2H), 2.15(d, 0.5H), 2.77(d, 1H), 3.23(d, 0.5H), 3.79(d, 3H), 6.64~6.88(m, 3H), 8.18(s, 0.5H), 8.35(s, 0.5H).
9. The general procedure for the preparation of unsymmetrical chiral salen complexes is as follows: 10 mmol of the chiral half unit (**1a~1c**) in 20 mL ethanol was added dropwise to corresponding salicylaldehyde derivative (1mmol) in 20 mL of ethanol at room temperature. The mixture was heated to 60°C and stirred for 8 h. The resulting yellow solid was collected by filtration and recrystallized from ethanol.
   A: $[\alpha]_D^{20}$ +162.8 (c=1.0, $CHCl_3$), IR (CCl_4); 2942, 2861, 1632, 1581, 1498, 1479, 1461, 1407, 1389, 1361, 1279, 1263, 1251, 1201, 1173, 1150, 1117, 1093, 1043, 1030, 974, ^{1}H-NMR ($CDCl_3$/TMS); 1.31(s, 9H), 1.45(s, 9H), 1.62~2.01(m, 8H), 2.44(s, 2H), 2.97(m, 1H), 3.43(m, 1H), 3.75(q, 1H), 4.08(d, 1H), 6.87(t, 1H), 7.03(d, 1H), 7.12~7.28(m, 2H), 7.35(t, 1H), 7.46(d, 1H), 8.40(s, 2H), ^{13}C-NMR ($CDCl_3$/TMS); 24.4, 29.8, 31.3, 33.1, 37.2, 72.4, 116.8, 118.4, 122.2, 124.8, 125.5, 126.7, 128.2, 131.3, 132.0, 132.2, 136.2, 160.8, 164.6, 165.7 ppm.

C: $[\alpha]_D^{20}$ +423.6 (c=1.0, $CHCl_3$), IR (CCl_4): 2931, 2859, 1600, 1468, 1439, 1391, 1364, 1278, 1256, 1203, 1172, 1120, 1092, 1042, 1030, 973, 907, ^{1}H-NMR ($CDCl_3$/TMS); 1.19~1.40(m, 21H), 1.47~2.01(m, 8H), 3.29(m, 2H), 3.67(q, 2H), 3.85(s, 2H), 6.75(m, 1H), 6.98(s, 1H), 7.15~7.25(m, 1H), 7.30(s, 1H), 7.46(d, 1H), 8.30(s, 2H), ^{13}C-NMR ($CDCl_3$/TMS); 24.0, 29.4, 31.3, 33.9, 34.9, 55.7, 72.3, 113.7, 117.8, 123.0, 125.9, 136.2, 139.8, 157.9, 164.7, 165.7 ppm.