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Asymmetric borohydride reduction of aromatic ketones catalyzed by chiral salen–Co(II) complexes

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Abstract

Chiral symmetrical salen–Co(II) complexes were used as the catalysts in the asymmetric borohydride reduction of aromatic ketones using sodium borohydride. Enantiomeric excesses up to 70% and >99% yield in 2.5 mol% catalytic amount were achieved at room temperature for 24 h.

Keywords: Chiral salen–Co(II) complexes; Asymmetric borohydride reduction; Aromatic ketones

1. Introduction

Development of efficiently catalytic asymmetric reactions is the most challenging task in current synthetic chemistry; much effort has been devoted to creation of the chiral metal complexes for asymmetric catalysis. In the last two decades, many brand-new ligands have been synthesized and their combination with various metal ions have been applied in asymmetric catalysis. However, most ligands have an only narrow range of applications and their use is limited to particular reactions. Exceptionally, a few ligands such as binaphthol, semicorrin and binap and their metal complexes show wide applicability. Chiral salen ligand is one of such ligands and their metal complexes are now used as the catalysts for a variety of asymmetric reactions such as epoxidation [1], aziridination [2], cyclopropanation [3,4], Diels–Alder reaction [5], and kinetic resolution of racemic epoxides [6,7], kinetic resolution of *sec*-alcohols [8], asymmetric ring opening of mesoepoxides [9–11], enantioselective C–H amination [12]and so on.

Mukaiyama et al. [13–15] demonstrated that optically active (β-oxoaldiminato) cobalt(II) complexes were effective catalysts in the enantioselective borohydride reduction of various aromatic ketones. It was reported that the enantioselective borohydride reduction of 2-phenacylpyridine was catalyzed by Jacobsen's manganese(III) complex to give in higher enantiomeric excess 1-phenyl-2-(2-pyridyl)ethanol [16]. The highly enantioselective borohydride reduction in sedamine derivative was also achieved by Yamada and coworkers [17]. Recently, Kim and Ikeno [18] reported a set of ketones were asymmetrically reduced using unsymmetrical chiral salen–Co(II) complexes; up to 67%ee in 20 mol% catalytic amount were achieved. Herein, we used a series of symmetrical chiral salen–Co(II) complexes in only 2.5 mol% catalytic amount for this type of reaction, and attained an enantioselectivity of up to 70% at room temperature.

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2. Experimental

2.1. Materials and equipment

R,R-(−)-*N,N′*-Bis(3, 5-di-*t*- butyl-salicylidene)-1,2-cyclohexanediamine, chromanone, α-tetralone (Acros), *R,R*-(−)-1,2-cyclohexanediamine, *S,S*-(−)-1,2-cyclohexanediamine, propiophenone, 2-*tert*-butylphenol, 2,4-di-*tert*-butylphenol, 2-*tert*-butyl-4-methylphenol (Fluka), $NaBH_4$ (Merck), and all other reagents were obtained from commercial sources and 3-*tert*-butyl-3-*tert*-butyl-5-methyl-[19,20] and 3,5-di-*tert*-butyl-salicylaldehyde [21] were prepared by the known methods.

Elemental analyses were conducted on a Varian EL apparatus. IR spectra was obtained with an IFS 120HR FT-IR instrument. GC analysis was carried out using HP-6890 with a CP-Chirasil-Dex CB capillary column.

2.2. Preparation of the catalysts

The chiral salen–Co(II) complex **1**, ent-1, 2, 3,6 were synthesized and characterized according to the methods reported in our previous communication [22].

2.2.1. Chiral salen–Co(II) complex *4*

R,R-(−)-1,2-Cyclohexanediamine (57 mg, 0.5 mmol) was added to a solution of 3-*tert*-butyl-5-methylsalicylaldehyde (192 mg, 1 mmol) in ethanol (3 ml) and refluxed for 5 h. The mixture was concentrated and to this residue were added ethanol (10 ml) and $Co(OAc)_2$ (106 mg, 0.6 mmol) under argon atmosphere. The mixture was refluxed for 10 h, and then allowed to cool to room temperature. The precipitates were separated from the solution by filtration, washed with ethanol and dried under vacuum to give complex **4** as dark red crystals.

IR (KBr): 2947, 2909, 2861, 1594, 1530 cm^{-1}. Anal. Calcd. for $C_{30}H_{40}N_2O_2Co$: C, 69.35; H, 7.76; N, 5.39. Found: C, 69.20; H, 7.56; N, 5.28.

2.2.2. Salen–Co(II) complex *5*

Salen–Co(II)complex **5** was synthesized from 3-*tert*-butyl-salicylaldehyde and *R,R*-(−)-1,2-cyclohexanediamine in the same procedure as described for the synthesis of salen–Co(II) complex **4**. Complex **5** was a dark red crystal.

IR (KBr): 2958, 2930, 2869, 1598, 1538 cm^{-1}. Anal. Calcd. for $C_{28}H_{36}N_2O_2Co$: C, 68.42; H, 7.38; N, 5.70. Found: C, 68.50; H, 7.24; N, 5.58.

2.3. A typical experimental procedure for borohydride reduction of aromatic ketones [13]

Under argon atmosphere, ethanol (0.25 ml) was added to $NaBH_4$ (30 mg, 0.75 mmol) in $CHCl_3$ (5 ml). After stirring for 1 h at room temperature, a solution of the chiral salen–Co(II) complexes (0.0125 mmol) and substrate (0.5 mmol) in 3 ml of $CHCl_3$ was poured into the mixture. The mixture was stirred for 24 h at room temperature. The reaction was quenched by the addition of saturated aqueous ammonium chloride, and the product was extracted with diethyl ether. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The yield and enantiomeric excess were determined by GC analysis using a CP-Chirasil-Dex CB capillary column.

2.4. A typical experimental procedure for borohydride reduction of acetophenone with pre-modified borohydride

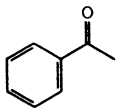
The procedure of Mukaiyama and Yamada was followed [14,15].

3. Results and discussion

Using acetophenone as a model compound, we studied the influence of time on the reaction results with complex **1** as catalyst at room temperature. Keeping room temperature for 24 h give a better result (Table 1). Mukaiyama and coworkers[14,15] found that higher reaction rate and higher enantioselectivity were obtained when the pre-modified borohydride with tetrahydridofurfuryl alcohol and ethanol were used in the enantioselective borohydride reduction of aromatic ketones. On the contrary, the bad results were found for salen–Co(II) when the pre-modified borohydride was used to reduce acetophenone (Table 1, entries 7 and 8).

The complexes **1**–**6** (Fig. 1) were used as the catalysts for asymmetric borohydride reduction of aromatic ketones. Data regarding the enantioselectivities were given in Table 2. Since salen metal complexes

Table 1
The influence of reaction time and pre-modification borohydride on the reaction results

Entry	Substrate	Catalyst	Time (h)	Yield (%)[a]	ee (%)[b]	Configuration
1[c]		**1**	1	47	26	*R*
2		–[d]	1	2	0	–
3[c]		**1**	7	58	31	*R*
4		–[d]	7	4	0	–
5[c]		**1**	24	63	35	*R*
6		–[d]	24	7	0	–
7[e]		**1**	1	39	3	*R*
8[f]		**1**	12	36	8	*R*

[a] Determined by GC using undecane as internal standard.

[b] Determined by GC using a CP-Chirasil-Dex CB capillary column.

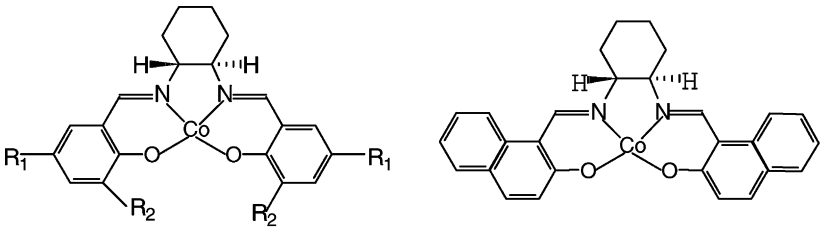
[c] Reaction conditions: substrate 0.5 mmol, catalyst **1** (0.0125 mmol), $NaBH_4$ (0.75 mmol), $CHCl_3$ (8 ml), ethanol (0.25 ml), room temperature.

[d] No catalyst.

[e] Reaction conditions: substrate 0.5 mmol, catalyst **1** (0.0125 mmol), $NaBH_4$ (0.75 mmol), $CHCl_3$ (10 ml), ethanol (0.75 mmol), tetrahydridofurfuryl alcohol (10.3 mmol), 0 °C.

[f] Reaction conditions: substrate 0.5 mmol, catalyst **1** (0.0125 mmol), $NaBH_4$ (0.75 mmol), $CHCl_3$ (10 ml), ethanol (2.22 mmol), tetrahydridofurfuryl alcohol (10.3 mmol), −20 °C.

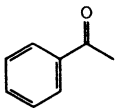
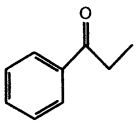
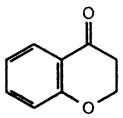
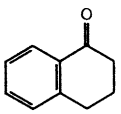
bearing bulky and/or chiral substituents at C3, C3′, C5 and C5′ had been known to be efficient catalysts for asymmetric epoxidation of simple olefins [1]. We first examined asymmetric borohydride reduction of aromatic ketones, using the complex **1** (*R,R*-Jacobsen ligand was a excellent ligand for many asymmetric catalytic reactions) as the catalyst. Contrary to our expectation, the complex **1** only showed moderate asymmetric inducement (Table 2, entries 1, 5, 9 and 17), and its enantiomer ent-**1** showed the same level but opposite sense of enantioselectivity. Complex **3** which had no C3 and C3′substituent and had nitro group at C5 and C5′, however, catalyzed the desired reaction with better catalytic activity (Table 2, entry 13, 60%ee, >99%yield). To further improve the enantioselectivity, we then modified the substituents of the salen ligand and obtained the complexes **2**, **4**, **5** and **6**. Complex **4** having a methyl group in place of the *tert*-butyl group at C3 and C3′ showed better catalytic activity than complex **1** in the borohydride reduction of acetophenone and propiophenone (Tables 2, entries 1 and 2), and also displayed the same level in catalyzing borohydride reduction of 4-chromanone and α-tetralone. Complex **2** which had no C3 and C3′substituent and has a bromo group at C5 and C5 showed better enantioselectivity, but the conversion was low (Table 2,



1: R_1=R_2=*t*-Bu; **2**: R_1=Br, R_2=H **6**
3: R_1=NO_2, R_2=H; **4**: R_1=CH_3, R_2=t-Bu
5: R_1=H, R_2=t-Bu.

Fig. 1. Structure of chiral salen–Co(II) complexes.

Table 2
Catalytic borohydride reduction of various aromatic ketones using chiral salen–Co(II) complexes[a]

Entry	Substrate	Catalyst	Yield (%)[b]	ee (%)[c]	Configuration
1		**1**	63	35	*R*
2		ent-**1**	63	32	*S*
3		**4**	77	40	*R*
4		**5**	>99	14	*R*
5		**1**	52	37	*R*
6		ent-**1**	49	36	*S*
7		**4**	76	41	*R*
8		**5**	>99	17	*R*
9		**1**	65	38	–[d]
11		ent-**1**	71	35	
12		**2**	27	56	–[d]
13		**3**	>99	60	–[d]
14		**4**	95	28	–[d]
15		**5**	>99	54	–[d]
16		**6**	21	37	–[d]
17		**1**	40	31	*R*
18		ent-**1**	34	31	*S*
19		**2**	6	60	*R*
20		**3**	45	51	*R*
21		**4**	52	32	*R*
22		**5**	>99	70	*R*
23		**6**	14	56	*R*

[a] Reaction conditions: substrate 0.5 mmol, Co(II) catalyst (0.0125 mmol), $NaBH_4$ (0.75 mmol), $CHCl_3$ (8 ml), ethanol (0.25 ml); room temperature, 24 h.
[b] Determined by GC with undecane as internal standard.
[c] Determined by GC using a CP-Chirasil-Dex CB capillary column.
[d] The configuration of the product *sec*-alcohol was not determined.

entries 12 and 19). Complex **5** bearing a *tert*-butyl group at C3 and C3′substituent and no substituent at C5 and C5′ exhibited the best catalytic activity, up to 70%ee (Table 2, entry 22). Based on the reaction results, the influence of the substituent of the C3 and C3′, C5 and C5 on the catalytic activity was obvious.

In addition, the enantioselectivity is highly dependent on the bulkiness of substrate. Reduction of α-tetralone using complex **5** as the catalyst gave the chiral alcohol with 70%ee and >99% yield, and 4-chromanone with the same catalyst also gave the chiral alcohol with 54%ee and >99% yield. However, complex **5** showed low enantioselectivity in catalytic borohydride reduction of acetophenone and propiophenone. Acyclic aromatic ketones showed moderate results (Fig. 2). Cyclic aromatic ketones were successfully transformed to the corresponding chiral alcohols with the system and showed better results (Fig. 3). Although the reaction mechanism was not clear at present, it was shown that effective stereochemical and electronic communication between substrate and catalyst was essential for attaining high enantioselectivities in asymmetric catalytic reaction.

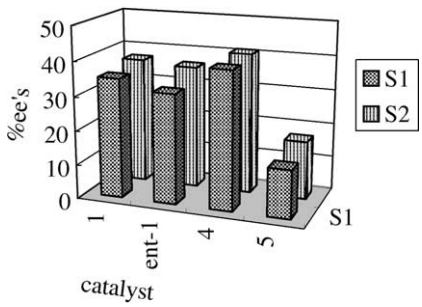


Fig. 2. 3D view of % ee's acyclic aromatic ketones to chiral *sec*-alcohols. S1: acetophenone, S2: propiophenone.

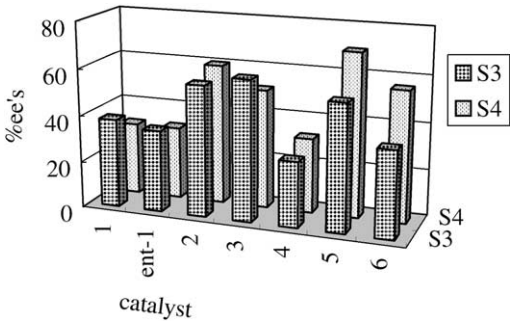


Fig. 3. 3D view of % ee's cyclic aromatic ketones to chiral *sec*-alcohols. S3: chromanone, S4: α-tetralone.

4. Conclusion

This work showed that optically active salen–Co(II) can be used for catalyzing asymmetric borohydride reduction of aromatic ketones. Up to 70%ee and >99% conversion were achieved. It enlarged the application of chiral salen ligand in asymmetric catalysis. To further improve the enantiomeric excesses with the development of other chiral salen–Co(II) complexes is currently in progress in our laboratory.

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