

# Studies on the Preparation of (S)-3-chloro-phenyl-1-propanol by Catalytic Asymmetric Hydrogenation of $\beta$ -chloro-propiofenone

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## Abstract

The supported iron-based chiral catalysts were applied in the asymmetric catalytic hydrogenation reaction of  $\beta$ -chloro-propiofenone, and effects of the asymmetric catalytic reduction reaction temperature, pressure and KOH concentration on the output and e.e. value were investigated respectively. Results indicated that the reaction output and e.e. value attained 99% and 90%, respectively, when temperature, pressure and concentration was 60 °C, 1.2 MPa and  $2 \times 10^{-2}$  mol/L, respectively.

**Keywords:**  $\beta$ -chloro-propiofenone, (S)-3-chloro-phenyl-1-propanol, Iron-based chiral catalysts

(S)-3-chloro-phenyl-1-propanol was applied as intermediates for preparing antidepressants (S)-fluoxetine intermediate, and studies on preparation of (S)-3-chloro-phenyl-1-propanol or (R)-3-chloro-phenyl-1-propanol have been exerted by many scholars among which Corey was the most successful (Zhao, 2003, PP. 18-21; Komarov, 2001, p. 1197). Corey used boron complex oxazolidine generated from the naturally occurring materials, namely L-amino acid and borane as catalyst to exert the chiral reduction of  $\beta$ -chloro-propiofenone, and obtained chiral alcohols with corresponding configuration among which e.e. value attained 97% (Corey, 1989, p. 5207; Corey, 1987, 7925; Corey, 1990, 611). Chen, et al. (2006, pp. 65-68) from Materials Chemistry Laboratory of Nanjing University of Science & Technology first used the natural D-camphor derivatives as materials to synthesize two new camphyl amino alcohols, and put them react with borane in situ to prepare the corresponding boron complex oxazolidine. Using chiral boron oxazolidine as catalyst and  $\text{BH}_3\cdot\text{MeS}$  as the reducing agent to reduce  $\beta$ -chloro-propiofenone, the output and e.e. value was 89% and 94.6%, respectively. This was an issue concerning the preparation of chiral alcohol by chiral reduction of aromatic ketones. Recently, we investigated this issue and developed a series of chiral catalysts (Zhao, 2010, CN201010292558). We designed the chiral complex using Fe as central atom which has been applied in the preparation of preparing antidepressants fluoxetine intermediate (S)-3-chloro-phenyl-1-propanol by the chiral hydrogenation reaction of  $\beta$ -chloro-propiofenone. This process was simple with low cost and suitable for industrial mass production with certain scale.

## 1. Experimental

### 1.1 Apparatus and drugs

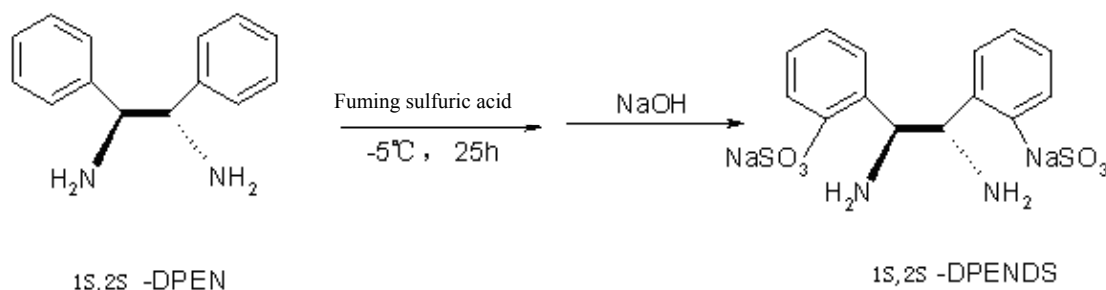
WRS-1B digital melting-point apparatus, Shanghai Yi measuring equipment Co., Ltd.; WZZ-2S digital automatic polarimeter, Shanghai Precision Scientific Instrument Co., Ltd.; Bruck-300 type NMR Measured resonance (TMS as internal standard); GC-7900, Shanghai Tian Mei Scientific Instruments Co., Ltd.; EQUINX55 type IR, Bruker. 1S, 2S-diphenyl diamine (1S, 2S-DPEN) and S-binaphthyl diphenyl phosphate (S-BINAP) were purchased from J & K Technology Co., Ltd., the rest are reagents are all of commercially available AR reagents.

### 1.2 Experimental procedure

#### 1.2.1 Preparation of iron-based catalyst

A little 98% concentrated sulfuric acid and 1S, 2S-diphenyl ethylene diamine (1S, 2S-DPEN) were added to three-neck flask, and cooled down to -5 °C. Fuming sulfuric acid followed, and reacted for 25 h with agitation. NaOH solution was added slowly to neutralize till neutrality. The resultant solution was heated till room temperature and undertaken vacuum filtration. Filter cake was rinsed by ethanol and water (V/V = 1:1) to for

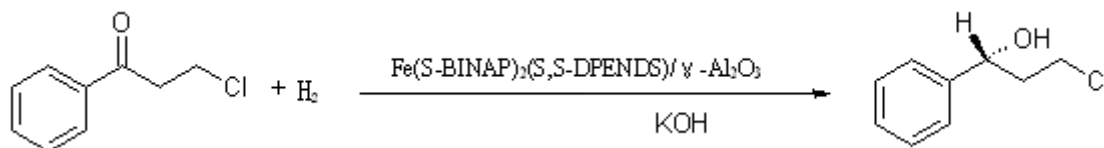
several times, and the filtrate was collected, concentrated to remove solvent and marked as 1S, 2S-DPENDS (1S, 2S-diphenylethylenediamine sulfate).



Isopropanol solution (V/V = 1:1) containing  $\text{FeCl}_3$ , S-binaphthyl double-diphenyl phosphate (S-BINAP), (1S, 2S)-diphenylethylenediamine sulfate ((S, S)-DPENDS) reacted for 12h under the protection of  $\text{N}_2$  at  $60^{\circ}\text{C}$ , then  $\gamma\text{-Al}_2\text{O}_3$  was added to the reaction solution, and after stewing for 24h, 10mL formaldehyde solution was added. After reflux for 10 h under the protection of  $\text{N}_2$ , cooling down to room temperature, the resultant solution was filtered by vacuum filter funnel, rinsed by clean water for several times, and after vacuum drying for 24 h, the yellow supported chiral catalyst (loading, 5.0%) was obtained and marked as  $\text{Fe}(\text{S-BINAP})_2(\text{S, S-DPENDS})/\gamma\text{-Al}_2\text{O}_3$ , the catalyst was impregnated in the [EPy] B ionic liquid and kept for further investigation. TEM and SEM of the catalyst were depicted in Figure 1.

### 1.2.2 Asymmetric hydrogenation of $\beta$ -chloro-propiophenone

A certain amount of  $\text{Fe}(\text{S-BINAP})_2(\text{S, S-DPENDS})/\gamma\text{-Al}_2\text{O}_3$  chiral catalysts,  $\beta$ -chloro-propiophenone, KOH, isopropyl alcohol were added into the autoclave with magnetic stirring, and the air in autoclave was replaced by nitrogenization, and  $\text{N}_2$  was replaced by hydrogen charging for several times to a predetermined pressure. The resultant solution reacted for 2 h at a certain temperature, then catalysts were removed, the filtrate was concentrated to remove solvent by rotary evaporator. The resultant product recrystallized several time in hexane, and white solid was obtained. The corresponding parameters of the solid was as follows: melting point,  $58^{\circ}\text{C}$ ;  $[\alpha]_D^{25} -26$  (c1,  $\text{CHCl}_3$ ),  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 7.973~7.260 (m, 5H, ArH), 3.946~3.918 (m, 2H,  $\text{CH}_2\text{Cl}$ ), 3.485~3.457 (m, 2H,  $\text{CH}_2$ ), 1.596, 1H,  $\text{CHOH}$ ; IR (film)  $\nu$ : 3330 (O-H)  $\text{cm}^{-1}$ .



## 2. Results and discussion

### 2.1 Effects of reaction temperature on e.e. value of (S)-3-chloro-phenyl-1-propanol

The 0.5 g substrate  $\beta$ -chloro-propiophenone was dissolved in 20 mL isopropanol, and 15 mg catalyst  $\text{Fe}(\text{S-BINAP})_2(\text{S, S-DPENDS})/\gamma\text{-Al}_2\text{O}_3$ , 20 mg KOH was added subsequently. After sealing the reactor, the  $\text{O}_2$  was replaced by high pure  $\text{N}_2$  for 3 times, and then  $\text{N}_2$  was replaced by  $\text{H}_2$  for 3 times.  $\text{H}_2$  pressure was adjusted to 1.2 MPa, and chiral reaction was undertaken at  $0^{\circ}\text{C}$ ,  $25^{\circ}\text{C}$ ,  $40^{\circ}\text{C}$ ,  $60^{\circ}\text{C}$ ,  $80^{\circ}\text{C}$ ,  $100^{\circ}\text{C}$  for 1.5 h, respectively. The output Y and e.e. value were determined by gas chromatography, and result was listed in Table 1.

As seen from Table 1, the output of  $\beta$ -chloro-propiophenone increased gradually with the increasing of temperature. Y ranged from 48.5% to 99% when temperature increased from 0 to  $60^{\circ}\text{C}$ . However, when temperature increased from 0 to  $100^{\circ}\text{C}$ , the e.e. value decreased from 91.2% to 70%, which might be ascribed to the reason that the energy range of enantiomers became smaller with the increasing of temperature, which made catalytic hydrogenation products of  $\beta$ -chloro-propiophenone, S and R type 3-chloro-1-phenyl-propanol mutual change, and e.e. value of enantiomers thus decreased. Therefore, during the heterogeneous catalytic asymmetric hydrogenation process of  $\beta$ -chloro-propiophenone, low temperature lead to slower reaction, but high temperature resulted in the low enantioselectivity. As seen from Table 1, temperature about  $60^{\circ}\text{C}$  was appropriate.

### 2.2 Effects of reaction pressure on Y and e.e. value of (S)-3-chloro-phenyl-1-propanol

The 0.5 g substrate  $\beta$ -chloro-propionophenone was dissolved in 20 mL isopropanol, and 15 mg catalyst  $\text{Fe}(\text{S-BINAP})_2$  (S, S-DPENDS) /  $\gamma\text{-Al}_2\text{O}_3$ , 20 mg KOH was added subsequently. After sealing the reactor, the  $\text{O}_2$  was replaced by high pure  $\text{N}_2$  for 3 times, and then  $\text{N}_2$  was replaced by  $\text{H}_2$  for 3 times.  $\text{H}_2$  pressure was adjusted to 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.5 MPa respectively, and chiral reaction was undertaken at 60 °C for 1.5 h. The output Y and e.e. value were determined by gas chromatography, and result was listed in Table 2.

As seen from Table 2, the conversion rate of  $\beta$ -chloro-propionophenone increased from 30% to 99% with the increasing of pressure. When pressure increased to 1.2 MPa, the catalyst activity almost never changed further, perhaps because the catalyst activity was related to the number of active hydrogen adsorbed in the surface of catalysts, when the pressure inside the reactor increased, the number of active hydrogen adsorbed in the surface of catalysts increased, and thus the catalytic activity increased. When the pressure attained a certain level, the active hydrogen would be in a state of saturation, and at this time, the number of active hydrogen adsorbed in the surface of catalysts would not increase with the increasing of pressure but tend to be stable. Enantioselectivity e.e. value first increased with the increasing of pressure and then decreased slightly when the pressure attained 1.2 MPa, which might be ascribed to the fact that the complex deformed in the surface of catalyst due to excessive high hydrogen pressure.

### 2.3 Effects of alkali concentration on Y and e.e. value of (S)-3-chloro-phenyl-1-propanol

The 0.5 g substrate  $\beta$ -chloro-propionophenone was dissolved in 20 mL isopropanol, and 15 mg catalyst  $\text{Fe}(\text{S-BINAP})_2$  (S, S-DPENDS) /  $\gamma\text{-Al}_2\text{O}_3$  was added subsequently. A certain amount of KOH was added to make the alkali concentration to be 0,  $2 \times 10^{-2}$ ,  $4 \times 10^{-2}$ ,  $6 \times 10^{-2}$ ,  $8 \times 10^{-2}$ ,  $10 \times 10^{-2}$  mol/L, respectively. After sealing the reactor, the  $\text{O}_2$  was replaced by high pure  $\text{N}_2$  for 3 times, and then  $\text{N}_2$  was replaced by  $\text{H}_2$  for 3 times.  $\text{H}_2$  pressure was adjusted to 1.2 MPa, and chiral reaction was undertaken at 60 °C, for 1.5 h. The output Y and e.e. value were determined by gas chromatography, and result was listed in Table 3.

As seen from Table 3, effect of KOH on catalyst activity was quite obvious, and the output of  $\beta$ -chloro-propionophenone was only 8.5% in the absence of KOH. When the KOH concentration was  $2 \times 10^{-2}$  mol/L, the catalyst activity increased rapidly, and its conversion rate attained 70%; When KOH concentration increased from  $2 \times 10^{-2}$  mol/L to  $4 \times 10^{-2}$  mol/L, the conversion rate increased rapidly from 70% to 99%, and after 1.5 h, the substrate converted completely. When KOH concentration increased continuously, the catalyst activity changed less. At the same time, high alkali concentration had a great impact on e.e. value of products, and e.e. value could increase to 90.5%. However, when KOH concentration was larger than  $4 \times 10^{-2}$  mol/L, e.e. value changed less. Therefore, KOH played double roles in not only enhancing catalyst activities but also improving the selectivity of enantiomers.

### 2.4 The recycling of catalysts

In order to study the life of the catalyst, recycling experiment was exerted, and experimental data statistic was listed in Table 4. 0.5 g substrate  $\beta$ -chloro-propionophenone was dissolved in 20 mL isopropanol, and 15 mg catalyst  $\text{Fe}(\text{S-BINAP})_2$  (S, S-DPENDS) /  $\gamma\text{-Al}_2\text{O}_3$  was added subsequently. A certain amount of KOH was added to make the alkali concentration to be  $1.63 \times 10^{-2}$  mol/L. After sealing the reactor, the  $\text{O}_2$  was replaced by high pure  $\text{N}_2$  for 3 times, and then  $\text{N}_2$  was replaced by  $\text{H}_2$  for 3 times.  $\text{H}_2$  pressure was adjusted to 1.2 MPa, and chiral reaction was undertaken at 60 °C for 1.5 h.

As seen from Table 4, after 6 cycles, the output of  $\beta$ -chloro-propionophenone decreased from 99% to 10.5%, the catalyst activities almost lost, but e.e. value of products changed less perhaps because several portion of catalysts lost during the process of cycling, and the catalysts exposed excessive long in the air which resulted in the oxidization of iron complexes.

## 3. Conclusions

Using  $\text{Fe}(\text{S-BINAP})_2$  (S, S-DPENDS) /  $\gamma\text{-Al}_2\text{O}_3$  as chiral catalysts, chiral fluoxetine intermediate S-3-Chlorine-1-phenyl propanol was prepared by catalytic hydrogenation of  $\beta$ -chloro-propionophenone, and its chemical output and optical yield were much higher with the yield of 99% and e.e. value of 90%. This process used iron to replace precious metals,  $\gamma\text{-Al}_2\text{O}_3$  as the carrier, and hydrogen as reducing agent, lowered cost and attenuated pollution, and thus was suitable for industrial mass production with certain scale.

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Table 1. Effects of temperature on the enantioselective hydrogenation

T (°C)	Y (%)	e.e. value (%)	R/S
0	48.5	91.2	S
25	63.0	90.5	S
40	70.2	90.4	S
60	99.3	90.4	S
80	99.2	86.5	S
100	99.1	70.0	S

Table 2. Effects of pressure on the enantioselective hydrogenation

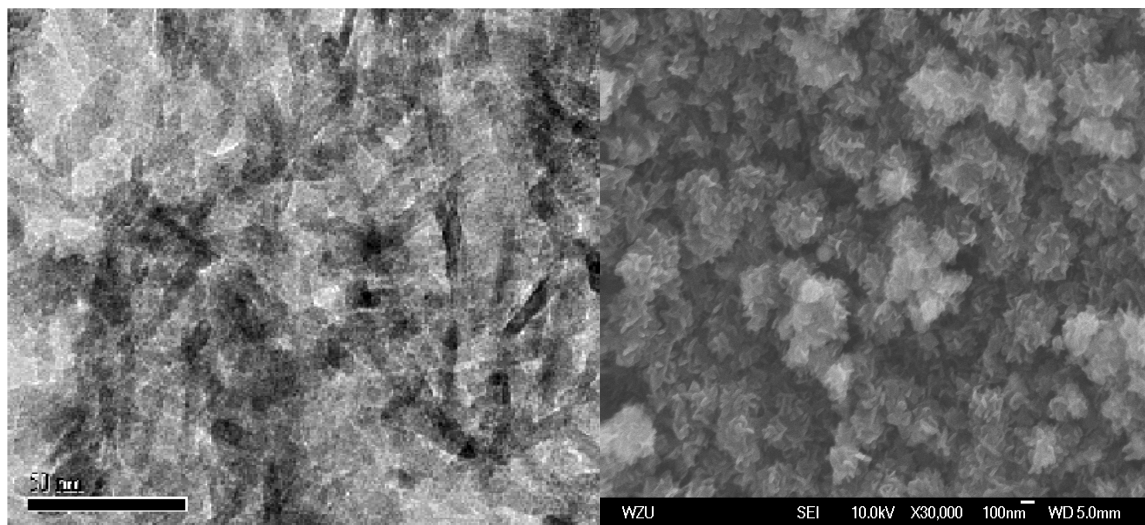
P (MPa)	Y (%)	e.e. value (%)	R/S
0.2	30.0	10.5	S
0.4	64.5	32.6	S
0.6	80.2	58.0	S
0.8	86.0	75.0	S
1.0	90.3	82.0	S
1.2	99.1	90.4	S
1.4	99.3	87.0	S
1.5	99.4	85.0	S

Table 3. Effects of KOH concentration on the enantioselective hydrogenation

$C_{\text{KOH}} \times 10^2$ mol/L	Y (%)	e.e. value (%)	R/S
0	8.50	6.50	S
2	70.0	88.2	S
4	99.0	90.4	S
6	98.3	89.0	S
8	99.0	90.0	S
10	93.5	90.5	S

Table 4. Catalyst recycling in asymmetric hydrogenation

Recycling number	Output (%)	e.e. value (%)	R/S
1	99.5	90.4	S
2	99.3	89.0	S
3	95.8	90.0	S
4	70.5	90.2	S
5	35.0	88.6	S
6	10.5	87.0	S

Figure 1. TEM and SEM of  $\text{Fe}(\text{S-BINAP})_2(\text{S,S-DPENDS}) / \gamma\text{-Al}_2\text{O}_3$