

Heterogeneous Catalytic Hydrogenation of Chiral Amino Acid Methyl Esters to Amino Alcohols with Retention of Configuration Over Mg-Modified Cu/ZnO/Al₂O₃ Catalyst

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Abstract Selective hydrogenation of amino acid methyl esters to chiral amino alcohols is an important and fascinating process. The $CuZn_{0.3}Mg_{0.1}AlO_x$ catalyst for the synthesis of chiral amino alcohols was prepared by the fractional co-precipitation method in the 50–100 g scale. The effect of the reduction gas on the catalytic activity, and the effects of the reaction conditions (R-p-m/Cat, temperature, reaction time, H₂ pressure and solvent) on the catalytic hydrogenation of R-phenylglycine methyl ester (marked as R-p-m)

were investigated. When R-p-m in the ethanol solvent was hydrogenated at 5 MPa of H₂ and 80 °C for 10 h over this catalyst reduced by H₂, 87.7% yield of R-phenylglycinol with ~100% ee value was obtained, and its reaction activation energy (E_a) was 36.7 kJ/mol. After repeated usage 16 times, its catalytic activity was hardly varied. Using this catalyst to catalyze the preparation of other amino alcohols, the high yield of product with ~100% ee value was obtained also.

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Graphical Abstract

CuZn_{0.3}Mg_{0.1}AlO_x

1 Introduction

Chiral amino alcohols are widely used chiral compounds and contained in many synthetic and natural products [1, 2], and often used as the intermediates in pharmaceutical industries, synthesis of insecticidal compounds and chiral auxiliaries [3–5]. And they are also popularly applied as chiral ligands in asymmetric catalysis and resolving agents in asymmetric synthesis [6–8]. Therefore, developing valid methods to synthesize chiral amino alcohols has extremely vital significance for chemists. Conventionally, chiral amino alcohols can be achieved by hydrogenation of amino acids or esters with metal hydrides [9-11], which can occur at low temperatures thereby retaining the integrity of the stereogenic center. However, most of the metal hydrides are only used for the preparation of amino alcohols in a scale of 100–150 g, and these routes suffer from the production of a large amount of salts, and using expensive or excessive reagents. In recent years, the precious metal catalysts were used to prepare chiral amino alcohols under relatively mild reaction conditions, such as Pt, Ru, Os oxide and their complexes [12–15]. Although the Pt catalyst was employed at lower temperature and not required to be reduced, these catalysts are

not only extremely expensive to mass production, but also its reactant conversion was relatively low [12]. But these catalytic systems are not commercially available. To overcome these problems, a high efficient, inexpensive and stable catalyst for the hydrogenation of chiral amino acids or esters is desperately needed. Therefore, we have developed the special structure Cu/ZnO/Al₂O₃ catalyst for the selective hydrogenation of L-phenylalanine methyl esters to L-phenylalaninol with high ee value [16–19], which will provide a new and green synthetic approach for the manufacture of chiral amino alcohols. Compared with the Pt catalyst, the $CuZn_{0.3}Mg_{0.1}AlO_x$ is not only very cheap, but also much higher reactant conversion and product yield with ~100% ee value can be obtained, although they need to be reduced before being used.

As a kind of chiral amino alcohols, chiral phenylglycinol has the extremely widespread application, and it and its derivatives can be used as the starting materials, chiral auxiliaries, protection reagents and ligands in the pharmaceutical, fine chemical industries and other fields [20–25]. For example, it can be used to prepare morpholine compounds to treat asthma and alleviate pain, indole compounds to resist atherosclerosis, isoquinoline drugs and so on [26]. Chiral phenylglycinol itself is a kind of high value-added fine chemical products.

In this paper, we used the inexpensive $CuZn_{0.3}Mg_{0.1}AlO_x$ heterogeneous catalyst prepared in a relatively big scale to catalyze the hydrogenation of

R-phenylglycine methyl ester to R-phenylglycinol, its reaction formula was described as follows and the effects of different reaction conditions on this catalytic hydrogenation were investigated. We also expanded the application of this catalyst for producing a series of other amino alcohols.



where R represents



2 Experimental Section

2.1 Catalyst Preparation

The $CuZn_{0.3}Mg_{0.1}AlO_x$ catalyst was prepared by the coprecipitation method [18], but we have enlarged the scale of preparing catalyst more than ten times, and the activity



Fig. 1 Effect of the calcination temperature on the catalyst performance. (Reaction conditions: 5 MPa H_2 , 1.0 g catalyst, 1.5 g reactant, at 80 °C for 10 h)

of this catalyst prepared was hardly decreased compared with the results reported [18]. In detail, the mixed solution (A) of 1.0 M Cu(NO₃)₂ and 1.0 M Zn(NO₃)₂, and 0.5 M Na₂CO₃ solution were co-precipitated at 70 °C under strong stirring by adjusting the flow rates of two solutions to keep pH=7.5. The mixed solution (B) of 1.0 M Al(NO₃)₃ and 1.0 M Mg(NO₃)₂, and 0.5 M Na₂CO₃ solution were coprecipitated under the same conditions above. Then (A) and (B) was mixed at 70 °C under strong stirring. After this synthesis solution was stirred for 2 h and cooled statically for 1 h, the catalyst precursor was filtrated and washed with deionized water until the filtrate was neutral, followed by dry at room temperature for 12 h and at 120 °C for 24 h. Finally, it was heated to 450 °C at 5 °C/min and calcined at 450 °C for 4 h. The calcined sample was pressed and crushed to 20-40 mesh.

2.2 Raw Material Preparation

3 g amino acid methyl ester hydrochloride was dissolved in deionized water, and pH of mixed solutions was controlled to 8 by adding 0.5 M Na_2CO_3 aqueous solution. After this mixed solution was extracted with ethyl acetate, the upper liquid was obtained. Then ethyl acetate was removed by rotary evaporation, and amino acid methyl ester was obtained as the raw material. All the chemicals were commercially available and used without further purification.

2.3 Testing of the Catalyst Activity

The activity of catalyst for hydrogenation of R-phenylglycine methyl ester was tested in a 0.5 L stainless steel autoclave under stirring at a speed of 500 rpm. After 1 g catalyst (20–40 mesh) was put in the reactor, the reactor was swept with H₂ five times to flush out air. Then the catalyst was reduced at 1 MPa H₂ and 250 °C for 4 h. After the autoclave was cooled in H₂ atmosphere to room temperature, 1.5 g R-phenylglycine methyl esters (R-p-m) diluted in 150 mL ethanol was added (R-p-m/Cat=1.5, wt.). The typical reaction conditions were at 5 MPa of H₂ and 80 °C for 10 h. After the reaction was ended, the autoclave was cooled in H₂ atmosphere to room temperature. Then solid catalyst was separated by centrifugation. The product was purified by column chromatography on

Table 1 The effect of reductiongas on the catalytic activity ofthe $CuZn_{0.3}Mg_{0.1}AlO_x$ catalyst

Entry	Reduction gas (mol)	Conv. (%)	Sel. (%)	Yield (%)	ee (%)
1	$H_2(10\%) + N_2(90\%)$	>99.9	45.9	45.9	>99.9
2	$CO(29.7\%) + N_2(10.1\%) + H_2(60.2\%)$	>99.9	71.9	71.9	>99.9
3	CO (1.51%) + N ₂ (98.49%)	>99.9	62.8	62.8	>99.9
4	H ₂	>99.9	80.4	80.4	>99.9

Reaction conditions: 4 MPa H2, 1.0 g catalyst, 1.5 g reactant, at 80 °C for 10 h



Fig. 2 Effect of the reaction condition on the yield of R-phenylglycinol over the CuZn_{0.3}Mg_{0.1}AlO_x catalyst: **a** R-p-m/Cat, **b** temperature, **c** reaction time, and **d** H₂ pressure. (Reaction conditions: **a** at

Table 2 Solvent effect on the yield of R-phenylglycinol over the $\text{CuZn}_{0.3}\text{Mg}_{0.1}\text{AlO}_x$ catalyst

Solvent	Methanol	Ethanol	Isopropanol	THF
Yield (%)	83.3	87.7	63.2	56.8

silica gel with ethyl acetate/methanol (3/2, v/v) as the eluent. Thus we obtained the light yellow powder product by rotary evaporation. Reactants and products were analyzed by High Performance Liquid Chromatograph (HPLC, Agilent 1260 Infinity) equipped with an ultraviolet detector and a column (Eclipse XDB-C18, 150×4.6 mm, 5 mm particle size), then the conversion of R-phenylglycine methyl ester (X), yield (Y) and chemoselectivity to R-phenylglycinol (S) were calculated [18, 19], in which the yield is the LC yield. And the ee value of products was determined by HPLC equipped with an ultraviolet detector (wavelength 258 nm) and a chiral column (CHIRALPAK AY-H, 250×4.6 mm, 5 µm particle size) [19].



80 °C and 5 MPa of H₂ for 10 h; **b** R-p-m/Cat=1.5, at 4 MPa of H₂ for 5 h; **c** R-p-m/Cat=1.5, at 80 °C and 4 MPa of H₂; and **d** R-p-m/Cat=1.5, at 80 °C for 10 h)



Fig. 3 Arrhenius plots of ln r against to 1/T for hydrogenation of R-phenylglycine methyl ester to R-phenylglycinol over the $CuZn_{0.3}Mg_{0.1}AlO_x$ catalyst

Table 3 Hydrogenation of R-phenylglycine methyl ester to R-phenylglycinol over the CuZn_{0.3}Mg_{0.1}AlO_x catalyst

Entry	Temp. (K)	W _{Catal} . (mg)	Time (h)	Conv. (%)	Yield (%)	Sel. (%)	ee (%)	$r \pmod{g^{-1} h^{-1}}$
1	333	1000	0.5	21.9	10.2	46.5	>99.9	1.85
2	343	1000	0.33	13.2	10.1	76.5	>99.9	2.76
3	353	1000	0.5	29.8	18.4	61.7	>99.9	3.34
4	363	1000	0.17	12.2	10.8	88.5	>99.9	5.91
5	373	1000	0.33	29.9	28.4	94.9	>99.9	7.74



Fig. 4 Repeated usage of the $CuZn_{0.3}Mg_{0.1}AlO_x$ catalyst in the hydrogenation of R-phenylglycine methyl ester at 80 °C and 5 MPa H₂ for 10 h (R-p-m/Cat=1.5, wt.). Experimental errors of the conversion and yield are within $\pm 2\%$

 ^{1}H R-phenylglycinol (product): NMR (Bruker AVANCE-III 500, CDCl₃) & 7.43-7.22 (m, 5H), 4.07 (dd, J=8.4, 4.4 Hz, 1H), 3.77 (dd, J=10.7, 4.4 Hz, 1H), 3.58 (dd, J=10.7, 8.4 Hz, 1H), 2.16 (s, 3H). FT-IR (Nicolet iN10 FT-IR spectrometer, KBr): 3330, 3275, 1604, 1497, 1453, 1361, 1198, 1080, 1050, 759, 702, 532 cm⁻¹. (3S, 6R)-3,6-diphenylpiperazine-2,5-dione (byproduct): ^{1}H NMR (CDCl₃) δ 7.58 (s, 2H), 7.45 (d, J=10.0 Hz, 4H), 7.36 (d, J = 10.0 Hz, 4H), 7.33 (d, J = 5.0 Hz, 2H), 6.74 (s, 2H). FT-IR (KBr): 3342, 3203, 1705, 1679, 1610, 1490, 1206, 1043, 795, 760, 705, 564 cm⁻¹.

3 Results and Discussion

3.1 Pretreatment of the Catalyst

Prior to reaction, the catalyst was treated by different reduction gases under the same reaction condition, and their effects on the activity of the $CuZn_{0.3}Mg_{0.1}AlO_x$ catalyst are shown in Table 1. The results show that the catalyst reduced by pure H₂ exhibited the best catalytic activity with 80.4% selectivity to product. Thus we selected pure

 H_2 as the reduction gas for the CuZn_{0.3}Mg_{0.1}AlO_x catalyst. The effect of the calcination temperature of the catalyst on its activity was tested also and the results are shown in Fig. 1, which shows that the appropriate calcination temperature is 450 °C.

We have compared the catalytic performance of the $CuZn_{0.3}Mg_{0.1}AlO_x$ catalyst with industrial Copper catalyst used in the manufacture of hydrogen (HTCB-7), ammonia (HT-CB5/9) and methanol (MS-2) from Liaoning Haitai Sci-Tech Development Co., Ltd. (China). The results showed that they exhibited poor performances with very low yield (<10%) of amino alcohols, which should be ascribed to the different compositions and preparation methods [16–18].

3.2 Effect of the Reaction Condition

Figure 2a shows the effect of the catalyst amount (R-p-m/ Cat) on the yield of R-phenylglycinol at 80 °C and 5 MPa of H₂ for 10 h. The results show that with the increase in the catalyst amount from R-p-m/Cat = 1.15 to 1.5, the yield of R-phenylglycinol was increased, and when R-p-m/Cat was >1.5, the product yield was obviously reduced with increasing the catalyst amount. The optimized catalyst amount should be R-p-m/Cat = 1.5, which was adopted in the following experiments.

The influence of the reaction temperature on the yield of R-phenylglycinol was tested in 4 MPa of H₂ for 5 h. As shown in Fig. 2b, the yield of R-phenylglycinol was increased with the increase in the reaction temperature from 60 to 80 °C. When the reaction temperature was >80°C, the yield of the target product decreased. Therefore, the appropriate reaction temperature is 80 °C. The effect of the reaction time on the R-phenylglycinol yield is shown in Fig. 2c at 80 °C and 4 MPa of H_2 . With the increase in the reaction time from 2 to 10 h, the product yield was obviously increased, and after the reaction time was >10 h, the increase of yield tended to be gentle. Thus the appropriate reaction time should be 10 h when the reaction was operated at 80 °C. The effect of the hydrogen pressure was tested at 80 °C for 10 h, and the results (Fig. 2d) show that the product yield was increased with increasing H_2 pressure, and when H_2 pressure was 5 MPa, the highest

Fable 4	1	Hy	drogen	ation of	of various	amino aci	d methy	l esters o	ver the	CuZn _{0.3}	$Mg_{0.1}A$	AlO _x ur	nder optimal	reactio	n conditions
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Entry	Amino acid methyl ester	Amino alcohol	Conv. (%)	Sel. (%)	Yield (%)	ee (%)	Main byproduct
1		ИН2 ОН	>99.9	59.3	59.3	>99.9	
2		NH ₂ OH	>99.9	57.4	57.4	>99.9	
3			>99.9	60.6	60.6	>99.9	
4	NH ₂ 0	NH ₂ T OH	>99.9	63.2	63.2	>99.9	
5	OH O NH ₂	OH NH ₂ OH	>99.9	67.2	67.2	>99.9	
6	NH ₂ O	NH ₂ OH	>99.9	87.7	87.7	>99.9	
7		NH ₂ OH	>99.9	80.1	80.1	>99.9	O NH HN TO O
8		HO NH2. HCI	>99.9	22.7	22.7	>99.9	HO HN INH OH

Reaction conditions: 5 MPa H₂, 1.0 g catalyst, 1.5 g reactant, at 80 °C for 10 h

yield was obtained. Hence 5 MPa of H_2 pressure should be most appropriate.

Based on the results mentioned above, the appropriate reaction conditions can be determined to be R-p-m/ Cat=1.5 at 5 MPa of H₂ and 80 °C for 10 h. Under these reaction conditions, the yield of R-phenylglycinol can reach 87.7% and its ee value is ~100% obtained by HPLC.

The solvent effect on this catalytic reaction was also examined and results are shown in Table 2. In comparison with other solvents (methanol, isopropanol and THF), when ethanol was used as a solvent, the highest product yield (87.7%) could be obtained.

3.3 The Calculation of Activation Energy (E_a)

The activation energy (E_a) for hydrogenation of R-phenylglycine methyl ester to R-phenylglycinol over the CuZn_{0.3}Mg_{0.1}AlO_x catalyst was calculated based on the data of the temperature effect in Table 3, in which the formation rate (*r*) of product and reactant conversion were below 30%. Based on Arrhenius plots of ln *r* against to 1/T (Fig. 3), the E_a value was calculated to be 36.7 kJ/mol. This result indicates that $CuZn_{0.3}Mg_{0.1}AIO_x$ is an excellent catalyst for hydrogenation of R-phenylglycine methyl ester, due to its relatively low activation energy.

3.4 Repeated Usage of the Catalyst

The stability of the $CuZn_{0.3}Mg_{0.1}AlO_x$ catalyst was tested by repeated usage. The results in Fig. 4 show that the catalyst has the good operation stability, and after repeated usage 16 times, the performance of the catalyst was hardly changed and the product yield was kept at 85.6–87.7%.

3.5 Hydrogenation of Different Amino Alcohols

To know the applicability of the $\text{CuZn}_{0.3}\text{Mg}_{0.1}\text{AlO}_{x}$ catalyst for the hydrogenation of other amino acid methyl esters to prepare amino alcohols, eight kinds of amino acid methyl esters were used as the reactants (Table 4). The concentrations of the reactants and products were analyzed by GC (FULI GC-7970) equipped with FID and a polar capillary chromatographic column (AE PEG-20 30 m×0.32 mm×0.5 µm). As shown in Table 4, when

eight kinds of reactants were catalytically hydrogenated, the corresponding eight kinds of amino alcohols (L-leucinol, D-valinol, L-isoleucinol L-alaninol, L-threoninol, R-phenylglycinol and L-phenylalaninol) can be obtained with relative high yields without racemization, which shows that the $CuZn_{0.3}Mg_{0.1}AlO_x$ catalyst exhibited also the high catalytic activity for other seven reactants besides L-tyrosinol hydrochloride (Table 4, entry 8), because the chloride ion may lead to a deactivation of the catalyst [27] and a low yield of L-tyrosinol hydrochloride. The byproducts of these reactions are show in Table 4. The products of the eight kinds of amino alcohols were all kept their own original configuration with high ee value. The main reason is that the coordination adsorption of amino acid methyl esters onto the catalyst active sites in the whole reaction process did not vary their configurations [19].

4 Conclusions

In summary, the CuZn_{0.3}Mg_{0.1}AlO_x catalyst was prepared in a relatively large scale by the fractional co-precipitation method under the conditions of aging at 70 °C for 2 h and calcination at 450 °C for 4 h. Using this catalyst reduced by H₂, 87.7% yield of R-phenylglycinol with ~100% ee value could be obtained by the hydrogenation of R-phenylglycine methyl ester (R-p-m) at 80 °C and 5 MPa of H₂ for 10 h with R-p-m/Cat=1.5(wt.). The reaction activation energy (E_a) is 36.7 kJ/mol. After repeated usage 16 times, its catalytic activity was hardly varied. When this catalyst was used to catalyze the preparation of other seven kinds of amino alcohols, the high yield of product with ~100% ee value can be obtained also. The CuZn_{0.3}Mg_{0.1}AlO_x is an efficient heterogeneous catalyst for hydrogenation of amino acid methyl esters to amino alcohols in ethanol.

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