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Synthesis of D-pantolactone via Combined a Novel Organocatalyst Catalyzed Asymmetric Aldol Reaction and Hydrogenation Catalyzed by Cu-/SiO_2

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Abstract: The combination of an asymmetric organocatalytic aldol reaction with a subsequent hydrogenation for the synthesis of D-pantolactone is demonstrated. This process consists of an initial aldol reaction catalyzed by a novel chiral L-histidine-modified-ionic-liquid- [EMIm] [His], which has been designed and synthesized as an efficient recoverable catalyst for the asymmetric aldol reaction with superior enantioselectivity in CH_2Cl_2, than L-histidine itself. [EMIm] [His] retains its activity and enantioselectivity over at least five reaction cycles, and its universal applicability has been demonstrated. Moreover optimum process of Cu-/SiO_2-catalysed hydrogenation of condensation product- (D) -3- formyl -2- hydroxy -3- ethyl butyrate to obtain D-pantolactone has been established allowing the synthesis of D-pantolactone in >99% purity, 93% yield and 93% enantiomeric excesse (ee). The results show that CuO-CeO_2/SiO_2 exhibits better catalytic activity than CuO/SiO_2 for better dispersion and larger surface area, and the best reaction conditions are as follows: 120°C, *n* (H_2): *n* (isobutylaldehyde) =80:1, P (H_2) =8.0 MPa, liquid airspeed: 0.6 h^{-1}.

Keywords: Asymmetric Aldol Reaction, Organocatalyst, L-Histidine-Modified-Ionic-Liquid, D-Pantolactone, Cu-/SiO_2, Hydrogenation

1. Introduction

D-pantolactone continues to be of interest to organic chemists due to its wide use as a chiral auxiliary [1-3] and an important intermediate in the synthesis of calcium D-pantothenate ($C_{18}H_{32}CaN_2O_{10}$) [4] which has the function of making antibodies [5] and is needed for the biosynthesis of CoA [6]. The mainly existing methods of the synthesis of D-pantolactone are based on the resolution of racemate [6] or asymmetric hydrogenation of the precursor of D-pantolactone [7], the drawbacks of both are the long and complicated technologies, which have led to the need for calcium D-pantothenate to be imported so far. The precursor of D-pantolactone is mainly synthesized by aldol reaction as a key step that has promoted a rapid development of numerous highly enantioselective chiral catalysts [8-10]. In nature, small organic molecules, in particular amino acids [11-13] and their derivatives [14-17], are rich chiral sources, which are used as the catalysts, but with recycling problems, such as extensive work-up procedures with the corresponding waste generation or more time to recover the catalyst between two cycles [18-20]. However ionic liquids (ILs) have been widely used as environmentally benign solvents to replace common organic media [21] with advantages of reusable, strong design ability, low pollution, low toxicity, and excellent miscibility with organic compounds [22-24]. Because of the above-mentioned highly tunable characteristics (broad cation/anion combinations) and the enhancement of reaction efficiency by using ILs as solvents [25-26], ILs have gained wide recognition in specific engineering, especially as catalysts to

catalyze aldol reactions [27-28]. So far poline-related-catalyzed asymmetric aldol reactions have been investigated extensively [29-31], but there are few reports on grafting L-histidine onto IL. Herein, L-histidine was selected and grafted onto IL to get a novel type of recyclable catalyst which can be recovered quickly and simply between two cycles by solubility difference between substrate, solvent and the product mixture as illustrated in Figure 1.

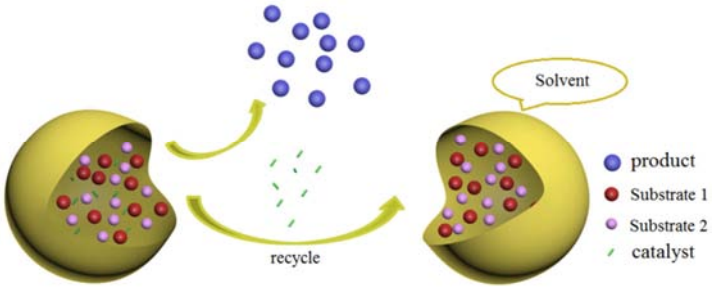

Figure 1. *General concept of ionic-liquid-supported catalysis.*

Cu-based catalyst had been widely known to activate hydrogen molecules and employed as hydrogenation catalysts, because of their high selectivity and stability [32-34]. So we synthesized CuO/SiO_2 and $CuO\text{-}CeO_2/SiO_2$ to catalyze the asymmetric hydrogenation reaction. Under the optimized condition of asymmetric hydrogenation for precursor-(D) -3- formyl -2- hydroxy -3- ethyl butyrate to obtain D-pantolactone with purity more than 99%, 93% yield and 93% ee, which lends this route a bright prospect in future industrial production.

2. Experimental

2.1. General Remarks

All reagents were obtained from commercial sources and used without further purification except for isobutanal, which was distilled before use and took 40~42°C distillate, and deionized water was always needed. ^1H NMR spectra was recorded on a 500 MHz instrument (kerAvance 500). Chemical shift was reported in parts per million (ppm, δ) downfield from residual $CHCl_3$ signal (δ (1 H), 7.26 ppm). Proton coupling patterns were described as singlet (s), multiplet (m). The aldol product- (D) -3- formy l -2- hydroxy -3- ethyl butyrate was also characterized by gas chromatograph-mass spectrometer (GC-MS) with a DB-35 ms column. The temperature was regulated at 60°C for 2 min, heated to 260°C at 10°C/min, and maintained at 260°C for 5 min. D-pantolactone was characterized by GC-MS with the above-mentioned settings, but the temperature was different which was regulated at 70°C for 2 min, heated to 250°C at 10°C/min, and maintained for 5 min. Ee values of D-pantolactone and (D) -3- formyl -2- hydroxy -3- ethyl butyrate were determined using WZZ-2 S digital automatic polarimeter with water and $CHCl_3$ were used as solvents respectively. Quantitative gas chromatography (GC) for conversion determination of (D) -3- formyl -2- hydroxy -3- ethyl butyrate was carried out on PEG column (30 m× 0.22 mm × 0.25 μm) at 240°C (isotherm, 4 min) with N_2 as a carrier gas. The conversion of D-pantolactone was also determined with the above-mentioned settings, just a different temperature (220°C).

The X-ray diffraction patterns were recorded on D-MAX 2500-PC (Rigaku Corp.) operated at 50 kV and 200 mA equipped with nickel-filtered Cu Kα radiation (λ=1.5418 Å). The SEM images of $Cu\text{-}/SiO_2$ were recorded on a scanning electron microscope (JEOL-6700 F, Japan Electron Co., Ltd.)

2.2. Preparation of Ionic-Liquid-Supported-Catalyst-[EMIm] [His]

As synthesis procedure [35], to 40 mL of bromic ether and 40 mL of ethyl acetate was added a mixed solution containing 20 mL of N- methyl imidazole and 20 mL of acetate. The reaction mixture was heated at room temperature for 6 h under magnetic stirring and refluxing. The white precipitate was then added a mixed solution containing 20 mL of methyl cyanide and 70 mL of ethyl acetate for recrystallization. The intermediate- [EMIm] Br was obtained with 92% yield. 1H NMR (CDCl3, 500 MHz):δ10.21 (s, 1H, NCHN), 7.66 (s, 1H, NCH), 7.37 (s, 1H, NCH), 4.45 (t, 2H, NCH2), 4.13 (s, 3H, NCH3), 1.62 (t, 3H, CH3).

[EMIm] OH was prepared according to the following method: to 5.73 g (0.03 mol) of [EMIm] Br was added appropriate amount of isopropyl alcohol. The reaction mixture was added equivalent molar of KOH and heated at 323 K under magnetic stirring for 10 h. After filtered and evaporated, the mixture was dissolved in CH_2Cl_2, then added appropriate amount of active carbon under magnetic stirring for 10 h. Subsequently, the mixture was filtered, evaporated solvent, extracted with ether for three times, and then dried in vacuum for 10 h.

To an aqueous solution of 4.65 g (0.03 mol) of L-histidine was added appropriate amount of an aqueous solution of [EMIm] OH. The reaction mixture was heated at room temperature under magnetic stirring for 24 h. After evaporating solvent, the buff precipitate was added a mixed solution containing 60 mL of acetonitrile and 10 mL methanol at room temperature under vigorous magnetic stirring for 2 h. The solid was filtered and evaporated to remove the unreacted L-histidine and solvent, dried in vacuum at 353 K for 24 h, then [EMIm] [His] was obtained. 1H NMR (CDCl3, 500MHz):δ1.52 (t, 3H, CH3), 1.93-2.09 (m, 2H), 3.07 (m, 2H), 3.90 (s, 1H), 4.23 (s, 3H, NCH3), 4.49 (t, 2H, NCH2), 6.86 (m, 1H), 7.72 (s, 1H, NCH), 7.77 (s, 1H), 7.89 (s, 1H),

10.11 (s, 1H, NCHN).

2.3. General Procedure for [EMIm] [His]-Catalyzed Aldol Reaction Using Ethyl Glyoxylate and Isobutanal

To a solution of 2.04 g (0.01 mol) of ethyl glyoxylate and 10- 40 mol% (each with reference to ethyl glyoxylate) of [EMIm][His] in 2 mL solvent was added 0.86 g (0.012 mol) of isobutanal all at once and reacted for 5-72 h under magnetic stirring. The reaction mixture was washed with deionized water (10 mL×3), extracted with ethyl acetate (10 mL×3), dried over anhydrous magnesium sulfate. Colorless oily viscous liquid - (D) -3- formy l -2- hydroxy -3- ethyl butyrate was obtained. ^{1}H NMR ($CDCl_3$, 500MHz):δ1.26 (s, 3H, -CH_3), 1.27 (s, 3H, -CH_3), 3.58 (s, 1H, OH), 4.32 (m, 2H, -CH_2-), 4.37 (s, 1H, -CH-), 9.62 (s, 1H, -CHO). GC (quantitative, GC 6890): tr=13.490 min.

2.4. Preparation of Cu-/SiO_2

The preparation of CuO/SiO_2 was prepared via the method of co-precipitation. Aqueous solution of Cu $(NO_3)_2{\cdot}3H_2O$ and aqueous solution of NaOH were added slowly into a three-necked flash under vigorous stirring at 45°C, then silica sol was added to the precipitation system. Finally, the resulting suspension was aged at 80°C for 6 h under stirring, and then filtered and washed with a large amount of deionized water. The precipitates were dried overnight and calcined for 6 h at 500°C in air to obtain the final catalyst. $CuO–CeO_2/SiO_2$ was prepared the same way as CuO/SiO_2, except for adding an appropriate amount of $H_{12}CeN_3O_{15}$ solution.

2.5. General Procedure for the Synthesis of D-pantolactone

D-pantolactone was obtained by (D) -3- formyl -2- hydroxy -3- ethyl butyrate via a fixed bed continuous hydrotreating catalyzed by CuO/SiO_2 and $Cuo-CeO_2/SiO_2$ under the conditions of 80-160°C, *n* (H_2) (2-9Mpa): *n* (isobutanal) = 40-100:1, liquid airspeed 0.6-1.4 h^{-1} and vacuum distillation (0.096 MPa) [36]. GC-MS:t_r=7.379min, *m*/*z*=71 (-C_4H_7O) (*m*/*z*=57 (-C_3H_5O), *m*/*z*=14 (-CH_2)), *m*/*z*=59 (-$C_2H_3O_2$) (*m*/*z*=43 (-C_2H_3O), *m*/*z*=16 (-CH_2)).

3. Results and Discussion

We systematically tested some L-amino acids in the aldol addition of isobutanal to ethyl glyoxylate, and the results are depicted in Table 1. The relatively high yield and ee (entry 1, Table 1) demonstrated the suitability of L-histidine as a catalyst for this reaction. We thus selected L-histidine to graft onto IL to get a novel type of recyclable catalyst according to Figure 2.

Table 1. *L-amino acids catalyzed aldol reaction.*

Entry	L-amino acid	Solvent[a]	Reaction time[b] (h)	Catalyst content[c] (mol%)	Yield[d] (%)	Ee (%)
1	histidine	glycol	24	30	77	73
2	leucine	DMSO	10	30	57.8	57
3	isoleucine	DMSO	10	30	74.2	71
4	prolinamide	CH_2Cl_2	36	35	68	83
5	alanine	DMSO	10	50	67	63
6	valine	DMSO	10	50	71	70
7	lysine	DMSO	12	50	88	12
8	asparagine	DMSO	10	50	72	75
9	arginine	DMSO	14	50	72	14
10	phenylalanine	DMSO	10	50	73	69

To a solution of 0.01 mol of ethyl glyoxylate and 10-60 mol% (each with reference to ethyl glyoxylate) of L-amino acid in 2 ml solvent was added 0.012 mol of isobutanal all at once and reacted for 5-72 h under magnetic stirring. [a] Optimal solvent, [b] optimal reaction time, [c] optimal catalyst content, [d] isolated yield.

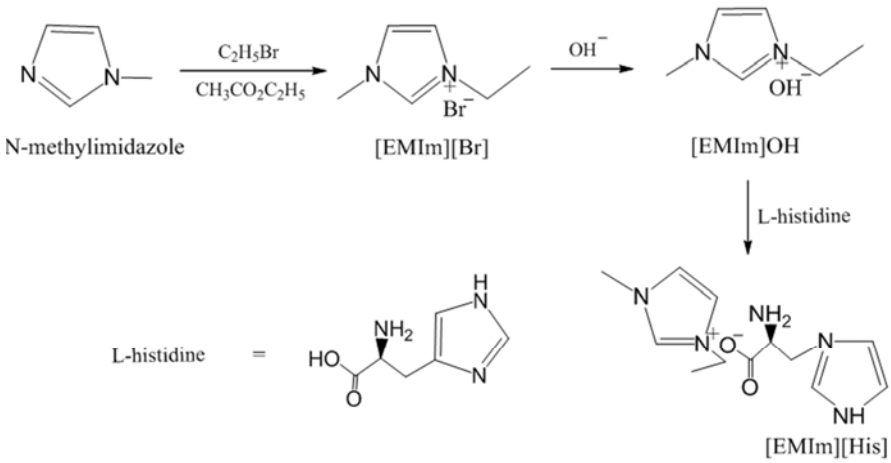

Figure 2. *Schematic illustration of synthesis of [EMIm] [His].*

3.1. The Influence of Solvent, Reaction Time, and Catalyst Content on the Aldol Reaction Rate Catalyzed by [EMIm] [His]

To clarify role of solvent, reaction time, and catalyst content in [EMIm] [His]-catalysted aldol reaction, we varied the above-mentioned factors. As the results shown in Figure 3-5, maximum yield and ee were reached when the reaction was performed using CH_2Cl_2 as solvent. A lower yield of aldol product was isolated when more than 30 mol% of [EMIm] [His] was used in the reaction. Meanwhile, it was found that the reaction was accomplished as the reaction was carried out for 30 h.

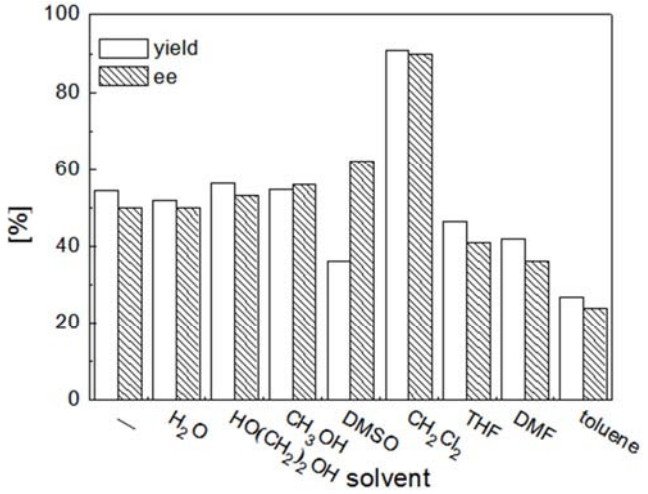

Figure 3. *Influence of solvent on the reaction rate catalyzed by [EMIm] [His]. Reaction conditions: catalyst content, 30 mol%; reaction time, 30 h.*

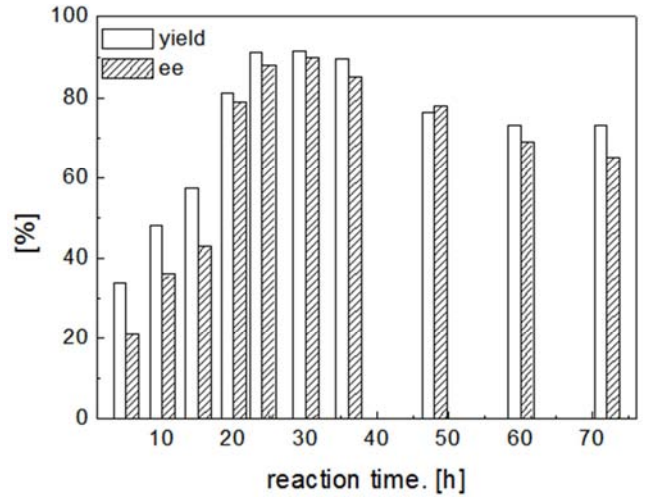

Figure 4. *Influence of reaction time on the reaction rate catalyzed by [EMIm] [His]. Reaction conditions: solvent, CH_2Cl_2; catalyst content, 30 mol%.*

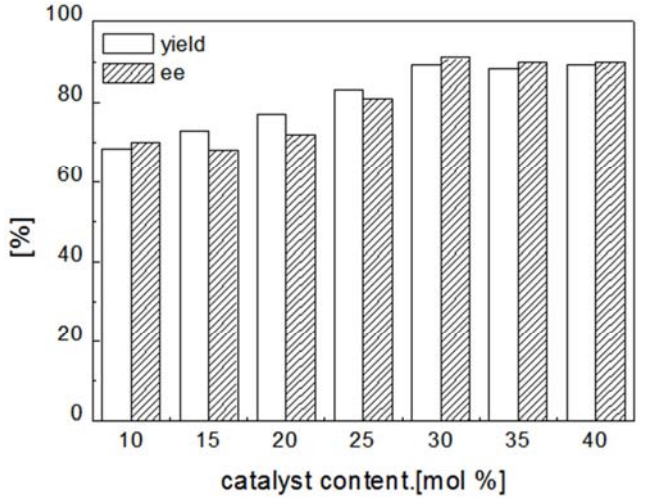

Figure 5. *Influence of catalyst content on the reaction rate catalyzed by [EMIm] [His]. Reaction conditions: solvent, CH_2Cl_2; reaction time, 30 h.*

3.2. Studies on the Universality of [EMIm] [His]

To test the general scope of the prepared [EMIm] [His] as catalyst, a series of enolizable aldehydes were subjected to the same reaction conditions except for the solvent (see Figure 6, Table 2 in the supporting information).

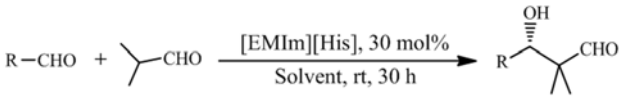

Figure 6. *[EMIm] [His]-catalyzed aldol reaction between enolizable aldehydes.*

Table 2. *[EMIm] [His] and L-histidine catalyzed aldol reactions.*

Entry	R	Optimal solvent	Yield (%)	Ee (%)
1	EtO_2C	CH_2Cl_2	91 (77 [a])	95 (73 [b])
2	$ClCH_2$	DMSO	68 (44 [a])	89 (72 [b])
3	$(MeO)_2CH$	DMSO	89 (91 [a])	99 (99 [b])
4	$(Me)_2CHCH_2$	DMSO	41 (40 [a])	99 (97 [b])
5	2-$NO_2C_6H_4$	DMSO	71 (54 [a])	59 (46 [b])
6	4-BrC_6H_4	DMSO	65 (60 [a])	73 (71 [b])
7	Ph	acetone	49 (49 [a])	53 (48 [b])
8	4-CNC_6H_4	acetone	61 (45 [a])	60 (52 [b])
9	2-ClC_6H_4	acetone	90 (88 [a])	59 (60 [b])
10	4-NO_2-C_6H_4	acetone	80 (53 [a])	65 (70 [b])

[a]Yield of aldol products catalyzed by L-histidine, [b]ee of aldol products catalyzed by L-histidine.

We can see from Table 2 that the result was rather poor compared to that from the unsupported L-histidine under almost identical condition except for solvent. The aldol reactions catalyzed by two catalysts afforded nearly similar yields and ee values (entry3, 4, 6, 7, 9). [EMIm] [His]-catalyzed aldol reaction in CH_2Cl_2 using ethyl glyoxylate as enolizable aldehyde afforded highest yield and ee of aldol product (entry 1). In contrast to L-histidine as catalyst, the difference in yield and ee were up to 14% and 22% respectively. Those rendered

[EMIm] [His]-catalyzed aldol reactions performed superior results than L-histidine itself.

3.3. Studies on the Recycle of [EMIm] [His]

We have also evaluated the recyclability of [EMIm] [His] as catalyst. The reaction between ethyl glyoxylate and isobutanal (entry 1, Table 2) shown the highest yield and ee, so they were served as a model reaction for the evaluation of [EMIm] [His]. When the first run of the reaction was completed, the reaction mixture was concentrated and rinsed with water for three times, extracting with ethyl acetate, drying, and recovering [EMIm] [His]. Fresh starting materials were charged into the reaction system, and the reaction still proceeded well. [EMIm] [His] was recycled five repetitive cycles with only minor decreases in product yields, but always maintenances ee value (see Figure 7 in the supporting information).

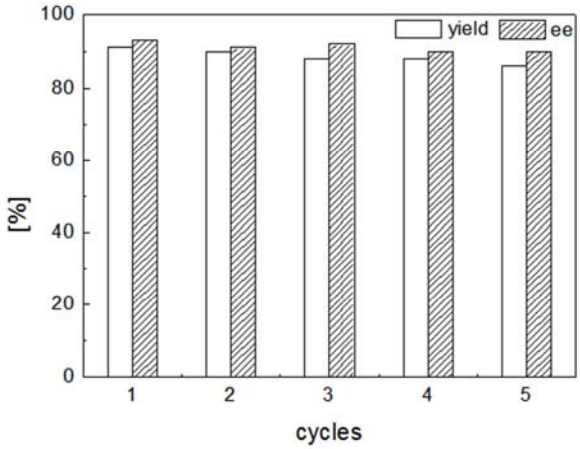

Figure 7. *Reuse of [EMIm] [His]. Reaction conditions: solvent, CH_2Cl_2; reaction time, 30 h; catalyst content, 30 mol%.*

3.4. Cu-/SiO_2 Characterization

The powder x-ray diffraction patterns of Cu-/SiO_2 samples were shown in Fig. 8. From the XRD patterns, it can be observed that Cu-/SiO_2 samples had retained CuO structure, by exhibiting three diffraction peaks at 2θ values around 35.7°, 38.8° and 48.6°. CuO–CeO_2/SiO_2 shown relatively weak characteristic peaks of CuO in comparison with CuO/SiO_2, indicating the former had a smaller average particle size and better dispersion than the latter.

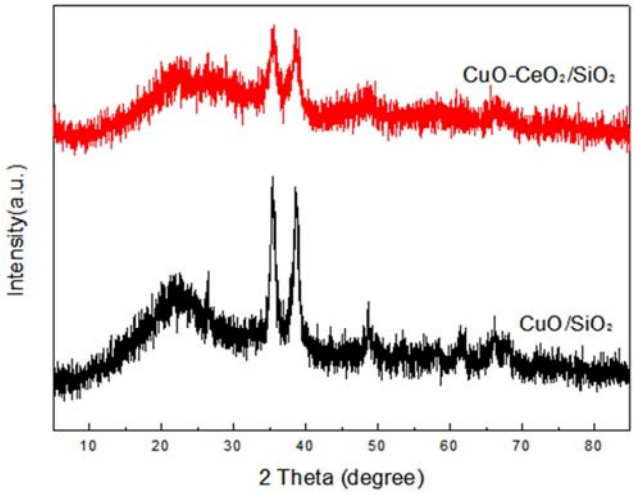

Figure 8. *XRD patterns of CuO/SiO_2 and CuO-CeO_2/SiO_2.*

SEM image of the Cu-/SiO_2 samples were depicted in Fig. 9. The morphology of the Cu-/SiO_2 samples were well dispersed with excellent resolution.

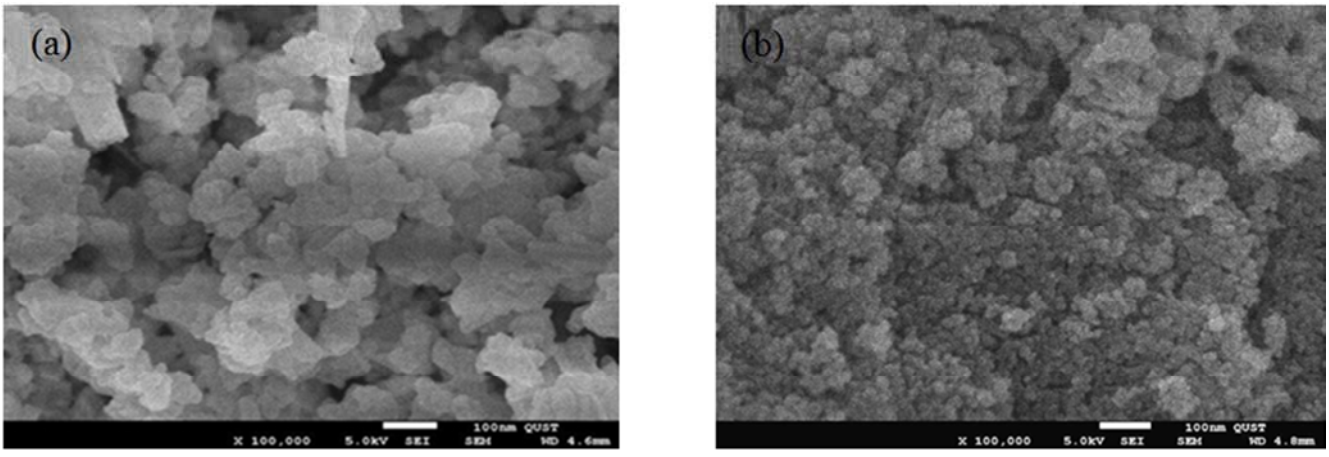

Figure 9. *SEM images of CuO/SiO_2 (a) and CuO–CeO_2/SiO_2 (b).*

3.5. The Influence of Temperature, H_2 Pressure, Liquid Airspeed, and Molar Ratio of H_2 to Isobutanal on the Hydrogenation Catalyzed by Cu-/SiO_2

The Influence of temperature, H_2 pressure, liquid airspeed, and molar ratio of H_2 to isobutanal on the hydrogenation catalyzed by Cu-/SiO_2 were shown in Figure 10-13, maximum yield of D- pantolactone was reached when the reaction was performed in 120°C, molar ratio of H_2 to isobutanal was 80:1, liquid airspeed was around 0.6 h^{-1}, and H_2 pressure was 8 MPa. Meanwhile, it was found that the catalytic activity of CuO-CeO_2/SiO_2 was generally higher than that of CuO/SiO_2.

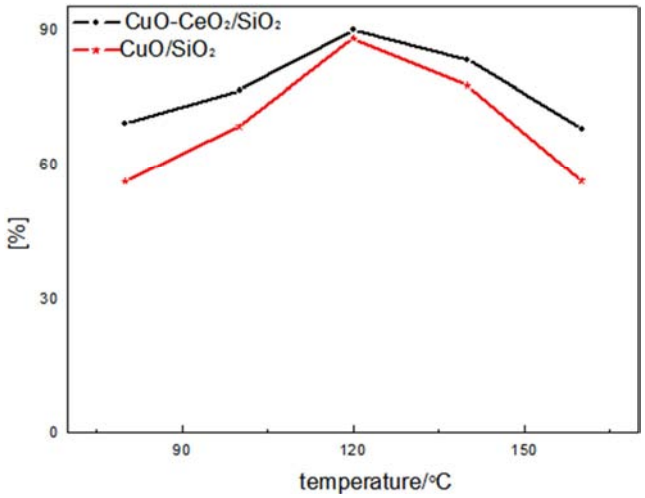

Figure 10. *Influence of reaction temperature on the yield of D-pantolactone. Reaction conditions: n (H_2):n (isobutanal), 80:1; H_2 pressure, 8 MPa; and liquid airspeed, 0.6 h^{-1}.*

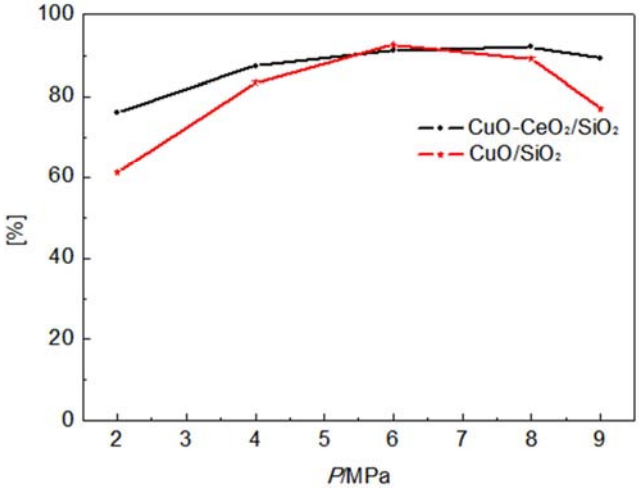

Figure 11. *Influence of H_2 pressure on the yield of D-pantolactone. Reaction conditions: n (H_2):n (isobutanal), 80:1; liquid airspeed, 0.6 h^{-1}; and temperature, 120°C.*

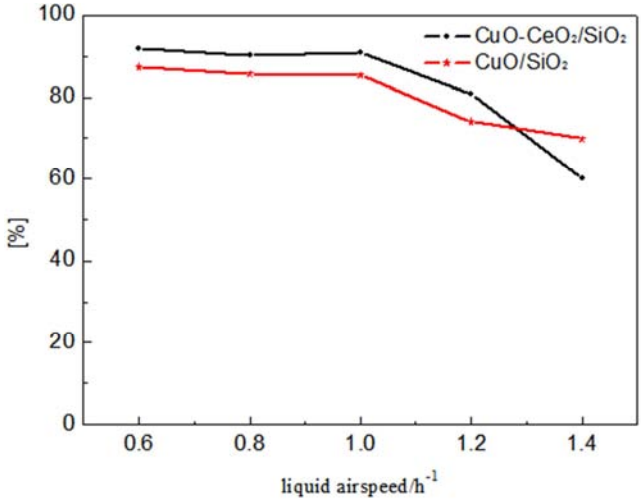

Figure 12. *Influence of liquid airspeed on the yield of D-pantolactone. Reaction conditions: temperature, 120°C; n (H_2):n (isobutanal), 80:1; and H_2 pressure, 8 MPa.*

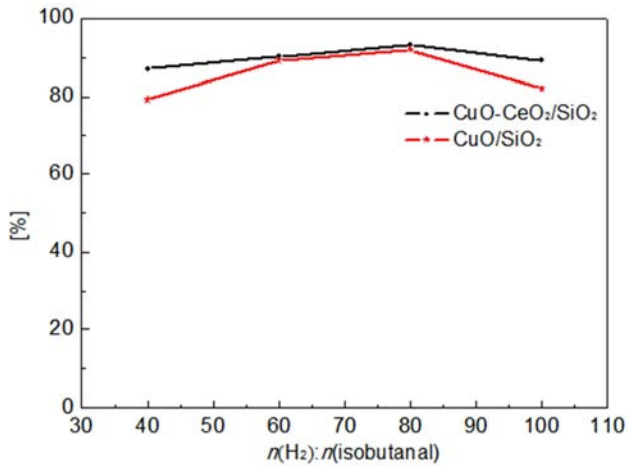

Figure 13. *Influence of molar ratio of H_2 to isobutanal on the yield of D-pantolactone. Reaction conditions: liquid airspeed, 0.6 h^{-1}; temperature, 120°C; and H_2 pressure, 8 Mpa.*

4. Conclusions

In conclusion, we have developed a chiral ionic liquid containing L-histidine unit for asymmetric aldol reaction. The aldol reaction was carried out in the presence of [EMIm] [His] (30 mol%) at room temperature. The reactions generated the corresponding products with satisfactory isolated yields and ee. It is noteworthy that [EMIm] [His] are recycled up to five times with only minor decreases in product yields, but always maintenances in ee, and its universal applicability has been demonstrated. Moreover we optimize process of CuO/SiO_2 and $CuO\text{-}CeO_2/SiO_2$-catalysed hydrogenation of condensation product - (D) -3- formyl -2- hydroxy -3- ethyl butyrate to synthetize D-pantolactone in a purity of >99%, yield of 93% and high ee of 93% under a reaction temperature of 120°C, H_2 pressure of 8 MPa, H_2 to isobutanal molar ratio of 80:1, and liquid airspeed of 0.6 h^{-1}. Meanwhile, we find that the catalytic activity of $CuO\text{-}CeO_2/SiO_2$ is generally higher than that of CuO/SiO_2 for hydrogenation.

Acknowledgements

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