

Promotional Effect of Tertiary Amine on Asymmetric Catalytic Hydrogenation of Ethyl Pyruvate Over Pt/Al₂O₃ in Acetic Acid

GUOZHONG TAO, GUANZHONG LU*, YUN GUO, YANQIN WANG and YANGLONG GUO

Key Laboratory for Advanced Materials, Research Institute of Industrial Catalysis,
East China University of Science and Technology,
130, Meilong Road, Shanghai 200237, P.R. China
Fax: (86)(21)64252923; Tel: (86)(21)64253703

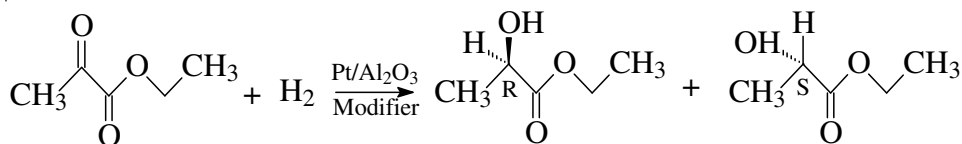
E-mail: gzhlu@ecust.edu.cn; gzhlu@online.sh.cn; gztao@ecust.edu.cn

In the asymmetric hydrogenation of ethyl pyruvate over cinchona alkaloid modified Pt/Al₂O₃ in acetic acid under atmospheric pressure, the enantioselectivity was improved and the reaction rate was accelerated upon addition of tertiary amine. The size of the alkyl substitute in tertiary amine molecule has significant impact on the improvement. Triethylamine is the most effective additive compared with tri-*n*-butylamine, tri-*n*-propylamine and trimethylamine. There is an optimum adding amount (0.4 mol/L) of all tertiary amines, at which triethylamine can increase the enantioselectivity of product from 51 to 72 %. The role of tertiary amine in the promotional effect was discussed.

Key Words: Asymmetric hydrogenation, Promotional effect, Tertiary amine, Ethyl pyruvate, Cinchona alkaloid, Pt/Al₂O₃.

INTRODUCTION

Heterogeneous asymmetric catalytic hydrogenation of α -ketoesters and related activated carbonyl compounds over cinchona alkaloid modified Pt catalyst has been studied widely. Since such reactions were first discovered by Orito and co-workers¹, ethyl pyruvate (EtPy) and Pt/Al₂O₃ are often used as a model compound (**Scheme-I**) and an effective catalyst, respectively¹⁻⁵. Many researches show that the coordination between the substrate and the modifier is necessary in this asymmetric hydrogenation reaction and those factors stereochemically boosting the formation of 1:1 modifier-substrate as an enantiodifferentiating intermediate result in a high enantioselectivity.



Scheme-I: Hydrogenation of EtPy catalyzed by cinchona-alkaloid modified Pt/Al₂O₃

Recently, many achievements in the heterogeneous asymmetric catalytic hydrogenation of α -ketoesters have been reported, including the optimization of the catalytic conditions, the elucidation of reaction mechanism and the improvement of the chirally modified catalysts⁶⁻⁹. However, less attention has been paid to the chemistry related to the promotional effect of additive and the understanding on the behaviour of additive is poor until now.

Arx and co-workers¹⁰ have reported that the enantioselectivity increased while the reaction rate decreased when trifluoroacetic acid was used as an additive in the asymmetric hydrogenation of ethyl-4,4,4-trifluoroacetoacetate with cinchonidine or O-methylcinchonidine as a modifier under 10 bar pressure in toluene. The results reported by Margitfalvi and co-workers^{11,12} show that the enantioselectivity could be improved in the asymmetric hydrogenation of ethyl pyruvate with cinchonidine as a modifier under 50 bar pressure in toluene when 1,4-diazabicyclo[2,2,2]-octane, quinuclidine and triethylamine was used as an additive, but this promotional effect disappeared in the coordinative solvent. However, the interaction between the modifier and the additive, the effects of the hydrogen pressure and solvent on the promotional effect of the additive are still unclear.

In this paper, it is aimed to study the promotional effect in the enantioselectivity of product and hydrogenation rate of substrate upon addition of tertiary amine on the asymmetric catalytic hydrogenation of ethyl pyruvate under atmospheric pressure in acetic acid over cinchona alkaloid modified Pt/Al₂O₃ catalyst. The impact of the size of the alkyl substitute in tertiary amine molecule on the improvement degree as well as the role of tertiary amine in the promotional effect on the asymmetric hydrogenation of ethyl pyruvate will be discussed.

EXPERIMENTAL

Ethyl pyruvate (Lancaster, 98 %) was used immediately after being freshly distilled. Cinchonidine (CD, Lancaster, 99 %), cinchonine (CN, Fluka, 99 %), quinidine (QD, Sigma, ≥ 98 %) and quinine (QN, Sinopharm Chemical Reagent Co., Ltd. ≥ 98.5 %) were dried at 120 °C for 2 h under a continuous flow of nitrogen and cooled down to ambient temperature before being reserved in a vacuum desiccator. Toluene (≥ 99.5 %) and acetic acid (≥ 99.5 %) were distilled and purged with nitrogen before use. Trimethylamine (TMA, ≥ 99.0 %), triethylamine (TEA, ≥ 99.5 %), tri-*n*-propylamine (TPA, ≥ 98.0 %), tri-*n*-butylamine (TBA, ≥ 99.0 %) and diethylamine (DEA, ≥ 99.0 %) were used as received. N₂ (≥ 99.999 %) and H₂ (≥ 99.999 %) were used as supplied.

Catalyst preparation: The Pt/Al₂O₃ catalyst was prepared by an impregnation method. In a typical run, 0.6 g pseudoboehmite (BET specific surface area of 288 m²/g; mean pore diameter of 5 nm and specific pore volume of 0.36 cm³/g) was impregnated with 1.32 mL hexachloro-platinic acid aqueous solution (80 mgPt/mL) for 6 h. This impregnated sample was dried at 120 °C for 9 h and then calcined in a muffle furnace at 400 °C for 3 h to obtain the Pt/Al₂O₃ catalyst. The properties of

this catalyst are: Pt loading of 15 % (wt.), Pt dispersion of 16 % (by H₂-O₂ titration method), BET surface area of 196 m²/g, mean pore diameter of 3 nm and specific pore volume of 0.15 cm³/g.

Catalytic hydrogenation of ethyl pyruvate: The catalytic hydrogenation of ethyl pyruvate was carried out in a 50 mL three-necked flask with a H₂ bubbler and a reflux condenser in oil bath under stirring at a rate of 1000 rpm. In a typical run, the reactor loaded with 0.5 g Pt/Al₂O₃ suspended in 20 mL solvent was first flushed with 100 mL/min nitrogen for 40 min to remove the residual air. After nitrogen was shut off, 100 mL/min hydrogen was bubbled into the reactor to pre-reduce the catalyst at 90 °C for 0.5 h. Then weighed modifier and tertiary amine were added carefully and pre-adsorbed on the catalyst for 5 min after the reactor was cooled down to defined reaction temperature. The reaction was started by charging 1 mL ethyl pyruvate into the reactor. The general reaction conditions are 0.5 g Pt/Al₂O₃, 30 mmol/L quinine, 1 mL ethyl pyruvate and 20 mL solvent at 20 °C. Special care should be taken to prevent any contact of the catalytic system with air throughout the whole hydrogenation reaction. After the hydrogenation of ethyl pyruvate was finished, the reaction mixture was filtered to remove the catalyst prior to GC analysis. In each run, substrate was completely converted.

Analysis of products: The reaction was monitored by periodically taking sample from the reactor with minimal perturbation to the reaction and the reaction products were chirally and chemically analyzed by gas chromatograph (FULI 9790 with FID and a chiral capillary column CP-Chirasil-Dex Cyclodextrin-B, 25 m × 0.25 mm, Chrompack). S-ethyl lactate (Lancaster, ≥ 99 %) was used as standard sample to determine the product configuration and cyclopentanone (Fluka, ≥ 99 %) as internal standard for quantitative measurement. The enantiomeric excess (e.e.) of ethyl lactate (EtLt) is defined as e.e. (%) = (R-S)/(R+S) × 100 %, where R and S are the concentrations of (R)- and (S)-ethyl lactate, respectively. The hydrogenation rate of ethyl pyruvate (r) is calculated by ethyl pyruvate moles converted per hour per gram of catalyst, $r = n_{\text{EtPy}} \text{ (mol)} / [\text{Catalyst (g)} \times \text{Time (h)}]$, n_{EtPy} is the mole number of reactant ethyl pyruvate. The e.e. and r are both calculated based on GC data.

RESULTS AND DISCUSSION

Using quinine as a modifier, the effects of adding different tertiary amines on the enantioselectivity of product were shown in Fig. 1. The e.e. of ethyl lactate is 51 % without adding tertiary amine. Upon addition of tertiary amine, the e.e. increased and reached a maximum at the tertiary amine concentration of 0.4 mol/L. Among trimethylamine, triphenylamine, tri *n*-butylamine and triethylamine is the most effective additive with a maximum e.e. of 72 %. It is interesting that for all four tertiary amines the highest e.e. always appeared at 0.4 mol/L. This implies that the N atom in tertiary amine may play a decisive role in promotional effect on the asymmetric hydrogenation of ethyl pyruvate.

Without and with 0.4 mol/L triethylamine, the effects of the quinine concentration and reaction temperature on the enantioselectivity were shown in Figs. 2 and 3. The e.e.

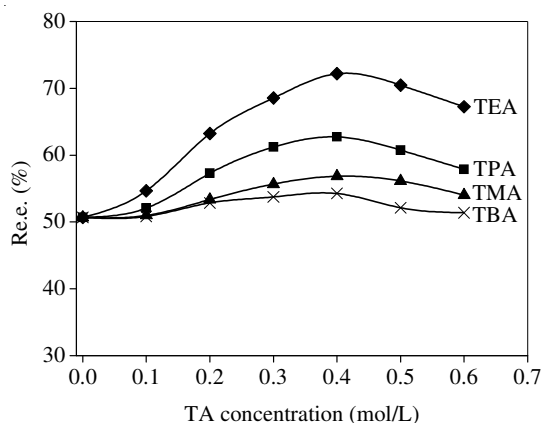


Fig. 1. Effects of different tertiary amines on Re.e. for the hydrogenation of ethyl pyruvate (0.5 g Pt/Al₂O₃, 1 mL ethyl pyruvate, 30 mmol/L quinine and 20 mL AcOH at 20 °C)

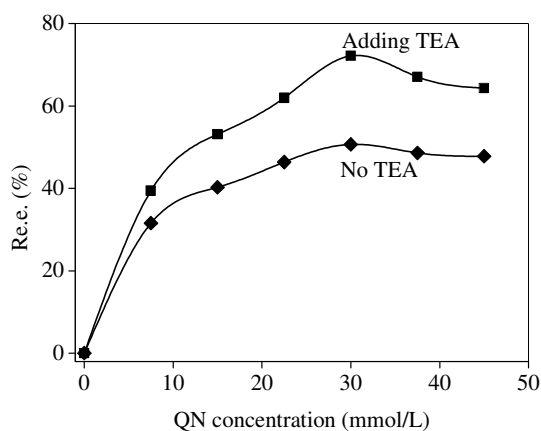


Fig. 2. Effect of the quinine concentration on Re.e. in the presence of 0.4 mol/L tertiary ethylamine. (0.5 g Pt/Al₂O₃, 1 mL ethyl pyruvate and 20 mL AcOH at 20 °C)

of ethyl lactate increased significantly with increasing the quinine concentration and a maximum e.e. (72 %, with triethylamine; 51 %, without triethylamine) was observed at 30 mmol/L quinine (Fig. 2). It reflects the fact that tertiary ethylamine is an effective promoter for the asymmetric hydrogenation of ethyl pyruvate. In Fig. 3, the promotional effect of triethylamine as well as the e.e. of ethyl lactate reached the maximum at low temperature (15-20 °C) and followed by a sharp decrease upon increasing the temperature. When the temperature reached 70 °C, the promotional effect of triethylamine almost disappeared. Obviously, the promotional effect of

tertiary ethylamine is sensitive to both quinine amount and the reaction temperature. A middle quinine concentration (30 mmol/L) and a low temperature (15-20 °C) are favourable for the promotional effect of tertiary ethyl-amine. It also confirmed that the modifier concentration and reaction temperature are two important factors for the heterogeneous asymmetric hydrogenation of α -keto-esters system over Pt/cinchona^{4,8}.

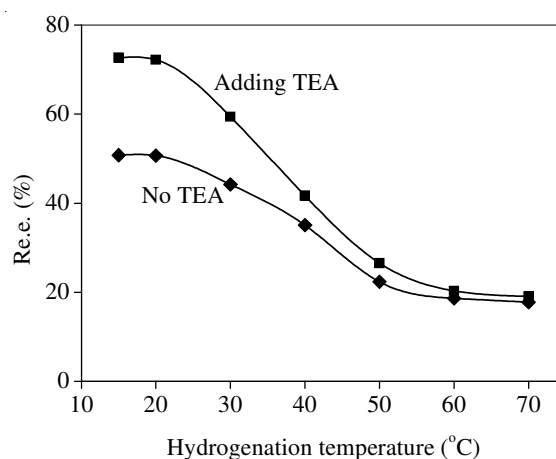


Fig. 3. Effect of the hydrogenation temperature on Re.e. in the presence of 0.4 mol/L triethylamine. (0.5 g Pt/Al₂O₃, 1 mL EtPy, 30 mmol/L quinine and 20 mL AcOH)

The effects of four modifiers of cinchonidine, cinchonine, quinine and quinidine on the asymmetric hydrogenation of ethyl pyruvate were listed in Table-1. It can be seen that quinidine and cinchonine are the effective modifiers for S-ethyl lactate and quinine and cinchonidine for R-ethyl lactate. The addition of triethylamine can evidently increase the enantioselectivity of product and the hydrogenation rate of substrate. As a modifier for R-ethyl lactate, quinine is more suitable than cinchonidine; while for S-ethyl lactate, quinidine is better than cinchonine (Table-1).

TABLE-1
EFFECT OF MODIFIER ON THE ASYMMETRIC
HYDROGENATION OF EtPy IN AcOH AT 20 °C*

Modifier	TA	e.e. (configuration/%)	r (mmol/h·g)
QN	–	R/51	14.6
QN	TEA	R/72	36.5
QD	–	S/44	12.4
QD	TEA	S/59	29.3
CD	–	R/48	13.9
CD	TEA	R/67	33.9
CN	–	S/40	11.0
CN	TEA	S/51	25.5

*Hydrogenation conditions: 0.5 g Pt/Al₂O₃, 1 mL EtPy, 30 mmol/L modifier, 0.4 mol/L TEA and 20 mL AcOH. r, hydrogenation rate of EtPy.

Conclusion

The promotional effect of tertiary amine on the asymmetric catalytic hydrogenation of ethyl pyruvate over cinchona alkaloid modified Pt/Al₂O₃ under atmospheric pressure in AcOH has been studied. The enantioselectivity can be improved and reaction rate accelerated upon addition of tertiary amine. The promotional effect depends on the size of the alkyl substitute in tertiary amine molecule and triethylamine is the most effective additive. There is an optimum adding amount (0.4 mol/L) of all four tertiary amines and the e.e. of product can increase from 51 to 72 % upon addition of triethylamine. Both the enantioselectivity of product and promotional effect of triethylamine reduce upon increasing the reaction temperature. The promotional effect of triethylamine is also dependent on the modifiers and their concentrations. The promotional effect of tertiary amine is to form dendritic electrophilic ammonium cation which is probably beneficial to the development of the chiral environment for asymmetric induction. It should be notable that this promotional effect disappeared with diethylamine as an additive in AcOH or with triethylamine in toluene, which can, to some extent, confirm the role of tertiary amine in the promotional effect on the asymmetric hydrogenation of ethyl pyruvate.

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REFERENCES

1. Y. Orito, S. Imai, S. Niwa and N.G. Hung, *J. Synth. Org. Chem.*, **37**, 173 (1979).
2. M. Bartók, *Curr. Org. Chem.*, **10**, 1533 (2006).
3. H.U. Blaser and M. Studer, *Accounts Chem. Res.*, **40**, 1348 (2007).
4. T. Mallat, E. Orglmeister and A. Baiker, *Chem. Rev.*, **107**, 4863 (2007).
5. D.M. Meier, D. Ferri, T. Mallat and A. Baiker, *J. Catal.*, **248**, 68 (2007).
6. J.L. Margitfalvi and E. Tálas, *Appl. Catal. A: Gen.*, **301**, 187 (2006).
7. T.A. Martinek, T. Varga, F. Fülöp and M. Bartók, *J. Catal.*, **246**, 266 (2007).
8. M. Studer, H.U. Blaser and C. Exner, *Adv. Syn. Catal.*, **345**, 45 (2003).
9. T.A. Martinek, T. Varga, K. Balázsik, G. Szöllösi, F. Fülöp and M. Bartók, *J. Catal.*, **255**, 296 (2008).
10. M.V. Arx, T. Bürgi, T. Mallat and A. Baiker, *Chem. Eur. J.*, **8**, 1430 (2002).
11. J.L. Margitfalvi, E. Tálas, E. Tfirst, C.V. Kumar and A. Gergely, *Appl. Catal. A: Gen.*, **191**, 177 (2000).
12. J.L. Margitfalvi, E. Tálas and E. First, *Top. Catal.*, **39**, 77 (2006).
13. M. Bartók, K. Balázsik, G. Szöllösi and T. Bartók, *J. Catal.*, **205**, 168 (2002).
14. M. Bartók, K. Balázsik and F. Notheisz, *React. Kinet. Catal. Lett.*, **77**, 363 (2002).
15. M. Bartók, K. Balázsik, T. Bartók and Z. Kele, *Catal. Lett.*, **87**, 235 (2003).
16. M. Bartók, K. Balázsik, G. Szöllösi and T. Bartók, *Catal. Commun.*, **2**, 269 (2001).