Asian Journal of Chemistry; Vol. 26, No. 2 (2014), 319-322

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.15372

Enantioselective Hydrogenation of Ethyl Pyruvate Catalyzed by 1,2-Diphenyl-ethylenediamine-Modified Iridium Complex: Effect of Solvent

YOU DU, CHUN LI, XIAOYUN TAN, HAIYAN FU, XUELI ZHENG*, RUIXIANG LI and HUA CHEN*

Key Lab of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P.R. China

*Corresponding authors: Tel/Fax: +86 28 85412904; E-mail: scuhchen@163.com

Received: 26 February 2013; *Accepted*: 6 August 2013; *Published online*: 15 January 2014; AJC-14533

The enantioselective hydrogenation of ethyl pyruvate was explored by a readily available homogeneous iridium catalysis system. It was found that (1R,2R)-(+)-1,2-diphenyl-ethylenediamine [(1R,2R)-DPEN] modified $[Ir(COD)Cl]_2$ (COD = *cis*,*cis*-1,5-cyclooctadiene) was highly active for the enantioselective hydrogenation of ethyl pyruvate, and the moderate enantioselectivity of 29 % was obtained (the best value reported by iridium catalysts was 39 %). NMR spectroscopy proved that hydrogen bond between the solvent and the α-carbonyl of ethyl pyruvate would be favor to the enantioselective hydrogenation.

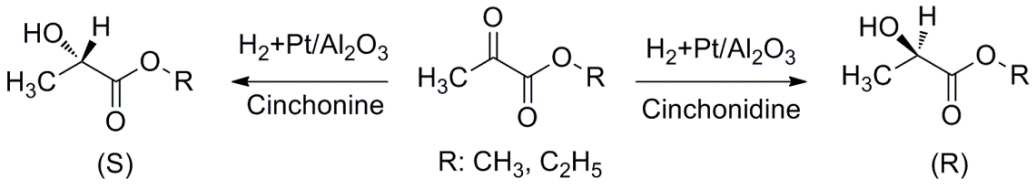
Keywords: Enantioselective hydrogenation, Iridium catalysts, Solvent effect, NMR Spectroscopy, Hydrogen bond.

INTRODUCTION

The enantioselective hydrogenation of methyl pyruvate (the Orito reaction, **Scheme-I**) was first explored by Orito *et al.*[1] with cinchona modified Pt/C as catalysts and (R)-methyl lactate was successfully obtained with up to 90 % ee. Since then, this reaction was widely studied with cinchona alkaloids modified metal catalysts, such as Pt[2-3], Ru[4], Rh[5] and Pd[6] catalysts. However, referring to the other metals in Group VIII, only a few has been reported in the enantioselective hydrogenation of α-ketoesters so far. In 1994, alkaloid-modified iridium catalysts were first employed in the enantioselective hydrogenation of methyl pyruvate with 90 % conversion and 39 % enantioselectivity by Wells *et al* [7]. Then, only a few reports were related[8,9], because compared to Pt and Ru catalysts, the hydrogenation of methyl pyruvate preferred to generate racemic products than chiral products under the Ir catalysis system[8]. Up to date the highest enantioselectivity for iridium catalysts was only 39 %, which was obtained by Wells *et al* [7].

As known, the reaction parameters, such as solvent, hydrogen pressure and reaction temperature, have significantly influences on the catalytic activity and enantioselectivity. In the commonly used Pt/cinchona system, different enantioselectivity could be obtained dependent on the solvent used[10,11]. The solvent not only can affect the adsorption of modifier on the surface of the catalysts[12], but also can interact with the substrates[13] or even change the conformation of the ligands[14]. Mean while the solvent effect, such as protonation, hydration, or hydrogen bond, is usually involved in the reaction mechanism. The aim of this study is to evaluate the influence of the solvent on both the activity and the enantioselectivity of the iridium catalyzed hydrogenation of α-ketoesters.

Herein, the enantioselective hydrogenation of ethyl pyruvate catalyzed by (1R,2R)-(+)-1,2-diphenyl-ethylenediamine [(1R, 2R)-DPEN] modified $[Ir(COD)Cl]_2$ (COD = *cis*,*cis*-1,5-cyclooctadiene) was reported. NMR spectroscopy was used to investigate the solvent effect on the reaction. It was found that the system was highly active for the enantioselective hydrogenation of ethyl pyruvate and the hydrogen bond between



Scheme-I: Orito's reaction

the solvent and the α-carbonyl of ethyl pyruvate was beneficial to the enantioselective hydrogenation.

EXPERIMENTAL

$[Ir(COD)Cl]_2$ was synthesized according to the procedures reported by Singer *et al*[15]. All chemicals, ethyl pyruvate, (1R,2R)-DPEN, (1S,2S)-DPEN, cinchonidine (CD) and cinchonine (CN), (1R,2R)-(+)-1,2-diamino-cyclohexane [(1R,2R)-DACH], (1S,2S)-(+)-1,2-diamino-cyclohexane [(1S,2S)-DACH], N-[(1R,2R)-2-amino-1,2-diphenylethyl]-4-methyl-benzenesulfonamide[(1R,2R)-Ts-DPEN], $H_2IrCl_6 \cdot 6H_2O$, *cis,cis*-1,5-cyclooctadiene (COD) were reagent grade and used as purchased without further purification. All solvents were purified and dried according to standard methods. ^1H NMR spectra were recorded on Bruker Avance II-400 MHz with reference to TMS as the internal standard, *J*-values are in Hz. Products were analyzed by GC-960 instrument with an FID detector and β-DEX120 capillary column (0.25 mm × 0.25 μm × 30 m).

Hydrogenation of ethyl pyruvate: The hydrogenation of ethyl pyruvate was performed in a 60 mL steel autoclave with magnetic stirring. The desired amounts of substrate, catalyst, ligand and solvent were added into the autoclave, which was then sealed and purged 3 times with hydrogen. Then, the hydrogen pressure was increased to desired value and the mixture was stirred under the preset temperature. After the reaction, the products were analyzed by GC. The ee' value was calculated according to the following:

$$ee\ (\%) = 100 \times (S\text{-}R)/(S + R)$$

RESULTS AND DISCUSSION

The enantioselective hydrogenation of ethyl pyruvate was investigated with three kinds of iridium complexes and seven N,N ligands as shown in Table-1. From Table-1, it can be seen that $[Ir(COD)Cl]_2$ with the central metal iridium in a low oxidation state, gave a relatively higher activity and enantioselectivity compared to other precursors $Ir(acac)_3$ and $H_2IrCl_6 \cdot 6H_2O$ (entry 1-3). Therefore, $[Ir(COD)Cl]_2$ was selected as the catalyst precursor in the other experiments. From entry 5 and 6, it can be seen that the commonly used ligands in the enantioselective hydrogenation of ethyl pyruvate, cinchonidine (CD) and cinchonine (CN), could accelerate the reaction rate[16], but resulted in racemic products. Among the seven-examined N,N ligands (1R, 2R)-DPEN, (1S, 2S)-DPEN, (1R, 2R)-Ts-DPEN, (1R, 2R)-DACH and (1S, 2S)-DACH, the (1R, 2R)-DPEN was found to be the most outstanding (entry 3-9). When (1R, 2R)-DPEN and $[Ir(COD)Cl]_2$ were used as ligand and catalyst precursor, respectively, 70 % of conversion with 29 % ee could be achieved, which was comparable with the results reported by Wells *et al*[7].

In an attempt to clarify the solvent effect on the enantioselective hydrogenation of ethyl pyruvate, the hydrogenation of ethyl pyruvate was investigated in different solvents and the results were summarized in Table-2. Both the conversion and enantioselectivity were highly dependent on the solvent. In the commonly used solvents in Pt-catalyzed heterogeneous hydrogenation[17], such as acetic acid, toluene and dichloromethane, *etc.*, only lower conversion (10-44 %) and enantioselectivity (0-14 %) were obtained (entry 1-6). While the alcoholic solvents, such as methanol, ethanol, 1-propanol and 1-butanol, were good solvent for this reaction. Wells *et al.*[7] and Liu *et al*.[8] reported that the moderate conversion and about 29 % ee in the hydrogenation of ethyl pyruvate. In those solvents, the highest activity and enantioselectivity were observed in the most polar methanol and lower activity or enantioselectivity was detected in the less polar ethanol and 1-propanol, it seems that the conversion and the enantioselectivity trend to decrease as the polarity of the solvents decreased (entry 7-10). However, when the more polar water was added in the methanol as solvent, the conversion and the ee' value were dropped quickly as the amount of water increased

TABLE-2
ENANTIOSELECTIVE HYDROGENATION OF ETHYL PYRUVATE IN VARIOUS SOLVENTS[a]

Entry	Solvent	Conversion (%)	Enantioselectivity (%)[b]
1	Acetic acid	44	5
2	Acetone	26	14
3	Ethyl acetate	19	6
4	THF	13	0
5	Dichloromethane	10	1
6	Toluene	10	0
7	Methanol	70	29
8	Ethanol	62	25
9	1-Propanol	36	23
10	1-Butanol	27	22
11	Methanol/water(6/1)[c]	44	22
12	Methanol/water(3/1)	36	16
13	Methanol/water(1/1)	17.6	14
14	Water	11.6	10

[a]Reaction conditions: substrate/Ir/ligand =1000:1:2, [Ir]: 0.003 mmol, 25°C, 1MPa, 2h
[b]S-ethyl lactate in excess
[c]Volume ratio

TABLE-1
ENANTIOSELECTIVE HYDROGENATION OF ETHYL PYRUVATE WITH DIFFERENT IRIDIUM COMPLEXES AND LIGANDS[a]

Entry	Iridium complex	Ligand	Con (%)	ee (%)	Configuration
1	$[Ir(COD)Cl]_2$	(1R,2R)-DPEN	70	29	S
2	$Ir(acac)_3$	(1R,2R)-DPEN	11	8	S
3	$H_2IrCl_6 \cdot H_2O$	(1R,2R)-DPEN	6	4	S
4	$[Ir(COD)Cl]_2$	(1S,2S)-DPEN	38	5	R
5	$[Ir(COD)Cl]_2$	CD	72	0	-
6	$[Ir(COD)Cl]_2$	CN	99	7	S
7	$[Ir(COD)Cl]_2$	(1R,2R)-TS-DPEN	94	10	S
8	$[Ir(COD)Cl]_2$	(1R,2R)-DACH	76	13	S
9	$[Ir(COD)Cl]_2$	(1S,2S)-DACH	77	9	R

[a]Reaction conditions: substrate/Ir/ligand = 00/1/2, [Ir]: 0.003 mmol, 25 °C, 1MPa, 2 h, metanol: 2 mL

(entry 11-14). As the solvent, methanol is of lower polarity than water, but higher activity and enantioselectivity were observed in methanol, which indicated that the activity and the enantioselectivity were not only dependent on the polarity of the solvent. The interaction between the solvent and the ethyl pyruvate might occur during the hydrogenation process and dramatically influence the conversion and the enantioselectivity[13,14].

In order to comprehend the interaction between the solvent and the ethyl pyruvate, ^{1}H NMR characterization of ethyl pyruvate in different solvents were investigated and the results were shown in Fig. 1. ^{1}H NMR of ethyl pyruvate in $CDCl_3$ (spectrum A), three sets of characteristic peaks, including a quartet centered at 4.30 ppm (CH_2 protons of the ethoxyl group OCH_2CH_3, H_a), a singlet at 2.45 ppm (CH_3 protons attached on keto-carbonyl group CH_3CO, Hb) and a triplet centered at 1.34 ppm (CH_3 protons of the ethoxyl group OCH_2CH_3, H_c), were observed[18]. While all of those peaks divided into two parts with different chemical shifts in CD_3OD, D_2O or mixture thereof (spectra B-F), especially for the singlet of H_b, which split into two singlet at 2.40 ppm and more upfield 1.47 ppm in CD_3OD. This phenomenon may hint that the hydrogen bond was probably formed between the solvent and ethyl pyruvate[19]. The presence of the hydrogen bond between CD_3OD and the α-carbonyl group of ethyl pyruvate[20], could somehow weaken the shielding effect of the α-carbonyl oxygen on the adjacent methyl group and the signal of the CH_3 adjacent to α-carbonyl group upshifted to 1.47 ppm. Theoretically, the ethoxy group, due to its electron-donating properties, would make the carbonyl oxygen of the ester group more electron rich and increase the hydrogen accepting capability of the ester carbonyl[21], thus make the carbonyl oxygen of the ester group more inclined to form hydrogen bond with the solvent. However, more obvious change was observed in the chemical shift of H_b (from 2.40 ppm to 1.47 ppm), instead of H_a and H_c, which are closer to ester group. This phenomenon indicated that the hydrogen bond might be formed between the α-carbonyl group of ethyl pyruvate and the solvent had a much more significant influence on the adjacent methyl. And the likely model of hydrogen bond between the α-carbonyl group of ethyl pyruvate and the solvent was assumed in Fig. 2a.

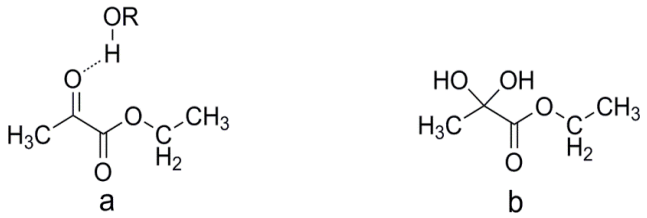


Fig. 2. Hydrogen bond and hydrate of ethyl pyruvate

It is noted that the two parts of the signal for H_c overlapped, so their peak areas were difficult to be calculated. Instead, the peak areas for two division parts of the protons H_a and H_b in the substrate molecules were calculated respectively and one part was affected by the hydrogen bond with solvent (hydrogen bonding part), another was not affected by the hydrogen bond with solvent (non-hydrogen bonding part). Table-3 summarized the peak areas and their ratios for the two parts of H_a and H_b, respectively. According to the data in Table-3, we can estimate the proportion of reactant molecules which have formed hydrogen bond with the solvent. As for ^{1}H NMR of -$COCH_3$ in CD_3OD, the area ratio of hydrogen bonding part (1.47 ppm) to non-hydrogen bonding part (2.40 ppm) is 6.12, which means that about 86 % of ethyl pyruvate formed the hydrogen bond with CD_3OD. The ratio followed a decreasing sequence as the CD_3OD/D_2O ratio decreased: CD_3OD (6.12), $CD_3OD:D_2O = 6$ (5.34), $CD_3OD:D_2O = 3$ (4.76), $CD_3OD:D_2O$

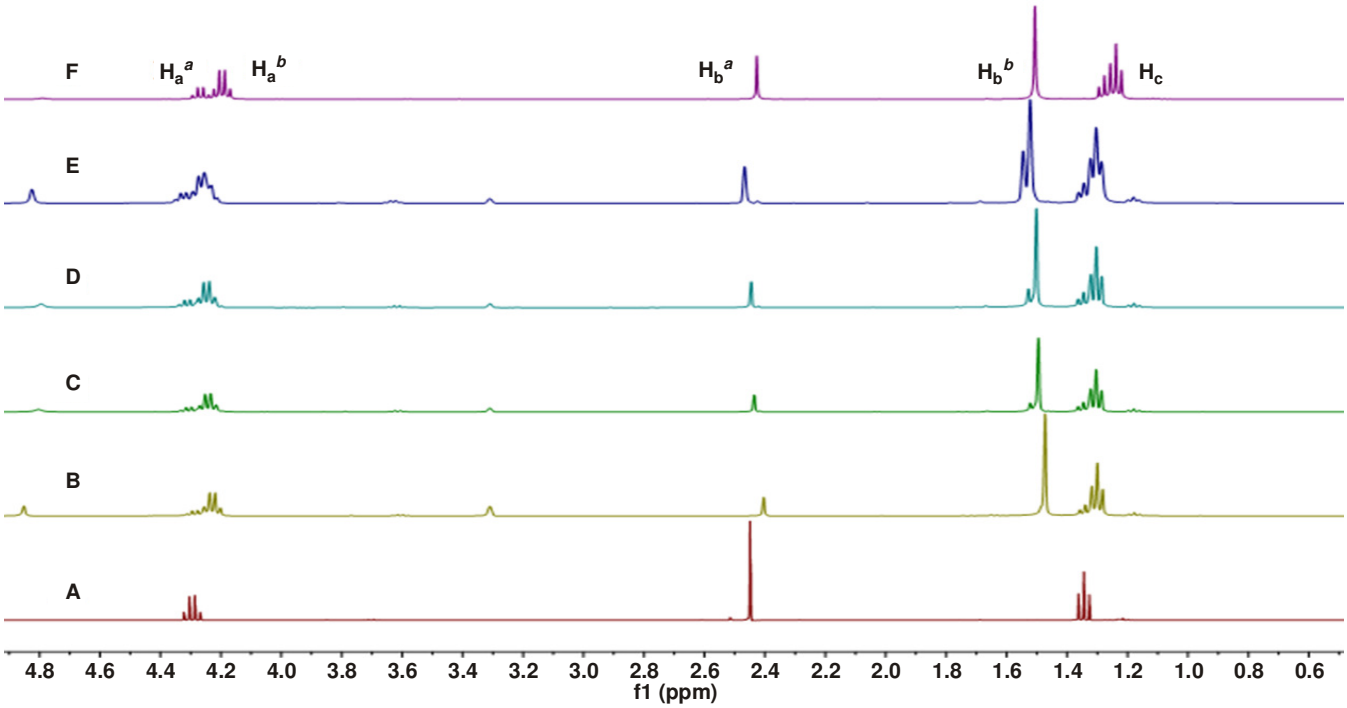


Fig. 1. ^{1}H NMR spectra of ethyl pyruvate in different solvents: (A) $CDCl_3$ (B) CD_3OD (C) $CD_3OD:D_2O = 6:1$, (D) $CD_3OD:D_2O = 3:1$ (E) $CD_3OD:D_2O = 1:1$ (F) D_2O (a) the protons of non-hydrogen bonding part (b) the protons of hydrogen bonding part

= 1 (4.63), D_2O (2.82). And the activity and enantioselectivity were also decreased as this trend, the conversion decreased from 70 to 12 % and the enantioselectivity decreased from 29 to 10 %. Although, compared to methanol (or CD_3OD), water is a stronger hydrogen bond donor, it seems that the methanol might be easier to form hydrogen bond with the carbonyl oxygen of ethyl pyruvate. The negative effect of water was probably due to rapid hydration of the activated ketone, as reported by Baiker *et al.*[22] that even 0.8 vol % water in the system could lead to approximate 1 % ethyl pyruvate hydrated (Fig. 2b). The hydrogenation of C-OH bond is much slower compared to ketone[23] and the hydration would hinder the coordination of α-carbonyl with iridium complex, so the presence of trace water caused the activity and the enantioselectivity to decrease. When acetic acid was used as solvent, though the hydrogen bond could be formed between the acetic acid and the ethyl pyruvate, the NH_2 group of the ligand could be protonated significantly by acetic acid, which was unfavorable for the coordination of ligand with iridium complex. So under our reaction conditions, the hydrogen bond between the α-carbonyl group of ethyl pyruvate and the solvent could be formed easily in MeOH (or CD_3OD), the α-carbonyl was activated by the hydrogen bond and could be hydrogenated more easily. Therefore, the highest conversion and enantioselectivity of ethyl pyruvate were observed in methanol.

TABLE-3
PEAK AREAS AND AREA RATIOS FOR THE TWO PARTS OF H_a AND H_b

Solvent	-OCH_2-			CH_3CO-		
	H_a^b	H_a^a	H_a^b/H_a^a	H_b^b	H_b^a	H_b^b/H_b^a
CD_3OD	1.60	0.40	4.00	2.57	0.42	6.12
CD_3OD: D_2O = 6:1	1.57	0.40	3.93	2.51	0.47	5.34
CD_3OD: D_2O = 3:1	1.51	0.50	3.02	2.57	0.54	4.76
CD_3OD: D_2O = 1:1	1.46	0.55	2.65	2.41	0.52	4.63
D_2O	1.43	0.59	2.42	2.20	0.78	2.82

[a]the integral area for the protons of non-hydrogen bonding part
[b]the integral area for the protons of hydrogen bonding part

Conclusion

In conclusion, we have demonstrated a highly active (1R, 2R)-DPEN modified $[Ir(COD)Cl]_2$ for the enantioselective hydrogenation of ethyl pyruvate, 29 % ee was obtained by our catalysis system (up to date, the best value of enantioselectivity was 39 % for iridium catalysts). NMR experiments have revealed that the hydrogen bond between the solvent and the α-carbonyl group of ethyl pyruvate facilitated this hydrogenation reaction.

ACKNOWLEDGEMENTS

Financial support of the National Science Talents Fund for Research Training and Research Ability Improvement project (J1103315) was gratefully acknowledged.

REFERENCES

1. Y. Orito, S. Imai. S. Niwa and N.-G. Hung, *J. Synth. Org. Chem.*, **37**, 173 (1979).
2. M.U. Azmat, Y. Guo, Y. Guo, Y. Wang and G. Lu, *J. Mol. Catal. A: Chem.*, **336**, 42 (2011).
3. Z. Chen, Z. Guan, M. Li, Q. Yang and C. Li, *Angew. Chem. Int. Ed.*, **50**, 4913 (2011).
4. M. Jahjah, M. Alame, S. Pellet-Rostaing and M. Lemaire, *Tetrahedron Asymm.*, **18**, 2305 (2007).
5. Z. Herseczki, I. Gergely, C. Hegedüs, Á. Szöllosy and J. Bakos, *Tetrahedron Asymm.*, **15**, 1673 (2004).
6. M. Vago, F.J. Williams and E.J. Calvo, *Electrochem. Commun.*, **9**, 2725 (2007).
7. K.E. Simons, A. Ibbotson, P. Johnston, H. Plum and P.B. Wells, *J. Catal.*, **150**, 321 (1994).
8. X.B. Zuo, H.F. Liu and C. Yue, *J. Mol. Catal. A: Chem.*, **147**, 63 (1999).
9. T. Marzialetti, M. Oportus, D. Ruiz, J.L.G. Fierro and P. Reyes, *Catal. Today*, **133**, 711 (2008).
10. H.U. Blaser, H.P. Jalett and J. Wiehl, *J. Mol. Catal.*, **68**, 215 (1991).
11. E. Toukoniitty, V. Nieminen, A. Taskinen, J. Päivärinta, M. Hotokka and D.Y. Murzin, *J. Catal.*, **224**, 326 (2004).
12. H.U. Blaser, H.P. Jalett, D.M. Monti, J.F. Reber and J.T. Wehrli, *Stud. Surf. Sci. Catal.*, 41, 153 (1988).
13. B. Minder, T. Mallat, P. Skrabal and A. Baiker, *Catal. Lett.*, **29**, 115 (1994).
14. J.L. Margitfalvi and M. Hegedus, *J. Mol. Catal. A: Chem.*, **107**, 281 (1996).
15. G. Winkhaus and H. Singer, *Chem. Ber.*, **99**, 3610 (1966).
16. Y.L. Huang, J.R. Chen, H. Chen, R.X. Li, Y.Z. Li, L.E. Min and X.J. Li, J. *Mol. Catal. A: Chem.*, **170**, 143 (2001).
17. J.T. Wehrli, A. Baiker, D.M. Monti, H.U. Blaser and H.P. Jalett, *J. Mol. Catal.*, **57**, 245 (1989).
18. P.A. Manis and M.W. Rathke, *J. Org. Chem.*, **45**, 4954 (1980).
19. F. Hoxha, T. Mallat and A. Baiker, *J. Catal.*, **248**, 11 (2007).
20. A. Vargas, F. Hoxha, N. Bonalumi, T. Mallat and A. Baiker, *J. Catal.*, **240**, 203 (2006).
21. A. Taskinen, V. Nieminen, E. Toukoniitty, D.Y. Murzin and M. Hotokka, *Tetrahedron*, **61**, 8109 (2005).
22. M. von Arx, T. Mallat and A. Baiker, *Angew. Chem. Int. Ed.*, **40**, 2302 (2001).
23. F. Notheisz and M. Bartok, Fine Chemical through Heterogeneous Catalysis, Wiley-VCH, Weinheim, p. 415 (2001).