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Homogeneous asymmetric hydrogenation of *o*-substituted acetophenones catalyzed by $NH_2Et_2\{Ru_2Cl_5[(S)\text{-}tol\text{-}BINAP]_2\}$

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Abstract

Acetophenones *o*-substituted by halogen and methoxyl groups were hydrogenated in the presence of $(NH_2Et_2)\{Ru_2Cl_5[(S)\text{-}tol\text{-}BINAP]_2\}$ at 35°C and 85 kg/cm^2 hydrogen pressure. The results showed that *o*-bromoacetophenone was a very active substrate and its asymmetric hydrogenation gave an *o*-bromo-α-phenylethanol with very high enantioselectivity (97% ee). *o*-Chloroacetophenone was moderately active and its hydrogenation product *o*-chloro-α-phenylethanol had a good enantioselectivity (82% ee). *o*-Fluoroacetophenone exhibited a low reactivity but its hydrogenation product *o*-fluoro-α-phenylethanol showed the highest enantioselectivity (99% ee) among all products. *o*-Methoxyacetophenone showed a low reactivity, and its hydrogenation product *o*-methoxyl-α-phenylethanol gave a low enantioselectivity (27% ee). The effects of various reaction conditions, such as hydrogen pressure, reaction temperature, solvents, reaction time, ligand concentration and addition of acid and base, were investigated.

Keywords: Ruthenium; (*S*)-*tol*-BINAP; *o*-substituted acetophenone

1. Introduction

It is well known that Ru(II)-BINAP (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) system was an excellent catalyst with very high catalytic activities and enantioselectivities in the asymmetric hydrogenation of a wide range of substrates [1–5]. Especially, it could be applied to convert the functioned prochiral ketones to optically active alcohols [3]. Optically active secondary alcohols are the synthetic intermediates of many pharmaceutical, agricultural and fine chemical products, but reports on the preparation of chiral *o*-substituted 1-phenylethanol with asymmetric hydrogenation of *o*-substituted acetophenones are scarce [6–8]. Recently, Fujii et al. [9] and Ohkuma et al. [10] have reported that simple aromatic ketones can be hydrogenated to corresponding alcohols at room temperature by a Ru-BINAP–diamine–KOH ternary system with high enantioselectivity. In general, 2-propanol was used as the source of hydrogen in transferring hydrogena-

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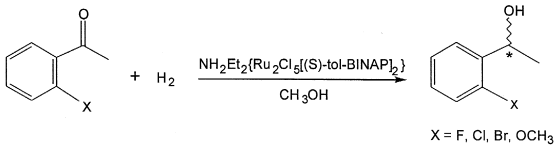
tion; strong base (KOH) and chiral diamine must be incorporated in order to improve the catalytic activity and enantiomeric excess (ee). However, homogeneous hydrogenation using a chiral metal complex as catalyst and hydrogen as reductant is obviously more advantageous than hydrogen transferring agent. Rane et al. [7] recently reported in a communication the hydrogenation of *o*-chloroacetophenone by Ru(II)-BINAP complex with ligand *p*-cymene. Doucet et al. [11] also reported that the coordination spheres of Ru(II)-BINAP complexes modified with the various carboxylate ligands could influence the hydrogenation of *o*-chloroacetophenone, but they did not investigate the effects of the various reaction conditions on catalytic activity and ee value of product in detail. Generally, reaction rate and product stereoselectivity are delicately influenced by reaction conditions as well as steric and electronic properties of the substituents of ketones. In this report, we study asymmetric hydrogenation of different o-substituted acetophenones using dinuclear $NH_2Et_2\{Ru_2Cl_5[(S)\text{-}tol\text{-}BINAP]_2\}$ complex as catalyst (reaction (1)) and the effect of reaction conditions.



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2. Experimental

Catalyst was synthesized by the reported method [12,13]. *o*-Chloroacetophenone, *o*-bromoacetophenone, *o*-fluoroacetophenone, and *o*-methoxyacetophenone were purchased from Aldrich.

Appropriate amount of $NH_2Et_2\{Ru_2Cl_5[(S)\text{-}tol\text{-}BINAP]_2\}$, solvents, and substrates were introduced into a teflon-lined stainless steel autoclave equipped with stirrer (Parr 4561 minireactor). The autoclave was flushed consecutively with high pure hydrogen (99.95%) for five times. The autoclave was then filled with hydrogen to the desired pressure. The reaction solution was stirred at 400 rpm at the desired temperature.

Products were analyzed with GC (HP 5890 Series II) with FID and a capillary column (HP-FFAP, 25 m × 0.2 mm × 0.33 μm), and GC graphs were handled with HP 3396 Integrator. The components were identified by GC and GC-MS (HP 5890 GC with Series Mass Selective Detector) technique with authentic samples. The ee values were determined by HPLC with OJ chiral column. The mobile phase was a 1000:1 mixture (v/v ratio) of *n*-hexane to 2-propanol.

3. Results and discussion

3.1. Effect of temperature

The effect of reaction temperature is shown in Fig. 1. The results exhibited that enantiomeric excess of product was highly dependent on the reaction temperature. The increase of reaction temperature was in favor of the hydrogenation of *o*-chloroacetophenone. More-

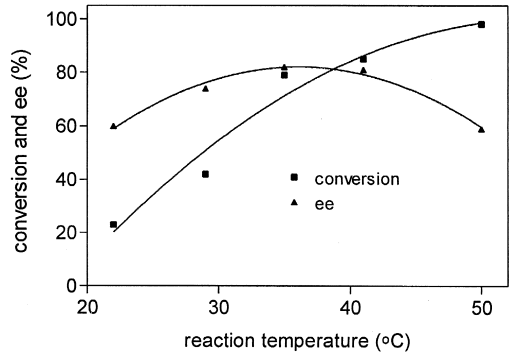


Fig. 1. Effect of reaction temperature. Reaction conditions: catalyst 10.0 mg; *o*-chloroacetophenone 2.0 ml; methanol 8.0 ml; hydrogen pressure 85 kg/cm^2; reaction time 48 h.

over, the change of ee value of the product, *o*-chloro-α-phenylethanol exhibited a maximum value (82%) at 35°C. When the reaction was carried out at room temperature (22°C), the conversion was 23.9% with 60% ee value. When the reaction was performed at 40°C, the ee value of product was 79%. Further increasing to 50°C of reaction temperature, the ee value dropped to 48%. Similar phenomenon was also reported by other researchers [14].

3.2. Effect of hydrogen pressure

According to the results shown in Fig. 2, reaction conversion increased from 43.7% to 90.2% when hydrogen pressure was increased from 40 to 85 kg/cm^2. However, the further increase of hydrogen pressure led to the decrease of conversion. When H_2 pressure was 120 kg/cm^2, the conversion dropped to 69%. The ee values of products decrease a little with the increase of hydrogen pressure.

3.3. Effect of ligand concentration

As shown in Fig. 3, the increase of the ratio of excess phosphine to ruthenium complex greatly inhibited the catalytic activity of ruthenium complex and caused the decrease of enantioselectivity of product. When the molar ratio of excess ligand to ruthenium complex was only 0.5, the reaction had been obviously suppressed and the conversion decreased from 90.2% to 60.6%. Furthermore, when the ratio was up to 1.5, the catalytic activity of complex was almost inhibited and the conversion dramatically dropped to 4.8% with 40.4% ee value. It suggested that the excess phosphine ligand could occupy the coordination vacant position of catalytic active species and block the coordination of substrate to active species; therefore, the hydrogenation activity of the catalyst was greatly depressed. Meanwhile, this would also influence bidentate coordination of substrate molecule with metal atom through halide atom and carbonyl unit to cause enantioselectivity decrease.

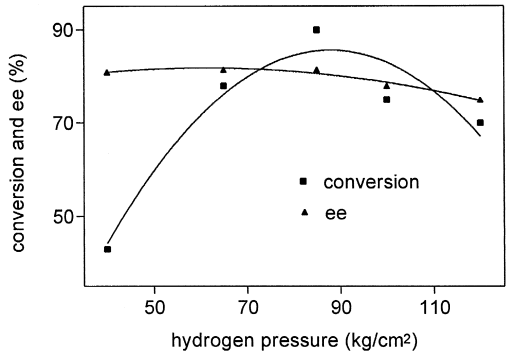


Fig. 2. Effect of hydrogen pressure. Reaction conditions: *o*-chloroacetophenone as substrate; temperature 35°C; others were the same as Fig. 1.

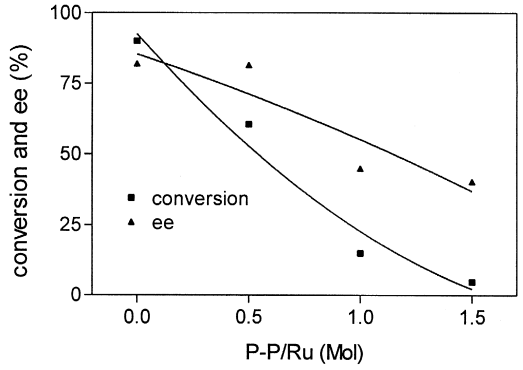


Fig. 3. Effect of ligand. Reaction conditions: *o*-chloroacetophenone as substrate; temperature 35°C; others were the same as Fig. 1.

3.4. Effect of acid and base

The results in Table 1 indicated that hydrogenation was remarkably promoted by the intro-

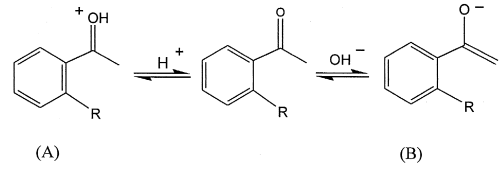
Table 1
Asymmetric hydrogenation of *o*-chloroacetophenone under the different concentrations of HCl and NaOH
Reaction conditions: catalyst 10.0 mg; substrate 2.0 ml; methanol 8.0 ml; hydrogen pressure 85 kg/cm^2; reaction temperature 35°C; reaction time 24 h.

Conc. of acid or base (M)	HCl			NaOH			
	0.1	0.05	0.01	0	0.001	0.01	0.1
Conversion (%)	74.2	63.9	50.8	43.6	36.8	29.5	6.2
ee	81.0	82.1	81.5	81.5	79.2	45.2	3.5

duction of hydrochloric acid. Without addition of acid (or base) to the reaction system, the conversion was only 43.6%. In the range of acid concentration from 0.01 to 0.1 M, the higher the concentration of acid, the higher the conversion was. In the presence of 0.1 M hydrochloric acid, the conversion was up to 74.2%. Interestingly, in spite of the great improvement of conversion by the introduction of acid, the ee value did not change obviously. However, when strong inorganic base (NaOH) was introduced into the reaction system, both conversion and ee value of the product dropped substantially. The conversion and ee value were only 6.2% and 3.5%, respectively, when the concentration of base in the reaction system was 0.1 M. According to reaction (2), part of substrate was converted to A in acid solution. Although the protonated substrate was unfavorable for the substrate coordination to catalytically active species HRuCl(P–P) [15,16], the fact that catalytic activity was greatly improved confirmed that the coordination of substrate was not the step of rate determination in this reaction. The promotion of the catalytic activity by HCl solution should be owing to that the protonated substrate was a better acceptor of the hydride in the catalytically active intermediate. As a result, it proved that the step of rate determination was the transferring of hydride in the catalytically active species to the coordinated substrate. In contrast, the formation of B not only decreased the reaction activity of substrate, but also ee value of the product was deteriorated. Probably, Cl^- in the catalytically active species HRuCl(P–P) would be substituted by OH^- in the presence of a higher concentration of NaOH solution to form a new species HRu(OH)(P–P) that could be unfavorable for the hydrogenation reaction.

Table 3
Effect of aprotic/protic solvents on conversion and ee value
Reaction conditions: *o*-chloroacetophenone as substrate; others were the same as in Table 2.

Solvent (CH_2C1_2:CH_3OH)	Conversion (%)	ee	Optical rotation
1:0	51.6	56	+
0:1	90	82	−
1:1	24.5	75	−
3:1	22.6	55.8	−
10:1	8.3	5.7	−



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3.5. Effect of aprotic and protic solvents

The effects of aprotic and protic solvents on the hydrogenation reaction are listed in Tables 2 and 3. According to the results in Table 2, the

Table 2
Asymmetric hydrogenation of *o*-chloroacetophenone in different solvents
Reaction conditions: time 48 h, others were the same as in Table 1.
a = Chiral alcohol. *b* = Acetophenone. *c* = Condensation product of substrate with methanol.

Run	Solvents	Conversion (%)	Distribution of products (%)			ee (%)	Rotation light
			a	*b*	*c*		
1	Methanol[a]	90	97.2	0.7	2.1	82	(−)
2	Dried methanol	76	93.2	1.0	5.8	83	(−)
3	CH_2Cl_2	51.6	98.0	2.0	0	56	(+)
4	Toluene	60	99.1	0.9	0	65	(+)
5	THF	7.2	95.0	5.0	0	34	(+)
6	CH_2Cl_2:methanol (1:1)	25	85.5	1.6	12.9	75	(−)

[a]A.R. agent, containing 0.1% water.

aprotic solvents were poor solvents in this reaction system, and the asymmetric hydrogenations of acetophenone derivatives in these solvents exhibited low conversions and low ee values. When a mixture of methanol and dichloromethane was used as solvent, the conversion and ee value of the product were 27% and 75%, respectively. One interesting phenomenon was that the sign of optical rotation of hydrogenation product changed with using protic and aprotic solvents. For the protic solvent (methanol), the optical rotation was negative (−), and for the aprotic ones, it was positive (+). However, in comparison with that in Run 2 in Table 2, the result in Run 1 suggested that the trace amount of water in the reaction system would promote the asymmetric hydrogenation reaction, and similar result has also been reported by other authors [17]. Furthermore, the trace amount of water in the reaction system would also suppress the dehalogenated reaction and the condensation reaction of ketone with methanol.

Interestingly, when a mixed solvent was used in the reaction system, the reaction conversion and ee value could change with the ratio change of aprotic to protic solvents (Table 3). Methanol played a major role in deciding the direction of optical rotation. Even though the ratio of dichloromethane to methanol was up to 10 times, the optical rotation still exhibited negative signal as in pure methanol. However, the conversion and ee value dropped considerably to 8.3% and 5.7%, respectively.

3.6. Hydrogenation of o-substituted acetophenones

The results of the asymmetric hydrogenations of acetophenones with different *o*-substituted groups are listed in Table 4. These results showed that because of the auxiliary coordination of halogen in the *ortho* position of acetophenone, the asymmetric hydrogenation results were greatly influenced. The methoxyl substituent did cause not only the decrease of reaction activity of the substrate, but also the drop of ee value of the product, giving a conversion of 12% and ee of 27%. The chloro substituent in acetophenone remarkably promoted both the hydrogenation activity of the substrate and enantioselectivity of product, giving a conversion of 90% and ee of 82%. Furthermore, bromo substituent gave the best conversion of 99% and very high ee of 97% under the similar reaction conditions. Although a fluoro substituent did not give a high conversion (27%), the product was of the highest ee value (99%). The order of the conversion increase may be reasonably explained by the Lewis acid and base theory. Bromo group was a softer Lewis base than the oxygen, chloro and fluoro groups, so *o*-bromoacetophenone would be more favorable for its coordination to ruthenium being a soft Lewis acid and sped up the hydrogenation reaction. Similarly, the reaction activity of *o*-chloroacetophenone would be better than *o*-fluoroacetophenone.

Table 4
Asymmetric hydrogenation of acetophenones with the different substitute groups
Reaction conditions: same as Table 2.
a = Chiral alcohol. *b* = Acetophenone. *c* = Condensation product of ketone with methanol.

Entry	Substrates	Conversion (%)	Distribution of products (%)			ee (%)	Rotation of light or configuration
			a	*b*	*c*		
1	Acetophenone	8.0	100	0	0	42	(−)
2	*o*-Methoxyacetophenone	12	95.1	0	4.9	27	(−)
3	*o*-Fluoroacetophenone	27	79.3	0	20.7	> 99	(−)
4	*o*-Chloroacetophenone	90	97.2	0.7	2.1	82	(−)
5	*o*-Bromoacetophenone	99	95.7	4.3	0	97	(−) S

4. Conclusion

The $NH_2Et_2\{Ru_2Cl_5[(S)$-*tol*-BINAP$]_2\}$ was a good catalyst for the hydrogenation of *o*-chloroacetophenone and a very excellent catalyst for *o*-fluoroacetophenone and *o*-bromoacetophenone with very high ee value, but it was a poor catalyst for *o*-methoxyacetophenone to form enantiomerically pure secondary alcohol.

References

[1] S.A. King, A.S. Thompson, A.O. King, T.R. Verhoeven, J. Org. Chem. 57 (1992) 6689.
[2] H. Kawano, Y. Ishii, M. Saburi, Y. Uchida, J. Chem. Soc., Chem. Commun. (1998) 87.
[3] K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, J. Org. Chem. 59 (1994) 3064.
[4] K. Mashima, T. Akutagawa, X. Zhang, H. Takaya, J. Organomet. Chem. 428 (1992) 213.
[5] M. Marchetti, E. Alberico, C. Bertucci, C. Botteghi, G.D. Ponte, J. Mol. Catal. A: Chem. 125 (1997) 109.
[6] H. Doucet, T. Ohkuma, K. Murata, T. Yokozawa, M. Kozawa, E. Katayama, A.F. England, T. Ikariya, R. Noyori, Angew. Chem. Int. Ed. 37 (1998) 1703.
[7] V.H. Rane, D. Tas, R.F. Parton, P.A. Jacobs, Catal. Lett. 41 (1996) 111.
[8] J. Gao, T. Ikariya, R. Noyori, Organometallics 15 (1996) 1087.
[9] A. Fujii, S. Hashiguchi, N. Uemastu, T. Ikariya, R. Noyori, J. Am. Chem. Soc. 118 (1996) 2521.
[10] T. Ohkuma, H. Doucet, T. Pham, K. Mikami, T. Korenaga, M. Terada, R. Noyori, J. Am. Chem. Soc. 120 (1998) 1086.
[11] H. Doucet, P.L. Gendre, C. Bruneau, P.H. Dixneuf, J.C. Souvie, Tetrahedron: Asymmetry 7 (1996) 525.
[12] T. Ikariya, Y. Ishii, H. Kawano, T. Arai, M. Saburi, S. Yoshikawa, S. Akutagawa, J. Chem. Soc., Chem. Commun. (1985) 922.
[13] H. Takaya, T. Ohta, R. Noyori, N. Sayo, H. Kumobayashi, S. Akutagawa, E.P. 256634 1988, C.A. 109, 73668.
[14] D. Blanc, J. Henry, V. Ratovelomanana-Vidal, J. Genet Tetrahedron Lett. 38 (1997) 6603.
[15] D. Evans, J.A. Osborn, F.H. Jardine, G. Wilkinson, Nature 208 (1965) 1203.
[16] M.T. Ashby, J. Halpern, J. Am. Chem. Soc. 113 (1991) 589.
[17] K. Mashima, Y. Matsumura, K. Kusano, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, J. Chem. Soc., Chem. Commun. (1991) 609.