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An improved synthesis of chiral diols via the asymmetric catalytic hydrogenation of prochiral diones

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Abstract: The rates of the asymmetric hydrogenation of prochiral diketones catalyzed by Ru(BINAP) catalysts were substantially accelerated in the presence of small amounts of a strong acid. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

Chiral diols are highly useful ligands for the preparation of chiral reagents, catalysts, and other chiral ligands. For example, enantiomerically pure 1,2-, 1,3-, and 1,4-diols are important intermediates for the preparation of the useful chiral diphosphine ligands such as CHIRAPHOS,[1] SKEWPHOS,[2] and DuPHOS,[3] respectively. Traditionally these diols can be prepared from the asymmetric reduction of the corresponding diones via hydrogenation,[4] borane reduction,[5] hydrosilylation,[6] or enzymatic reduction.[7] Burk *et al.* also developed a method based on the asymmetric hydrogenation of β-ketoesters followed by Kolbe electrochemical coupling for the preparation of the 1,4-diols.[3] From a practical standpoint, the catalytic asymmetric hydrogenation of the corresponding diones is probably the most convenient method for the preparation of these diols if high yields can be obtained. Both Kawano *et al.* and Kitamura *et al.* studied the asymmetric hydrogenation of 1,3-diketones with Ru(BINAP) catalysts and achieved high e.e.s for the 1,3-diol products.[4] The hydrogenation of 1,2-diketone gave mostly *meso* products. In both cases the rates of reaction were quite slow. The asymmetric hydrogenation of 1,4-diketone was not successful, giving complex mixtures of unidentified high boiling by-products. In this paper we report a simple Ru(BINAP) catalyst system which gives a much faster rate of reaction in the hydrogenation of diketones. The system can be used for the convenient preparation of a variety of chiral diols including the highly useful chiral 1,4-diols.

Results and discussion

Ru(BINAP) type complexes have been well established as versatile catalysts for the asymmetric hydrogenation of a variety of prochiral unsaturated compounds. However, the rate of reaction and the enantioselectivity of these catalysts are quite sensitive to the reaction conditions. Depending on the type of substrates used, changing reaction conditions can either be beneficial or detrimental. Halpern *et al.* found that the presence of small amounts of a strong acid significantly retarded the rate of the Ru(BINAP)$(OAc)_2$-catalyzed hydrogenation of substituted acrylic acids.[8] In contrast, King *et al.* discovered that the addition of a strong acid can substantially increase the rate of the Ru(BINAP)-catalyzed hydrogenation of α-, β-, or γ-ketoesters.[9] Since diketones bear more similarity to ketoesters, we decided to investigate the effect of acids on the hydrogenation of diketones.

The asymmetric hydrogenation of diketones is a complex reaction. Because of the existence of four enantiofaces in the starting material, theoretically there are eight possible products as shown below.

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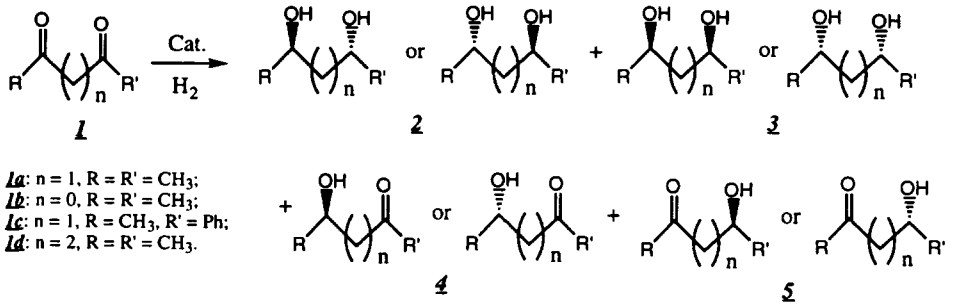

When R=R′, the two isomers of **3** are identical *meso* compounds; and **4** and **5** are identical pairs of enantiomers. The challenge of asymmetric catalysis is to produce only one of these compounds at will. In this study the target is to produce only one isomer of **2.**

In the initial phase of this study we chose the Ru(BINAP)-catalyzed hydrogenation of 2,4-pentanedione as a model reaction for the investigation of the effect of acids on the rate of reaction. This reaction was successfully carried out, albeit with rather slow rate, by Kawano *et al.*[4a] using $[Ru(BINAP)Cl_2]_2 \cdot NEt_3$ as catalyst precursor and by Kitamura *et al.*[4b] using an empirically designated catalyst precursor $Ru(BINAP)Cl_2$ which was prepared in situ by mixing $Ru(OAc)_2(BINAP)$ with HCl. [Based on recent reports in the literature, the exact formula of the catalyst precursor used by Kawano *et al.* probably should be $[NH_2Et_2][\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3].$][10] Because of the simplicity of synthesis and because of the well characterized nature of this species, we chose $[NH_2Et_2][\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]$ as a catalyst precursor for our investigation. Similar to previous investigators, we found that the rates of the hydrogenation of diketones were very slow with this catalyst although the enantioselectivities were extremely high. However, the rates of hydrogenation were found to increase substantially upon the addition of small amounts of a strong acid such as hydrochloric acid or sulfuric acid. For example, in the absence of added acid, the hydrogenation of 2,4-pentanedione using $[NH_2Et_2][\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]$ as catalyst precursor with a substrate/catalyst molar ratio of 5000 and under 69.0 kg cm^{-2} H_2 at 60°C, produced only 16.3% of the monohydrogenated product **4** in 40 minutes. No dihydrogenated product was obtained. When a small amount of hydrochloric acid (0.4 mol% with respect to the substrate) was added to the reaction mixture, the same reaction under otherwise identical conditions gave 87.4% hydrogenation products out of which 97.5% were dihydrogenated products (DL/*meso*=161.5) and only 2.5% was monohydrogenated product. It was observed in these experiments that in addition to the hydrogenation products **2**, **3** and **4**, some of the starting material was converted to condensation by-products. Although the structures of the condensation by-products have not yet been clearly established, the condensation reaction appeared to be reversible and the by-products were found to be converted to the hydrogenation products under hydrogenation conditions, particularly in the presence of hydrochloric acid. More detailed data on the effect of acid on the rate of the hydrogenation of 2,4-pentanedione are summarized in Table 1.

It was quite clear from Table 1 that the rate-enhancing effect of the strong acid in the Ru(BINAP)-catalyzed hydrogenation of 2,4-pentanedione was highly significant. It should be noted that the e.e.s in the acid-promoted reactions were not sacrificed for the rate enhancement effect: essentially quantitative e.e. for the chiral 1,3-diol was obtained in all of these experiments. These results indicate an excellent opportunity for the investigation of the acid-promoted, Ru(BINAP)-catalyzed asymmetric hydrogenation of diketones as a practical method for the production of chiral diols.

The rate acceleration by strong acids in the Ru(BINAP)-catalyzed hydrogenation of diketones was observed in all of the diketones examined. Most interestingly, the hydrogenation of 2,5-hexanedione, which did not give any hydrogenation product in the absence of added acids, gave reasonably good yields of the desired hydrogenation product in >99.5% e.e. This finding is interesting because the chiral 1,4-diol is an important intermediate for the preparation of the DuPhos type chiral phosphine ligands which have been reported to be highly effective in asymmetric hydrogenation reactions. We

Table 1. The effect of hydrochloric acid on the rate of the hydrogenation of 2,4-pentanedione (**1a**)[a]

Entry	Sub./Cat. (M/M)	HCl/Sub. (M/M)x100	Reaction time (min)	Conv. (%)[b]	Yield of alcohols (%)[b]	Ratio of products[b] (2)[c] : (3) : (4)			Condensation byproduct (%)[b]
1	5000	0	40	44.5	16.3	0	0	100	28.2
2	5000	0	150	73.5	43.3	1.8	0	98.2	30.2
3	2500	0	40	97.9	78.5	50.1	0.6	49.3	19.4
4	2500	0	150	99.0	91.7	92.7	0.5	6.8	7.3
5	5000	0.4	40	100	87.4	96.9	0.6	2.5	12.6
6	3500	0.2	30	100	82.2	83.1	0.6	16.3	17.8
7	3500	0.4	20	100	83.8	26.4	0	73.6	16.2
8	3500	0.4[d]	30	100	88.5	99.4	0.6	0	11.5
9	3500	0.4	30	100	89.4	99.4	0.6	0	10.6
10	3500	0.4	300	100	98.8	99.4	0.6	0	1.2
11	3500	0.8	20	100	67.2	17.5	0	82.5	32.8
12	3500	0.4	20	100	79.4	64.7	0.6	34.7	20.6
13	3500	0.4	60	100	82.4	70.4	0	29.6	17.6
14	3500	0.4	60	88.6	64.7	6.2	0	93.8	23.9
15	3500	0.4	300	100	>95[e]	>99.9	<0.1	0	0

a) The reactions were carried out in 1 M (substrate) methanol solution (except in entry 15) under the following conditions: reaction temperature = 60 °C except in entry 12 (T = 70 °C); P_{H2} = 69.0 kg cm^{-2} except in entry 13 (P_{H2} = 34.5 kg cm^{-2}) and entry 14 (P_{H_2} = 13.8 kg cm^{-2}). b) Based on GLC analysis with a Chrompack Chirasil-dex column (25 m x 0.25 mm). c) e.e.>99.5% in all cases (only one enantiomer was observed in the chiral GLC analyses.) d) sulfuric acid was used instead of HCl. e) Isolated yield. The reaction was carried out in 2M methanol solution with 30 g substrate. The analytical data were based on the isolated material.

believe this is the most convenient method for the preparation of enantiomerically pure 1,4-diols. More detailed data on the effect of acid on the hydrogenation of several diketones are summarized in Table 2.

In conclusion we have observed a significant rate-enhancement effect by the addition of a strong acid in the Ru(BINAP)-catalyzed asymmetric hydrogenation of diketones leading to the desired chiral diols. The method can be used for the preparation of chiral α, β, and γ diols in good yields and excellent e.e.s.

Experimental

Except as noted, all experiments were carried out under a nitrogen atmosphere and the commercial reagents were used as received without further purification. The catalyst precursor, $[NH_2Et_2][\{RuCl(S\text{-}BINAP)\}_2(\mu\text{-}Cl)_3]$, was prepared according to the procedure of King *et al.*[10]

A typical procedure for the catalytic hydrogenation of 2,4-pentanedione

A 45 mL glass-lined stainless steel reactor equipped with a magnetic stirring bar was charged with 0.5 g of 2,4-pentanedione, 2.4 mg of $[NH_2Et_2][\{RuCl(S\text{-}BINAP)\}_2(\mu\text{-}Cl)_3]$ and 5 mL of methanol which contained 0.02 mmol of HCl under a nitrogen atmosphere. The reactor was closed and pressurized with H_2 to 69.0 kg cm^{-2}. The mixture was stirred with a magnetic stirrer under the H_2 pressure at 60°C for 40 minutes. The H_2 was vented and the product was analyzed by GLC using a 25 m×0.25 mm Chrompack Chirasil-dex capillary column. In all cases the *S*-configuration was observed for the major isomers. The analytical data for the products were as follows.

Table 2. The effect of acid on the catalytic hydrogenation of diketones[a]

Entry	sub.	Sub./Cat. (M/M)	HCl/Sub (M/M)x100	Reaction time (hr)	1 left (%)[b]	Yield of[b] alcohols(%)	Ratio of products[b] (2)[c]: (3) : (4 +/or 5)			Condensation byprod. (%)[b]
1	1b	2000	0	4	5.2	19.1	29.1	70.9	8.2	75.7
2	1b	2000	0.4	4	0	86.4	26.8	73.2	0	13.6
3	1c	2000	0	4	76.6	17.3	0	0	100	6.1
4	1c	2000	0.4	4	0	76.2	95.4	4.6	0	23.8
5	1d	500	0	15	6.8	0	0	0	0	93.2
6	1d	500	0.6	15	1.5	14.1	83.5	16.5	0	84.4
7	1d	2000	0.2	96	1.3	53.3	83.9	16.1	0	45.4
8	1d	2000	0.2	300	1.0	86.4	83.9	16.1	0	12.6

a) The reactions were carried out in 1 M (substrate) methanol solution under the following conditions: reaction temperature = 70 °C; P_{H2} = 69.0 kg cm^{-2} except in entries 7 and 8 (P_{H2} = 82.8 kg cm^{-2}). b) Based on GLC analysis with a Chrompack Chirasil-dex column (25 m x 0.25 mm). c) e.e.>99.5% in all cases except for entry 4 in which the e.e. of the diol was 96.1%.

2S,4S-Pentanediol

$[\alpha]^{20}_D$ +41.2 (c=1.64, $CHCl_3$); mp=46.5–48°C; bp=60–63°C, 1 mmHg. GLC conditions: N_2, 1.0 kg cm^{-2}; oven temp.=100°C; t_R=4.30 min (*S*-β-hydroxyketone), 9.02 min (*S,R*), 9.96 min (*R,R*), and 10.20 min (*S,S*).

2,3-*Butanediol*

GLC analysis of the diacetyl derivative: N_2, 1.0 kg cm^{-2}; oven temp.=110°C; t_R=4.09 min (*S,S*), 4.25 min (*R,R*), and 4.62 min (*S,R*).

1-*Phenyl*-1,3-*butanediol*

GLC analysis of the diacetyl derivative: N_2, 1.0 kg cm^{-2}; oven temp.=150°C; t_R=13.46 min (*S,S*), 13.74 min (*R,R*), and 14.30 min (*S,R*).

2S,5S-Hexanediol

$[\alpha]^{20}_D$ +35.3 (c=1.36, $CHCl_3$) {lit.[7]: $[\alpha]^{20}_D$ +34.9 (c=9.48, $CHCl_3$); mp=52.5–53.5°C; bp=68–71°C, 1 mmHg. GLC analysis of the diacetyl derivative: N_2, 1.0 kg cm^{-2}; oven temp.=120°C; t_R=7.15 min (*S,S*), 8.46 min (*S,R*), and 9.52 min (*R,R*).

Acknowledgements

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