SHORT PAPER

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Asymmetric synthesis of chiral δ-lactones using BINAP-ruthenium(II) complexes hydrogenation catalysts†

Yanjun Li* and Taeko Izumi

Department of Chemistry and Chemical Engineering, Faculty of Engineering, Yamagata University, 3-16 Jonan 4-Chome, Yonezawa, 922-8510, Japan

Asymmetric hydrogenation of keto-acids was accomplished by catalytic amounts of BINAP-ruthenium complexes to afford the corresponding δ-lactones in high yields. The optical purity of the synthesised δ-lactones was determined by chiralcel (OD) in the 9–56% range.

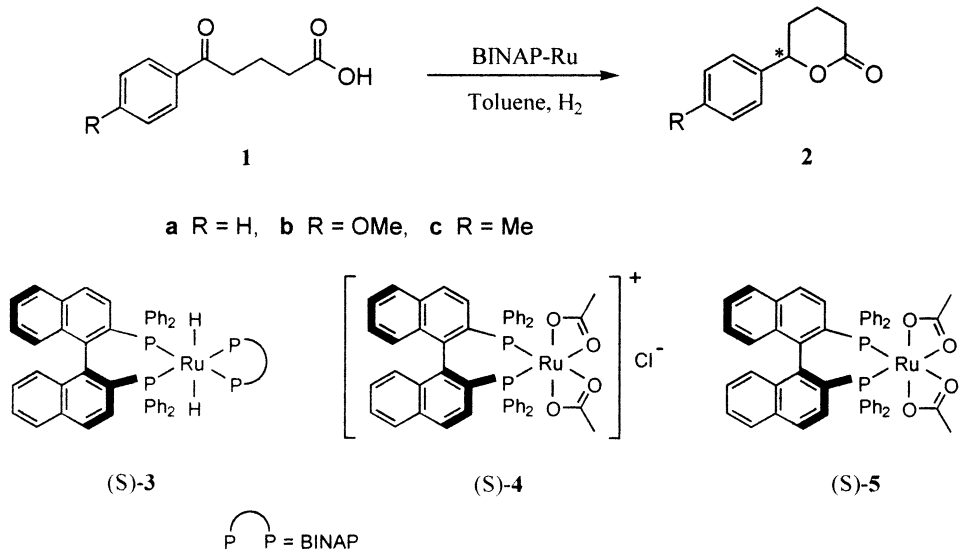
Keywords: asymmetric hydrogenation, keto-acids, BINAP-ruthenium complexes

A number of homogenous and heterogeneous ruthenium complexes catalyse hydrogenation of various substrates including olefins, aldehydes, ketones and nitro compounds.[1,2] It is also reported that ruthenium complexes generally have less effectice catalytic activities for hydrogenation of various alkenes.[3]

Due to the strong affinity of ruthenium toward heteroatom compounds, low-valent ruthenium complexes acts as efficient catalysts for reduction of different carbonyl compounds. Aldehydes,[4] ketones,[5] carboxylic acids[6] and carboxylic anhydrides[7] can be converted into the corresponding alcohols with various ruthenium complexes in an atmosphere of hydrogen gas.

Ruthenium catalysts are widely used also in organic synthesis with high chemoselectivity and regioselectivity.[8] Asymmetric hydrogenation of carbonyl compounds has been extensively studied in recent years.[9] To the best of our knowledge, there have been a few reports on enantioselective hydrogenation of alkylidene lactones catalysed to chiral lactones by BINAP-Ru(II) complexes.[10] Although Osakada *et al*, demonstrated racemic γ-lactones could be prepared by using $[RuH_2(PPh_3)_4]$ and $[RuCl_2(PPh_3)_3]$ catalysed hydrogenation of keto-acids,[11] there is no report on the synthesis of chiral δ-lactones from keto-acids by using chiral ruthenium complexes. Our ultimate goal is to devise a catalytic method for the synthesis of optically active δ-lactones, which often occur in nature or as parts of natural products.[12] Herein, we described our attempts to develop an enantioselective hydrogenation of keto-acids using a variety of chiral reduction catalysts. The asymmetric reduction of keto-acid derivatives (**1a–c**) was carried out to afford the corresponding chiral δ-lactones (**2a–c**) by using ruthenium-BINAP catalysts in the presence of H_2 (30 kg/cm^2) (Scheme 1).

The keto-acids (**1a–c**) were employed as the model substrates for our study since they are easily prepared by Friedel–Crafts reaction. $[RuH_2\{(S)\text{-BINAP}\}_2]$, $[RuCl_2\{(S)\text{-BINAP}\}]$ and $[Ru(OAc)_2\{(S)\text{-BINAP}\}]$ were prepared according to the literature procedure.[13] The asymmetric hydrogenation of keto-acids (**1a–c**) was then investigated. Three kinds of BINAP- ruthenium complexes were tested and the results are shown in Table 1. The reduction of **1a** was carried out by using (S)-**3** and (S)-**4** as catalysts, which afforded product **2a** in yields of 68%, 56% ee and 72%, 44% ee respectively. However, when the reaction was carried out below 150°C, it gave a very low conversion.[14] In the presence of



Scheme 1

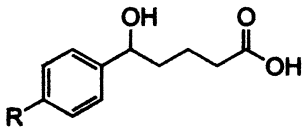
* To receive any correspondence. E-mail: tr230@dip.yz.yamagata-u.ac.jp

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Asymmetric hydrogenation catalysed by BINAP-Ru complexes[a]

Entry	Substrate	Catalyst	Temp./°C	Solvent	Yield[b]/%	e.e[c]/%	Config.[d]
1	**1a**	(S)-**3**	150	Toluene	68	56	R
2	**1a**	(S)-**4**	150	Toluene	72	44	S
3	**1a**	(S)-**5**	120	Toluene	82	22	S
4	**1b**	(S)-**5**	120	Toluene	88	9	S
5	**1c**	(S)-**3**	120	Toluene	56	26	S
6	**1c**	(S)-**5**	80	CH_2Cl_2	<5	—	—
7	**1c**	(S)-**5**	120	Toluene	92	38	S

[a]Reactions were carried out in autoclave under 30 kg/cm^2 of hydrogen gas for 24h using 2 mol% of catalyst.
[b]Isolated yield.
[c]Determined by HPLC on a Chiralcel OD column.
[d]Absolute configuration is based upon measurement of rotation and comparison with the literature.



6a-c R = H, -OMe, -Me

hydrogen gas (30 kg/cm^2), the [Ru(OAc)$_2${(S)-BINAP}] catalyst gave a relatively high yield (82–92%) via asymmetric reduction of **1a–c**. Since high reaction temperatures are necessary to carry out the dehydration process to synthesise the lactones **2a–c**, at 80°C in CH_2Cl_2 as solvent, the hydrogenation **1c** can only afford products like **2c** in less than 5% yield. It has been shown that the optimum reaction conditions for the synthesis of **2** is using dry toluene as solvent below 120°C.

The keto-acid was reduced to the corresponding intermediate δ-hydroxyacids (**6a–c**), which then cyclised immediately to afford the corresponding lactones (**2a–c**). The δ-hydroxyacids (**6a–c**) could not be isolated from the reaction. The mechanism of the hydrogen transfer reduction of α, β-unsaturated acids using [Ru(OAc)$_2${(S)-BINAP}] complex as catalyst has been established.[15] In a similar way the mechanism of the hydrogenation of keto-acids was suggested to be in Scheme 2.

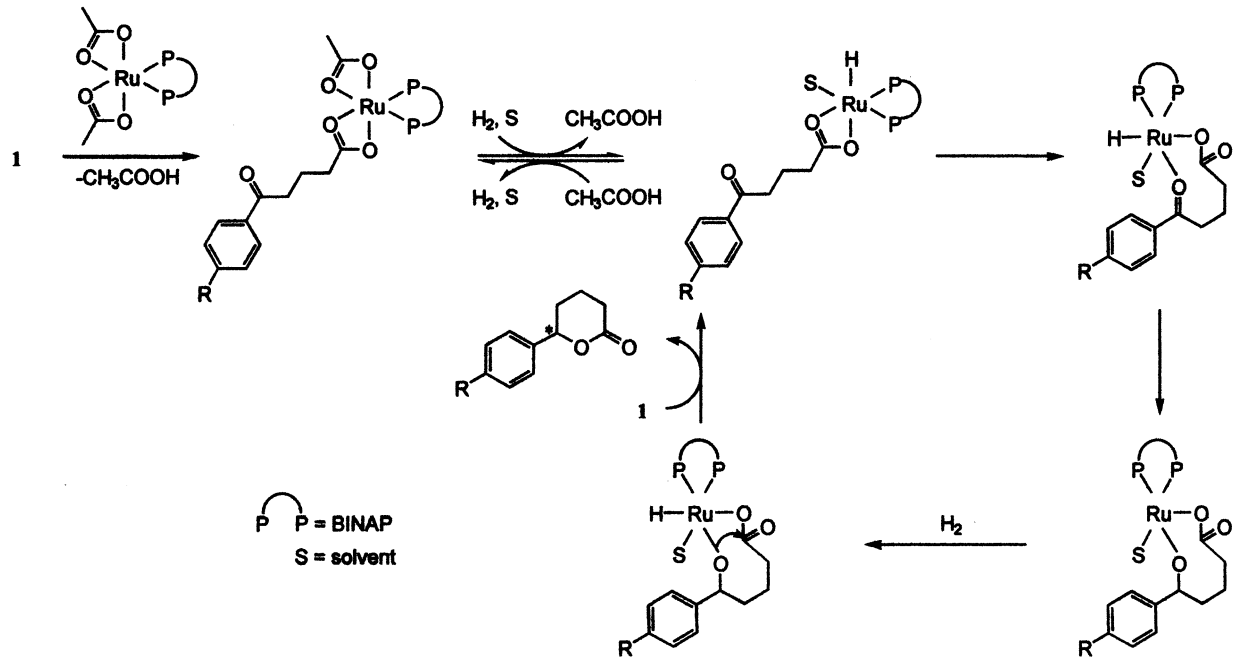
On the basis of these findings, the use of {Ru(OAc)$_2${(S)-BINAP}] is most effective for the acceleration of the reaction (Table 1, entry 3, 4, and 7), although the enantiomeric excess of the products is a little lower. The carboxylic acid has ester groups substituting at the coordination sites on the metal, and then the carbonyl of this intermediate binds the ruthenium-BINAP, where the reduction of the carbonyl group via the metal is a prerequisite to obtaining enantioselectivities in the hydrogenation reaction.

In conclusion, the use of [RuH$_2${(S)-BINAP}$_2$], [RuCl$_2${(S)-BINAP}] and [Ru(OAc)$_2${(S)-BINAP}] catalysts for reduction in dry toluene as solvent in the presence of hydrogen provides a highly efficient route for asymmetric hydrogenation of the keto-acids to form the corresponding chiral lactones.

Experimental

All substrates and ruthenium complexes were prepared according to the literature procedure. The solvent was purified by short path distillation. Melting points were determined on a Micro capillary melting point apparatus and uncorrected. IR spectra were obtained on a Horiba 710 FT-IR spectrometer. ^{1}H NMR was recorded an Varian 500 MHz spectrometer. Flash chromatography was carried out with silica gel 60 N (spherical, neutral) from Merck. Enantiomeric excesses were determined by HPLC analysis using a Chiralcel OD column. All reactions were run in autoclave under hydrogen (30 kg/cm^2).

General procedure for synthesis of chiral β*-lactones* **2a–c**: A mixture of **1c** 1.0 g (5.2 mmol) and ruthenium complex Ru(OAc)$_2$[(S)-BINAP] 0.09 g (0.104 mmol) in dry toluene (25 ml) were placed in a 100 ml stainless steel autoclave. After purging three times with



Scheme 2

hydrogen, the pressure was raised to 30 kg/cm^2 and the reaction mixture was stirred at 120°C for 24 h. The reactor was cooled and the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel using chloroform as solvent. The chiral δ-lactones **2a–c** were obtained as colourless crystals in variant yields.

δ-phenyl-δ-valerolactone (**2a**): m.p. 71–73°C; 82% yield; IR (thin film) 2979, 1731, 1261, 1108, 752, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (s, 5H), 5.36 (dd, 1H, *J* = 9.8 Hz, *J* = 3.2 Hz), 2.75–2.55 (m, 2H), 2.19–2.15 (m, 1H), 2.02–1.97 (m, 2H), 1.92–1.85 (m, 1H).

δ-(4-methoxyphenyl)-δ-valerolactone (**2b**): m.p. 59–60°C; 88% yield; IR (thin film) 2952, 1737, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, 2H, *J* = 10.3 Hz), 6.90 (d, 2H, *J* = 10.3 Hz), 5.29 (dd, 1H, *J* = 10.1 Hz, *J* = 3.5 Hz), 3.82 (s, 3H), 2.72–2.53 (m, 2H), 2.15–2.12 (m, 1H), 2.01–1.96 (m, 2H), 1.92–1.87(m, 1H).

δ-(4-methylphenyl)-δ-valerolactone (**2c**): m.p. 89–90°C; 92% yield; IR (thin film) 2954, 1735, 1241, 1043, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23 (d, 2H, *J* = 8.7 Hz), 7.18 (d, 2H, *J* = 8.7 Hz), 5.32 (dd, 1H, *J* = 9.7 Hz, *J* = 3.2 Hz), 2.73–2.54 (m, 2H), 2.36 (s, 3H), 2.17–2.13 (m, 1H), 2.00–1.95 (m, 2H), 1.91–1.84 (m, 1H).

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