Stereoselective Reduction of β-Hydroxy Ketones with Aldehydes *via* Tishchenko Reactions Catalyzed by Zirconocene Complexes[1]

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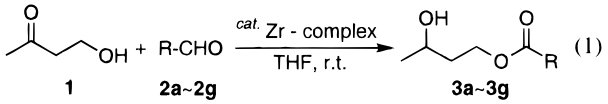
The stereoselective synthesis of 1,3-dioxygenated compounds is important from the synthetic point of view, since these fragments appear in the structure of various natural products.[2] The reduction of β-hydroxy ketones to *syn* 1,3-diols is usually carried out *via* an intermolecular hydride shift using several stoichiometric reducing agents, such as $(n\text{-Bu})_3B-NaBH_4$,[3] $Et_2BOMe-NaBH_4$,[4] terphenylboronic acid$-NaBH_4$,[5] $Ti(OPr^i)_4-NaBH_4$,[6] catecholborane,[7] tin hydride,[8] DIBAL-H,[9] and LiI$-LiAlH_4$.[10] However, there are only few reports on the stereoselective reduction of β-hydroxy ketones to *anti* 1,3-diols.[11] Recently, Evans *et al.* showed that the SmI_2-catalyzed intramolecular Tishchenko reduction of β-hydroxy ketones proceeds with excellent levels of stereochemical control to produce the corresponding *anti* 1,3-diol monoesters in high yields.[12]

In a previous paper, we showed that a zirconocene complex, Cp_2ZrH_2, serves as an efficient catalyst for the Tishchenko-type dimerization of aldehydes to esters.[13] We have now found that the reduction of β-hydroxy ketones with aldehydes can be achieved *via* the Tishchenko-type reaction in the presence of a catalytic amount of Cp_2ZrH_2 to form the corresponding diol monoesters with high levels of stereoselectivity under mild conditions. The reaction could be explained by assuming an eight-membered transition state involving the zirconocene complex.

4-Hydroxy-2-butanone (**1**) was chosen as a model substrate and allowed to react with *n*-butyraldehyde (**2a**) in the presence of a catalytic amount of zirconocene complexes (eq 1).



1 **2a~2g** **3a~3g**

Table 1 shows the representative results for the reaction of **1** with **2a** using various zirconocene complexes. The reaction of **1** with **2a** catalyzed by Cp_2ZrH_2 gave 3-hydroxy-1-butyl butanoate (**3a**) in 80% yield. $Cp_2Zr(H)Cl$ catalyzed the same reaction, but the reaction was slightly slower. When 20 mol % of $Cp_2Zr(H)Cl$ was used, **3a** was obtained in 70% yield. A low-valent zirconium species, equivalent to Cp_2Zr, derived from Cp_2ZrCl_2 and 2 equiv of *n*-BuLi, was moderately active, producing **3a** in 68% yield after 24 h. Cp_2ZrCl_2, which shows no catalytic activity for the dimerization of aldehydes, was also inactive for the present reaction.

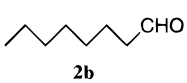
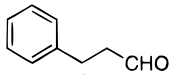
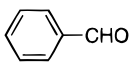
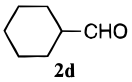
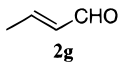
Table 1. Reduction of 4-Hydroxy-2-butanone (1) with *n*-Butyraldehyde (2a) by Various Zirconocene Complexes[a]

run	catalyst	convn (%)	**3a** (%)
1	Cp_2ZrH_2	100	80
2	$Cp_2Zr(H)Cl$	45	26
3[b]	$Cp_2Zr(H)Cl$	100	70
4[c]	Cp_2ZrCl_2/2 ^{n}BuLi	99	68
5	Cp_2ZrCl_2	36	trace

[a] **1** (1 mmol) was allowed to react with **2a** (4 mmol) under the influence of the zirconocene catalyst (0.05 mmol) in THF (0.25 mL) at room temperature for 5 h under Ar. [b] Catalyst (0.20 mmol), THF (1.0 mL), 24 h. [c] 24 h.

On the basis of these results, **1** was allowed to react with various aldehydes in the presence of Cp_2ZrH_2 (Table 2). The reaction of **1** with aliphatic aldehydes (**2b**−**e**) produced the corresponding diol monoesters in moderate to good yields, while no diol monoesters were obtained when benzaldehyde (**2f**) and crotonaldehyde (**2g**) were used as substrates. In a previous paper,[13] we showed that these aldehydes, **2f** and **2g**, were inert for the Cp_2ZrH_2-catalyzed Tishchenko reaction. This may be due to the difficulty of the hydride shift from the benzyloxy moiety to the carbonyl carbon due to the electron-withdrawing property of the phenyl group.

Table 2. Cp_2ZrH_2-Catalyzed Reduction of 1 with Various Aldehydes *via* Intramolecular Tishchenko Reaction[a]

Aldehyde	Product (%)	Aldehyde	Product (%)
 **2b**	**3b** (98)	 **2e**	**3e** (80)
 **2c**	**3c** (95)	 **2f**	no reaction
 **2d**	**3d** (55)	 **2g**	no reaction

[a] **1** (1 mmol) was allowed to react with aldehyde (4 mmol) under the influence of Cp_2ZrH_2 (0.05 mmol) in THF (0.25 mL) at room temperature for 5 h under Ar.

When 4-hydroxy-2-pentanone (**4**) was reacted with **2a** under the influence of Cp_2ZrH_2, the corresponding *anti* 1,3-diol monoester (**5**) was obtained in almost quantitative yield with high stereoselectivity (eq 2). The config-

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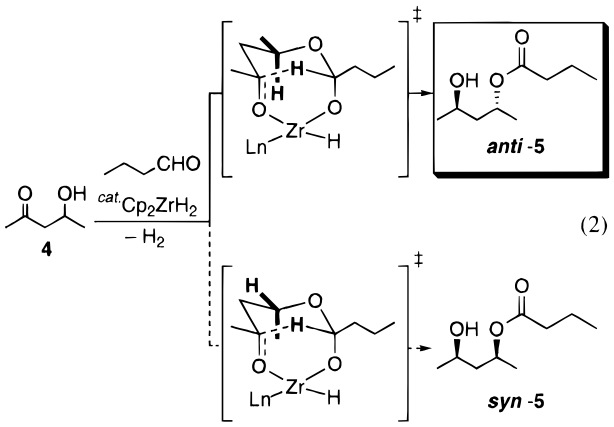
S0022-3263(97)00031-5 CCC: $14.00

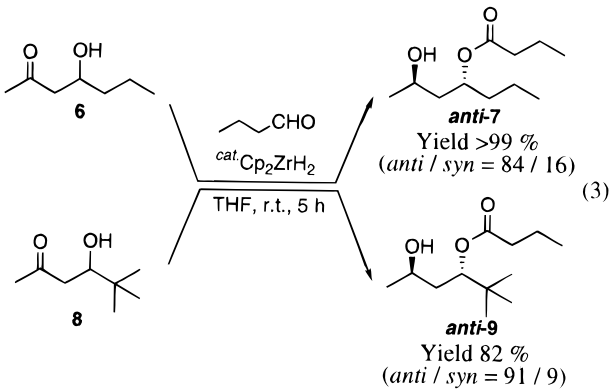


(2)

Yield >99 % (*anti* / *syn* = 97 / 3)

uration of *anti*-**5** was identified by comparison of its spectral data with those of the authentic sample derived from *anti*-2,4-pentanediol and butyryl chloride. In contrast to the reduction of β-hydroxy ketones with hydrides which produces *syn* 1,3-diols,[3−10] the present reaction gave *anti* 1,3-diols.

The reduction of unsymmetrical β-hydroxy ketones, such as 4-hydroxy-6-heptanone (**6**) and 4-hydroxy-2,2-dimethyl-6-heptanone (**8**), with 4 equiv of **2a** in the presence of Cp_2ZrH_2 (5 mol %) produced the corresponding *anti* 1,3-diol monoesters, *anti*-**7** and *anti*-**9**, with high diastereoselectivities (eq 3). It is interesting to note that

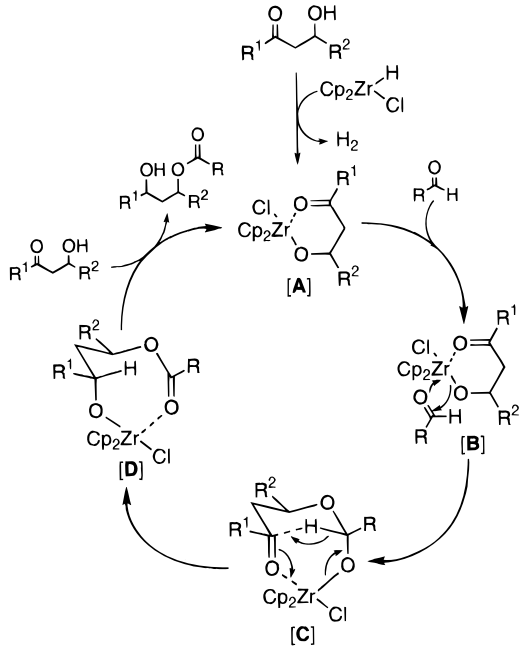


(3)

no acyl migration was observed even if the reaction was prolonged to 24 h because the Aldol−Tishchenko reaction of 3-pentanone with 2 equiv of butyraldehyde catalyzed by $BuTi(O^iPr)_4Li$ for 24 h is reported to form a regioisomeric mixture of the corresponding *anti* 1,3-diol monoesters such as (1*SR*,2*SR*,3*SR*)-3-hydroxy-2-methyl-1-propylpentylbutanoate and (1*SR*,2*RS*,3*SR*)-1-ethyl-3-hydroxy-2-methylhexyl butanoate based on an acyl migration.[14]

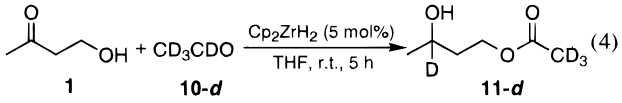
The present stereoselective reduction of β-hydroxy ketones with aldehydes *via* the Tischenko reduction is explained in Scheme 1. The fact that the reaction proceeds with high stereoselectivity can be explained by considering an eight-membered chelated transition state in which the methyl group locates favorably in the equatorial position. The reaction may be initiated *via* the formation of an alkoxyzirconium species [**A**] from β-hydroxy ketone and $Cp_2Zr(H)Cl$. The formation of the intermediate [**A**] is confirmed by the observation of the evolution of hydrogen gas, which indicates that the direct

Scheme 1. Possible Mechanism of Stereoselective Reduction of β-Hydroxy Ketone with Aldehyde *via* Tishchenko-Type Reduction Catalyzed by $Cp_2Zr(H)Cl$



hydride shift from the $Cp_2Zr(H)Cl$ to the carbonyl group of **1** occurs with difficulty. The coordination of an aldehyde to the zirconium species [**A**] followed by a migration of an alkoxy moiety to the carbonyl of the aldehyde leads to an eight-membered transition state [**C**] on which a subsequent intramolecular hydrogen transfer to the carbonyl group produces an alkoxyzirconium species [**D**]. The attack of [**D**] by a second molecule of β-hydroxy ketone results in the formation of 1,3-diol monoester as well as the original complex [**A**]. Similar paths are proposed in the SmI_2-catalyzed intramolecular Tishchenko reduction of β-hydroxy ketones, 3-hydroxy-2-methyl-5-undecanone and 2,6-dimethyl-5-hydroxy-3-heptanone,[12] and the Reformatsky-type reaction of bromoacetates derived from β-hydroxy carbonyl compounds.[15]

In order to obtain further information on the reaction mechanism, a deuterium label experiment was performed. The reaction of **1** with CD_3CDO (**10**-*d*) catalyzed by Cp_2ZrH_2 produced 3-hydroxy-3-deuteriobutyl acetate-d_3 (**11**-*d*) (eq 4). This finding indicates that the deute-



(4)

rium of the aldehyde transfers to the carbonyl carbon of **1**. The time dependence of **10** and **10**-*d* was followed by GC. A second-order plot provided almost a straight line except for the later stage of the reaction (Figure 1). The isotope effect (k_H/k_D) in the reaction of **1** with CH_3CHO (**10**) and CD_3CDO (**10**-*d*) by Cp_2ZrH_2 was estimated approximately as 1.8, suggesting that the hydride transfer may be involved in the rate-limiting step, although the hydride transfer step is not the rate-limiting step in the SmI_2-catalyzed Tishchenko reduction of β-hydroxy ketone with **10** and **10**-*d*, since no isotope effect (k_H/k_D = 1) is observed.

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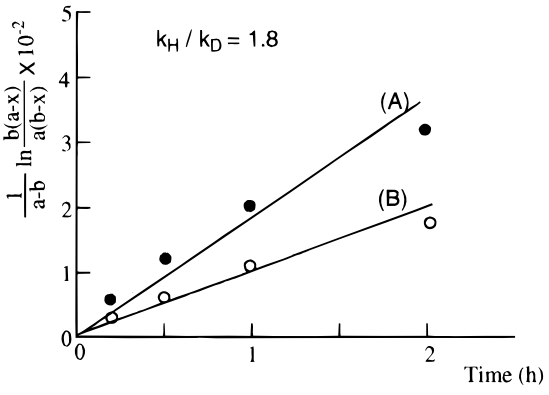
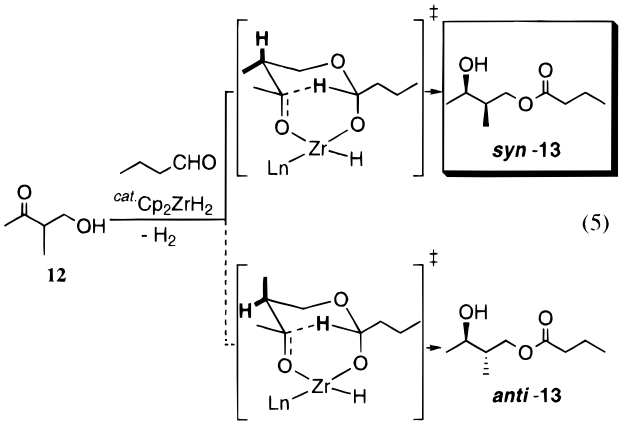


Figure 1. Plot of $(1/a-b)\ln(b(a-x)/a(b-x)) \times 10^{-2}$ vs time: (A) Reaction of **1** and **10** catalyzed by Zp_2ZrH_2; (B) Reaction of **1** and **10**-*d* catalyzed by Cp_2ZrH_2. *a* is the concentration of **1** at hourly intervals. *b* is the concentration of **10** or **10**-*d* at hourly intervals. *x* is the concentration of **11** or **11**-*d* at hourly intervals.

The reaction of **12** with **2a** under the same reaction conditions gave the corresponding diol monoester (**13**) with high stereoselectivity (*syn*/*anti* = 95/5) (eq 5). The configuration of *syn*-**13** was identified through an independent preparation of *syn*-2,3-2-methyl-1,3-butanediol according to the literature procedure.[16] The formation of *syn*-**13** was explained by assuming a similar mechanism. It is noteworthy that 1,2-*syn* diastereoselective induction was accomplished by the Tishchenko-type reduction using zirconocene complexes, because the diastereoselective reduction of this type of compounds was difficult to carry out by other methods. For instance, the reduction of 2,4-dimethyl-1-hydroxy-3-pentanone or 3-((*tert*-butyldimethylsilyl)oxy)-2-methyl-1-phenyl-1-propanone by $Me_4NHB(OAc)_3$[11a] or $LiAlH_4$[17] gave the 1,2-*syn* 1,3-diols in moderate diastereoselectivities, *syn*/*anti* = 83/71 or 70/30, respectively.



Yield 92 % (*syn* / *anti* = 95 / 5)

In conclusion, the highly stereoselective reduction of *β*-hydroxy ketones with aldehydes catalyzed by Cp_2ZrH_2 was successfully achieved under mild conditions. This method provides a new alternative stereoselective route to *anti*-1,3-diols, the preparation of which so far has been difficult.

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Experimental Section

General Procedures. All starting materials were commercially available and used after purification by distillation. Zirconocene complexes were prepared by the method reported previously.[13] GC analysis was performed with a flame ionization detector using a 0.2 mm × 25 m capillary column (OV-1). ^{1}H- and ^{13}C-NMR were measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard. Infrared (IR) spectra were measured using NaCl plates. GC-MS spectra were obtained at an ionization energy of 70 eV. The yields of products were estimated from the peak areas on the basis of the internal standard technique.

General Procedure for the Reduction of *β*-Hydroxy Ketones with Aldehydes. To a solution of Cp_2ZrH_2 (0.05 mmol) in THF (0.25 mL) were added *β*-hydroxy ketones (1 mmol) followed by aldehydes (4 mmol) under an Ar atmosphere at room temperature. After the mixture was stirred for 5 h, the reaction was quenched with wet ether. Products were purified by column chromatography on silica gel with *n*-hexane/AcOEt (10/1 v/v).

3a,[18] **3b**,[19] **3c**,[20] and **3d**[21] were reported previously.

3-Hydroxybutyl hydrocinnamate (3e): ^{1}H-NMR *δ* 7.18−7.31 (m, 5 H), 4.27−4.37 (m, 1 H), 4.07−4.15 (m, 1 H), 3.71−3.75 (m, 1 H), 2.94 (t, *J* = 7.83 Hz, 2 H), 2.64 (t, *J* = 7.83 Hz, 2 H), 2.17 (br s, 1 H), 1.61−1.74 (m, 2 H), 1.17 (d, *J* = 6.21 Hz, 3 H); ^{13}C-NMR *δ* 173.2, 140.3, 128.4, 128.2, 126.2, 64.6, 61.6, 37.9, 35.8, 30.9, 23.3; IR 3435.7, 2966.4, 2929.7, 1734.7, 1496.6, 1454.2, 1179.0, 751.0, 699.5 cm^{-1}.

(1*RS*,3*RS*)-3-Hydroxy-1-methylbutyl butanoate (*anti*-5): ^{1}H-NMR *δ* 5.16−5.11 (m, 1 H), 3.72−3.69 (m, 1 H), 3.19 (br s, 1 H), 2.28 (t, *J* = 7.56 Hz, 2 H), 1.68−1.55 (m, 4 H), 1.26 (d, *J* = 6.21 Hz, 3 H), 1.16 (d, *J* = 6.21 Hz, 3 H), 0.94 (t, *J* = 7.56 Hz, 3 H); ^{13}C-NMR *δ* 174.1, 67.9, 63.4, 45.8, 36.2, 22.9, 20.4, 18.2, 13.3; IR 3419.7, 2966.6, 1731.0, 1455.8, 1377.8, 1193.8 cm^{-1}.

(1*RS*,3*RS*)-3-Hydroxy-1-propylbutyl butanoate (*anti*-7): ^{1}H-NMR *δ* 5.10−5.05 (m, 1 H), 3.69−3.62 (m, 1 H), 2.32 (t, *J* = 7.56 Hz, 2 H), 1.71−1.26 (m, 8 H), 1.18 (d, *J* = 6.21 Hz, 3 H), 0.99−0.88 (tt, *J* = 7.56, 7.29 Hz, 6 H); ^{13}C-NMR *δ* 174.9, 71.3, 63.2, 44.6, 36.9, 36.3, 22.7, 18.6, 18.5, 13.7, 13.6; IR 3448.2, 2962.1, 1713.0, 1465.8, 1379.7, 1259.0, 1193.1, 1150.6 cm^{-1}. The configuration was identified through comparison of the spectral data of the corresponding 1,3-diol prepared by hydrolysis of **7** with the literature data.[22]

(1*RS*,3*RS*)-1-*tert*-Butyl-3-hydroxybutyl butanoate (*anti*-9): ^{1}H-NMR *δ* 4.83−4.78 (m, 1 H), 3.60−3.55 (m, 1 H), 3.04 (br s, 1 H), 2.36 (t, *J* = 7.29 Hz, 2 H), 1.73−1.62 (m, 2 H), 1.58−1.47 (m, 2 H), 1.19 (d, *J* = 6.48 Hz, 3 H), 1.00−0.89 (m, 12 H); ^{13}C-NMR *δ* 175.2, 78.2, 63.2, 39.0, 36.3, 34.0, 25.9, 22.7, 18.4, 13.7; IR 3503.5, 2966.1, 1717.5, 1458.5, 1264.8, 1188.6 cm^{-1}. The configuration was identified through comparison of the spectral data of the corresponding 1,3-diol prepared by hydrolysis of **9** with the literature data.[23]

3-Hydroxybutyl acetate (11): ^{1}H-NMR *δ* 4.33−4.24 (m, 1 H), 4.18−4.10 (m, 1 H), 3.92−3.85 (m, 1 H), 2.79 (br s, 1 H), 2.05 (s, 3 H), 1.81−1.67 (m, 2 H), 1.22 (d, *J* = 6.48 Hz, 3 H); ^{13}C-NMR *δ* 171.4, 64.5, 61.7, 37.7, 23.3, 20.8; IR 3413.1, 2968.9, 1370.2, 1245.6, 1049.1 cm^{-1}.

3-Hydroxy-3-deuteriobutyl acetate-*d*$_3$ (11-*d*): ^{1}H-NMR *δ* 4.30−4.21 (m, 1 H), 4.10−4.01 (m, 1 H), 2.07 (br s, 1 H), 1.72−1.64 (m, 2 H), 1.17 (s, 3 H); ^{13}C-NMR *δ* 171.5, 64.8, 64.4, 64.1, 61.7, 37.8, 23.3, 20.6; IR 3413.1, 2968.9, 1737.7, 1245.6, 1049.1 cm^{-1}.

(2*SR*,3*RS*)-3-Hydroxy-2-methylbutyl butanate (*syn*-13): ^{1}H-NMR *δ* 4.22−4.16 (m, 1 H), 3.99−3.93 (m, 1 H), 3.82−3.87

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(m, 1 H), 2.52 (br s, 1 H), 2.31 (t, J = 7.29 Hz, 2 H), 1.86−1.79 (m, 1 H), 1.71−1.60 (m, 2 H), 1.19 (d, J = 6.75 Hz, 3 H), 0.99−0.94 (m, 6 H); ^{13}C-NMR δ 173.8, 67.4, 66.4, 38.9, 36.0, 20.1, 18.2, 13.4, 10.6; IR 3452.3, 2966.7, 1737.0, 1462.4, 1379.7, 1258.9, 1136.2, 1093.0 cm^{-1}.

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Supporting Information Available: ^{13}C NMR, ^{1}H NMR, and IR spectra for compounds **3a**, **3b**, **3c**, **3d**, **3e**, *anti*-**5**, *anti*-**7**, *anti*-**9**, **11**, **11**-*d*, and *syn*-**13** (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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