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Highly Enantioselective Hydrogenation of β-Alkyl and β-(ω-Chloroalkyl) Substituted β-Keto Esters

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Abstract: Highly enantioselective hydrogenation of β-alkyl and β-(ω-chloroalkyl) substituted β-keto esters was achieved with Ru catalysts based on chiral diphosphines

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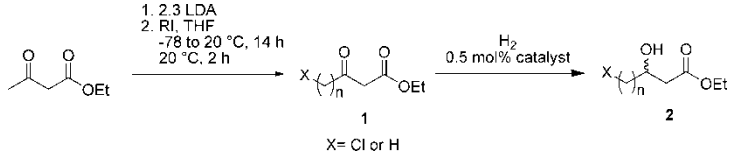
in EtOH at 50°C under 50-bar initial hydrogen pressure, affording the corresponding β-hydroxy esters in >98% ee.

Keywords: diphosphines, enantioselective hydrogenation, β-hydroxy esters, β-keto esters, ruthenium

Chiral β-hydroxy esters are important building blocks for the synthesis of biologically active compounds and natural products.[1] For example, (*R*)-3-hydroxytetradecanoic acid is the most common fatty acid constituent of the lipid A component of bacterial lipopolysaccharides (LPS).[2] (*R*)-Ethyl 3-hydroxydodecanoate is an interesting intermediate for the synthesis of Arthrobacilin, a cell-growth inhibitor.[3] (*R*)-Ethyl 6-chloro-3-hydroxy-hexanoate can be converted into (*R*)-(+)-α-lipoic acid, which is a cofactor in the biochemical decarboxylation of α-keto acids and has also been reported to be a growth factor for a variety of microorganisms.[4] Ethyl 7-chloro-3-hydroxyheptanoate can be transformed into 7-amino-3-hydroxyheptanoic acid, used in the preparation of spergualins, powerful antitumor agents.[5]

Catalytic asymmetric hydrogenation of β-keto esters is considered one of the most efficient methods for the preparation of β-hydroxy esters and acids.[6] Pioneering work came from Noyori et al., who showed that a Ru catalyst based on BINAP as a chiral diphosphine ligand may be highly useful for the reduction of β-keto esters.[7] Even ethyl γ-chloroacetoacetate could be reduced with this catalytic system. However, to obtain good enantioselectivity (97% ee), the reduction had to be conducted at 100°C.[8] More recently, the asymmetric hydrogenation of other β-alkyl and β-aryl substituted β-keto ester was reported.[9] Zhang and coworkers could achieve high enantioselectivities in the Ru-catalyzed hydrogenation of β-aryl substituted β-keto ester and of ethyl 4-chloroacetoacetate with TangPHOS as a chiral ligand.[10]Interestingly, homologues β-(ω-chloroalkyl) substituted β-keto esters were not used as prochiral substrates for the asymmetric reduction. One of the crucial problems is the availability of the required prochiral substrates. These β-keto esters are available by reaction of the dianion of ethyl acetoacetate with alkyl iodides (Scheme 1).[11] Based on this methodology, a large set of ω-chloro-functionalized and nonfunctionalized β-keto esters bearing a long alkyl chain could be prepared.



Scheme 1.

Herein, we report the highly enantioselective hydrogenation of these functionalized ketones using Ru catalysts containing the diphosphines **I**–**III** as ligands. BINAP and Tol-BINAP are commercially available at low prices. Ligand **III** can be derived from an economically beneficial cross-self-breeding process.[12]

Resultant β-hydroxy esters have great synthetic potential. Those that contain a chloro substituent may serve as intermediates for the synthesis of chiral ω-hydroxy acids, ω-amino acids, and lactones.

Results of the enantioselective hydrogenation are summarized in Table 1. Required precatalysts were prepared in situ by reaction of $[Ru(p\text{-cymene})Cl_2]_2$ with the chiral ligand in DMF prior to the catalytic reaction. Hydrogenations of both β-alkyl and β-(ω-chloroalkyl) substituted β-keto ethyl esters **1** were performed under an initial hydrogen pressure of 50 bar at 50°C in ethanol as solvent. Under these conditions, β-hydroxy esters **2** were obtained with excellent enantioselectivities. The use of MeOH as a solvent led to transesterification (Scheme 2).

Table 1. Enantioselective hydrogenation of **1a**–**f** with Ru-diphosphine catalysts

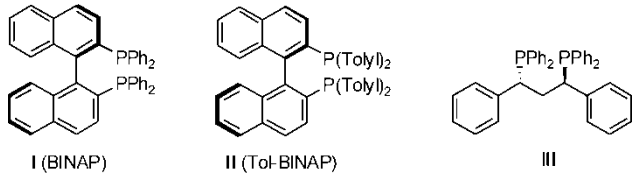
Entry	Ligand	Substrate	Product[a]	Ee (%)[b]	Prod. conf.[d]
1	**I** (BINAP)	**1a**	**2a**	98.1	(*R*)-(−)
2	**II** (Tol-BINAP)	**1a**	**2a**	98.7	(*R*)-(−)
3	**III**	**1a**	**2a**	89.0	(*S*)-(+)
4	**I** (BINAP)	**1b**	**2b**	98.1	(*R*)-(−)
5	**II** (Tol-BINAP)	**1b**	**2b**	98.5	(*R*)-(−)
6	**III**	**1b**	**2b**	86.0	(*S*)-(+)
7	**I** (BINAP)	**1c**	**2c**	98.0[c]	(*R*)-(−)
8	**II** (Tol-BINAP)	**1c**	**2c**	98.7	(*R*)-(−)
9	**III**	**1c**	**2c**	91.0	(*S*)-(+)
10	**I** (BINAP)	**1d**	**2d**	98.3[c]	(−)
11	**II** (Tol-BINAP)	**1d**	**2d**	98.6[c]	(−)
12	**III**	**1d**	**2d**	86.0[c]	(+)
13	**I** (BINAP)	**1e**	**2e**	98.0	(−)
14	**II** (Tol-BINAP)	**1e**	**2e**	98.4	(−)
15	**III**	**1e**	**2e**	91.0	(+)
16	**I** (BINAP)	**1f**	**2f**	98.6	(−)
17	**II** (Tol-BINAP)	**1f**	**2f**	98.7	(−)
18	**III**	**1f**	**2f**	91.0	(+)

[a]Conditions: catalyst/substrate ratio = 1/200; H_2 (initial pressure 50 bar), 50°C, EtOH; complete conversion, products were isolated in quantitative yields.

[b]Enantiomeric excess was determined by ^{31}P NMR after coupling with the chiral phosphorus derivatizing agent **3** derived from (*S*)-BINOL.

[c]Determined by chiral GC (Lipodex E column, 50 m).

[d]Absolute configurations of **2a**, **2b**, and **2c** were assigned by comparison of the sign of the optical rotation with that of known alcohols.[13]

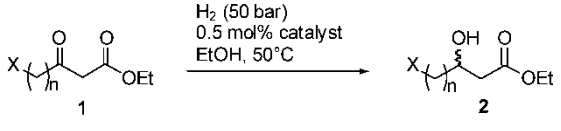


Scheme 2.

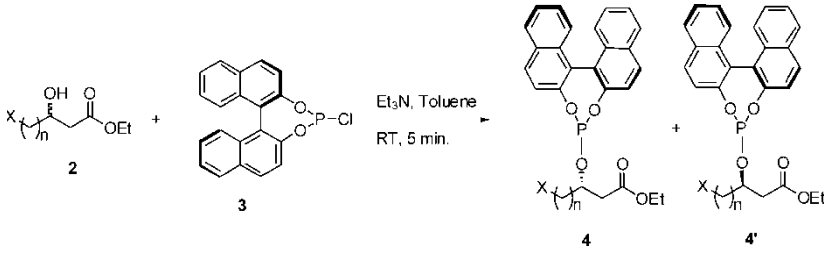
In all cases, enantioselectivities obtained with Ru-[(*R*)-TolBINAP] were slightly superior to those obtained with Ru-[(*R*)-BINAP]. Interestingly, the use of diphosphine **III** also gave good enantioselectivities (87–91% ee) (Scheme 3).

The use of the commercial Ru[(*R*)-BINAP]Cl_2 gave the same results as those obtained with a catalyst prepared in situ from (*R*)-BINAP and [Ru(*p*-cymene)Cl_2]$_2$. In contrast to results reported in the asymmetric hydrogenation of 4-chloroacetoacetate,[8] we did not observe any effect of the chloro substituent on the activity as well as on the enantioselectivity (Scheme 4).

The ee of the chiral products was determined by a method similar to that reported by Tang et al.,[14] reaction of β-hydroxy esters with enantiopure chlorophosphite **3** derived from (*S*)-BINOL and subsequent integration of the signals in the ^{31}P NMR spectrum. The derivatizing agent (^{31}P NMR, δ 179.2) reacted immediately and quantitatively with alcohol **2** to give diastereomeric phosphites **4** and **4′**. The ^{31}P NMR spectrum of both diastereomeric products is characterized by signals separated at the base line (Table 2); therefore it was possible to determine precisely the enantiomeric composition of the hydrogenation products.



Scheme 3.



Scheme 4.

Table 2. ^{31}P NMR chemical shifts of 1:1 mixtures of diastereomeric phosphites **4** and **4′**

Entry	β-Hydroxy ester **2**	^{31}P NMR chemical shifts		Δδ (ppm)	Ratio[a]
		4	**4′**		
1	**2a**	153.35	151.33	2.02	50.4/49.6
2	**2b**	153.31	151.23	2.08	49.9/50.1
3	**2c**	153.34	150.44	2.9	50.5/49.5
4	**2e**	153.35	150.31	3.04	49.9/50.1
5	**2f**	152.72	150.44	2.28	50.3/49.7

[a]^{31}P NMR integral ratio of **4** and **4′**.

In summary, a highly enantioselective hydrogenation catalyzed by Ru-BINAP, catalysts of β-alkyl and β-(ω-chloroalkyl) substituted β-keto ethylesters prepared by a unique method, afforded biologically interesting β-hydroxy esters with high enantioselectivities.

EXPERIMENTAL

General Procedure of the Asymmetric Hydrogenation

A dry 20-mL Schlenk tube containing a Teflon®-coated stirring bar was charged with $[Ru(p\text{-cymene})Cl_2]_2$ (2 mg, 6.5 μmol), chiral diphosphine ligand (6.75 μmol), and DMF (1 mL) under an argon atmosphere. The resulting reddish brown suspension was heated at 100°C under argon for 15 min to give a clear reddish brown solution. DMF was removed under vacuum at 50 °C; EtOH (3 or 4 mL) and β-keto ester (1.3 mmol) were added. The resultant solution containing precatalyst and substrate was transferred with a syringe under argon inside an autoclave, which was charged with hydrogen (50 bar). The reduction was performed under this pressure at 50°C overnight. β-Hydroxy esters (yield >95%) were purified by silica-gel column chromatography (*n*-heptane–AcOEt = 80:20) and characterized by NMR and HRMS. Enantiomeric excesses were determined by chiral capillary GC (Lipodex E column, 50 m) or by ^{31}P NMR analysis after coupling with chiral chlorophosphite derived from BINOL.

Determination of Ee Based on ^{31}P NMR

Preparation of chlorophosphite of (*S*)-BINOL was carried out according to the protocol of Minnaard et al.[15] For example, a dry NMR analysis tube was charged under argon with ethyl 3-hydroxytetradecanoate (20 mg, 0.073 mmol), (*S*)-BINOL-chlorophosphite (0.4 mL, 0.14 mmol) in toluene

(0.35 M), d_8-toluene (0.2 mL), and one drop of triethylamine. The resulting mixture was analyzed by ^{31}P NMR (d_8-toluene, 300 or 400 MHz). Three signals are obtained: one of nonreacted chlorophosphite and two related to the diastereomeric triesters.

Data

(*R*)-Ethyl 3-hydroxytetradecanoate (2a). Yellow oil; $[\alpha]_D^{20} = -6.1$ (*c* 1, CH_2Cl_2; 98.5% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (q, $J = 7.23$ Hz, 2H), 3.97 (m, 1H), 3.00 (bs, 1H, OH), 2.50–2.30 (m, 2H), 1.60–1.10 (m, 23H), 0.85 (t, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C═O), 68.1 (CH), 60.6 (CH_2), 43.8 (CH_2), 41.3 (CH_2), 36.5 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 25.5 (CH_2), 23.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 14.1 (CH_3); HRMS (EI, 70 eV): *m/z* 271.22577 (M-H$^+$ exact mass calcd. for $C_{16}H_{31}O_3$: 271.22677); ee determined by ^{31}P NMR (300 MHz, d_8-toluene) δ 153.35, 151.33.

(*R*)-Ethyl 3-hydroxydodecanoate (2b). Yellow oil; $[\alpha]_D^{20} = -9.4$ (*c* 0.5, CH_2Cl_2; 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, $J = 7.13$ Hz, 2H), 3.97 (m, 1H), 2.84 (bs, 1H, OH), 2.43 (m, 2H), 1.60–1.10 (m, 19H), 0.85 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz $CDCl_3$) δ 173.1 (C═O), 68.0 (CH), 60.6 (CH_2), 43.8 (CH_2), 41.3 (CH_2), 36.5 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 24.5 (CH_2), 22.7 (CH_2), 14.15 (CH_3), 14.08 (CH_3); HRMS (EI, 70 eV): *m/z* 243.19547 (M-H$^+$ exact mass calcd. for $C_{14}H_{27}O_3$: 243.19461); ee determined by ^{31}P NMR (300 MHz, d_8-*t*oluene) δ 153.31, 151.23.

(*R*)-Ethyl 6-chloro-3-hydroxyhexanoate (2c). Yellow oil; $[\alpha]_D^{20} = -3.7$ (CH_2Cl_2, *c* 0.1; 98.0% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (q, $J = 7.15$ Hz, 2H), 4 (m, 1H), 3.55 (dt, $J = 6.52$ and 2.6 Hz, 2H), 2.87 (bs, 1H, OH), 2.44 (m, 2H), 2.00–1.75 (m, 2H), 1.60 (m, 2H), 1.24 (t, $J = 7.147$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (C═O), 67.5 (CH), 61.0 (CH_2), 45.2 (CH_2), 41.6 (CH_2), 33.8 (CH_2), 28.9 (CH_2), 14.4 (CH_3). HRMS (EI, 70 eV): *m/z* 193.06187 (M-H$^+$ exact mass calcd. for $C_8H_{14}O_3Cl$: 193.06260); ee determined by chiral capillary GC (Lipodex E column (50 m), (*R*) $t_1 = 88.929$ min. and (*S*) $t_2 = 92.944$ min) and also by quantitative ^{31}P NMR (300 MHz, d_8-toluene) δ 153.34, 150.44.

Ethyl 7-chloro-3-hydroxyheptanoate (2d). Yellow oil; $[\alpha]_D^{20} = -9.6$ (CH_2Cl_2, *c* 0.25; 98.6% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, $J = 7.17$ Hz, 2H), 3.99 (m, 1H), 3.52 (t, $J = 6.64$ Hz, 2H), 3.10 (bs, 1H, OH), 2.54–2.33 (m, 2H), 1.85–1.72 (m, 2H), 1.65–1.40 (m, 4H), 1.25 (t, $J = 7.17$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C═O), 67.7 (CH), 60.7 (CH_2), 44.8 (CH_2), 41.2 (CH_2), 35.6 (CH_2), 32.4 (CH_2), 22.8

(CH_2), 14.2 (CH_3); HRMS (EI, 30 eV): m/z 209.09361 and 211.09135 ($M + H^+$ exact mass calcd. for $C_9H_{18}O_3^{35}Cl$: 209.09390 and for $C_9H_{18}O_3^{37}Cl$: 211.09095); ee determined by chiral capillary GC (Lipodex E column (50 m), 100°C, isothermal, (−) $t_1 = 128.59$ min. and (+) $t_2 = 129.15$ min).

Ethyl 9-chloro-3-hydroxynonanoate (2e). Yellow oil; $[\alpha]_D^{20} = -11.5$ (CH_2Cl_2, c 0.2; 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (q, $J = 7.15$ Hz, 2H), 3.98 (m, 1H), 3.52 (t, $J = 6.7$ Hz, 2H), 2.97 (bs, 1H, OH), 2.55–2.33 (m, 2H), 1.76 (m, 2H), 1.30–1.60 (m, 8H), 1.27 (t, $J = 7.15$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C═O), 67.9 (CH), 60.7 (CH_2), 45.0 (CH_2), 41.3 (CH_2), 36.3 (CH_2), 32.5 (CH_2), 28.8 (CH_2), 26.8 (CH_2), 25.3 (CH_2), 14.2 (CH_3); HRMS (EI, 30 eV): m/z 235.10901 (M-H^+ exact mass calcd. for $C_{11}H_{20}O_3Cl$: 235.10955); ee determined by ^{31}P NMR (300 MHz, d_8-toluene) δ 153.35, 150.31.

Ethyl 10-chloro-3-hydroxydecanoate (2f). Yellow oil; $[\alpha]_D^{20} = -15$ ($CHCl_3$, c 0.5; 98.6% ee); ^{1}H NMR (75 MHz, $CDCl_3$) δ 4.13 (q, $J = 7.13$ Hz, 2H), 3.95 (m, 1H), 3.50 (t, $J = 6.72$ Hz, 2H), 3.02 (bs, 1H, OH), 2.50–2.30 (m, 2H), 1.73 (m, 2H), 1.26–1.54 (m, 10H), 1.24 (t, $J = 7.13$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C═O), 67.9 (CH), 60.7 (CH_2), 45.0 (CH_2), 41.3 (CH_2), 36.4 (CH_2), 32.6 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 26.8 (CH_2), 25.3 (CH_2), 14.2 (CH_3); HRMS (EI, 30 eV): m/z 251.14027 and 253.13830 ($M + H^+$ exact mass calcd. for $C_{12}H_{24}O_3^{35}Cl$: 251.14085 and for $C_{12}H_{24}O_3^{37}Cl$: 253.13790); ee determined by ^{31}P NMR (300 MHz, d_8-toluene) δ 152.72, 150.44.

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