Lipase/Ruthenium-Catalyzed Dynamic Kinetic Resolution of β-Hydroxyalkylferrocene Derivatives

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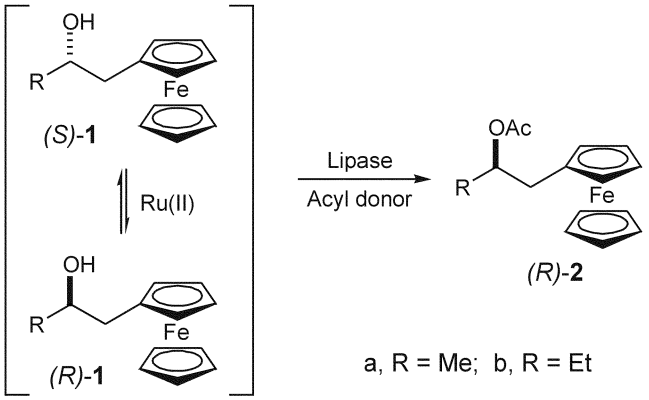
An efficient dynamic kinetic resolution of racemic β-hydroxyalkylferrocene and 1,1'-bis(β-hydroxyalkyl)-ferrocene derivatives was achieved using lipase/ruthenium-catalyzed transesterification in the presence of an acyl donor. The racemic β-hydroxyalkylferrocene derivatives were successfully transformed to the corresponding chiral acetates of high optical purities in high yields.

Key Words : Dynamic kinetic resolution (DKR), Enzyme/metal bicatalysis, Lipase, β-Hydroxyalkylferrocene

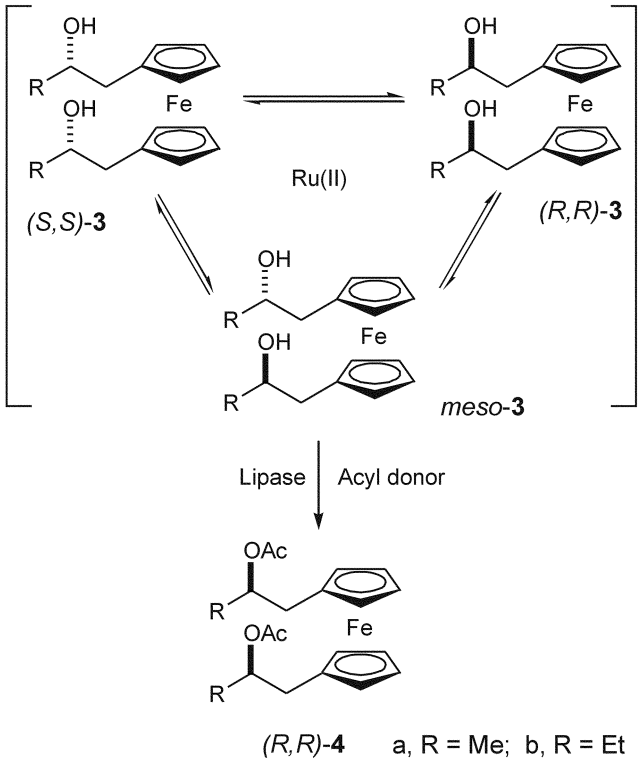
Introduction

The chiral ferrocene derivatives have been widely used as chiral ligands in asymmetric synthesis,[2] and their stereoselective preparation have been studied for many years.[3] The interest in the ferrocene derivatives is due to the feasibility of modification in α-substituents with retention of configuration, and the possibility of direct metallations. These exceptional features lead the class of ferrocene derivatives to the new potential ligands. Recently some C_2-symmetrical 1,1'-disubstituted ferrocene derivatives have also been used in asymmetric synthesis.[4] Although many studies were reported on the synthesis of chiral ferrocene derivatives, there still remained some problems in yield and enantioselectivity.

The lipase-catalyzed kinetic resolution of β-hydroxyalkylferrocene derivatives **1** was successfully achieved to provide (*R*)-**2** of high optical purities in previous work.[4] However, the enzymatic kinetic resolution still has a problem of low yield, theoretically the maximum 50% yield. In this work, the dynamic kinetic resolution (DKR)[5] of ferrocene-containing substrates was explored to overcome the problem of yield by the combination of enzyme and metal catalyst (Scheme 1). At the same time, the concurrent DKR of the two hydroxy groups of 1,1'-bis(-hydroxyalkyl)ferrocene derivatives **3** was also explored to form C_2-symmetrical 1,1'-dialkylferrocene derivatives (Scheme 2).



Scheme 1. DKR of β-hydroxyalkylferrocenes.



Scheme 2. DKR of 1,1'-bis(β-hydroxyalkyl)ferrocenes.

Results and Discussion

As the metal catalyst **5**[6] completely racemized (*R*)-**1a** at 70 °C within a day, the complex was proved to be a suitable racemization catalyst in DKR of the ferrocene derivatives.

In the previous work,[4] lipase from *Pseudomonas* species (LPS) showed good enantioselectivity in the kinetic

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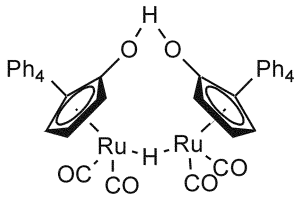

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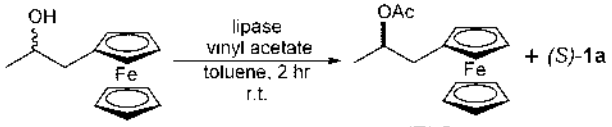
resolution of **1a** and **1b**. As the elevated temperature is required for the activation of the metal catalyst **5** in DKR, immobilized lipases should be used. Three commercially available immobilized lipases were selected for testing the enantioselectivity: LPS on ceramic (LPS-C), LPS on diatomite (LPS-D), and CALB (*Candida antarctica* lipase B) on macroporous acrylic resin. From the results of enzymatic acylation in toluene at room temperature using the substrate **1a** in the presence of an acyl donor (Table 1), LPS-D that showed the largest enantioselectivity was selected as a biocatalyst in DKR of the ferrocene derivatives. The absolute configurations of the products were confirmed by comparing the optical rotations with those of the previous work.

The first series of enantioselective synthesis was the DKR reactions of β-hydroxyalkylferrocene derivatives **1**. The reactions were performed in toluene in the presence of Ru(II) catalyst **5**, LPS-D, and acyl donor[7] at 70 °C for 3 days. The DKR reaction provided products of excellent optical purities (>99% enantiomeric excess) in high yields

Table 1. Lipase-catalyzed kinetic resolution of **1a**

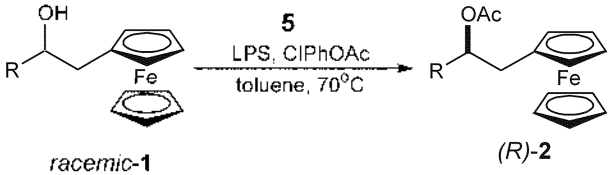


rac-**1a** (*R*)-**2a**

Enzyme	ee_s,[a] %	ee_p,[a] %	convn.,[b] %	E[c]
LPS-C	99	96	50.7	390
LPS-D	98	>99	49.7	1,927
CALB	95	>99	48.8	1,488

[a]On the basis of HPLC analysis. [b]Calculated from the equation, $c = ee_s/(ee_s + ee_p)$. [c]Enantioselectivities were calculated from the equation, $E = \ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$ or $\ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$.

Table 2. Dynamic kinetic resolution of **1**



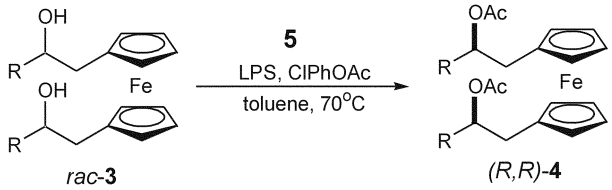
racemic-**1** (*R*)-**2**

a, R = Me; b, R = Et

Substrate	convn.[a] %	(*R*)-**2**,[a] %	yield.[b] %	ee_p,[c] %
1a	> 98	96	90	> 99
1b	> 98	> 97	95	> 99

[a]Determined on the basis of ^{1}H NMR analysis. [b]Isolated yields. [c]On the basis of HPLC analysis.

Table 3. Dynamic kinetic resolution of **3**



rac-**3** (*R,R*)-**4**

a, R = Me; b, R = Et

substrate	convn[a] %	(*R,R*)-**4**[a] %	yield[b] %	ee_p[c] %	de[c] %
3a	> 98	> 97	90	> 99.5	> 99.5
3b	> 98	96.8	90	> 99.5	> 99.5

[a]Determined on the basis of ^{1}H NMR analysis. [b]Isolated yields. [c]Determined on the basis of HPLC analysis.

(90 and 95% for **2a** and **2b**, respectively) (Table 2). The impurity detected (~1%) was the corresponding ketone of substrate **1**.

The second series was the DKR of 1,1'-bis(β-hydroxyalkyl)ferrocene derivatives **3**. The DKR reactions were also carried out in toluene in the presence of Ru(II) catalyst **5**, LPS-D, and acyl donor at 70 °C for 4 days (Table 3). In these reactions, the amounts of catalysts and acyl donor applied were twice as those in DKR of **1** because of the two hydroxy groups. The lipase/ruthenium-catalyzed DKR of **3** was achieved in high yields (90%), though small amount of ketones (~1%) were formed in both cases. The enantiomeric and diastereomeric excess values were exceedingly high in the both cases.

Highly enantioselective lipase/ruthenium-catalyzed DKR reactions of β-hydroxyalkylferrocene derivatives **1** and 1,1'-bis(β-hydroxyalkyl)ferrocene derivatives **3** were achieved in high yields. The formation of the corresponding ketone during DKR reaction seemed to be caused by incomplete hydrogen transfer from the metal catalyst.

The optically pure β-hydroxyalkylferrocenes and 1,1'-bis(β-hydroxyalkyl)ferrocenes can be obtained by simple hydrolysis from **2** and **4**, and are potentially useful as ligands in asymmetric synthesis. These successful DKRs provide an attractive alternative route to overcome the problems of low yields and optical purities in the asymmetric synthesis of the ferrocene derivatives.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300 MHz. Chemical shifts (δ) are reported in ppm relative to TMS in $CDCl_3$. Chiral HPLC analyses were performed on Chiralcel OD or Whelk-O1 column on a Spectra series P2000 instrument. Optical rotations were measured on Rudolph Research Autopol III digital polarimeter. High-resolution mass spectra were obtained from JMS 700 spectrometer.

Immobilized lipases from *Pseudomonas cepacia* (trade name, Lipase PS-C for LPS on ceramic, Lipase PS-D for LPS on diatomite) were obtained from Amano Enzyme Inc.,

and immobilized CALB (trade name, Novozym-435) was purchased from Novozymes Korea Ltd.

The β-hydroxyalkylferrocene derivatives were prepared from ferrocene and corresponding epoxide according to the literature procedure.[8]

Kinetic resolution for the selection of enzyme. To the solution of **1a** (56 mg, 0.23 mmol) and vinyl acetate (63.7 μL, 0.69 mmol) in dry toluene (1 mL) was added LPS-D (56 mg, trade name: Lipase PS-D). The resulting reaction mixture was stirred at room temperature (25 °C) for 2 hours. The enzyme was filtered out and the filtrate was concentrated and analyzed. The product (*R*)-**2a** was obtained in 49.7% conversion and in >99% ee. The HPLC analysis of (*R*)-**2a** was done using a chiral stationary phase (Whelk-O1, *n*-hexane/2-propanol = 99/1, flow rate = 0.5 mL/min, UV 217 nm). The remaining alcohol (*S*)-**1a** was analyzed and found to be 98% ee (HPLC analysis, Chiralcel OD, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV 217 nm).

(*R*)-2-Acetoxypropylferrocene, (+)-2a. A suspension containing **1a** (56 mg, 0.23 mmol), Ru(II) catalyst **5** (20 mg, 0.018 mmol), LPS-D (22.4 mg) and *p*-chlorophenyl acetate (58.8 μL, 0.35mmol) in dry toluene (0.5 mL) was stirred at 70 °C under argon atmosphere. After 3 days, the catalysts were filtered out and the filtrate was concentrated and analyzed by ^{1}H NMR spectroscopy, indicating that all of the substrate was consumed. The mixture was subjected to a flash chromatography (silica gel, *n*-hexane/ethyl ether = 6/1) to provide (*R*)-**2a** (59 mg, 0.21 mmol, 90%, >99% ee). Substantial amount of *p*-chlorophenyl acetate contained in the fractions of (*R*)-**2a** can be readily removed through selective hydrolysis. The HPLC analysis was performed using a chiral stationary phase (Whelk-O1, *n*-hexane/2-propanol = 99/1, flow rate = 0.5 mL/min, UV 217 nm). $[\alpha]_D^{25}$ +80.1 (*c* 1.01, CH_2Cl_2, >99% ee); ^{1}H NMR 4.88 (m, 1H), 4.08 (m, 9H), 2.67 (dd, *J* = 6.30, 14.2 Hz, 1H), 2.53 (dd, *J* = 6.30, 14.2 Hz, 1H), 2.10 (s, 3H), 1.16 (d, *J* = 6.30 Hz, 3H); ^{13}C NMR 171.2, 84.2, 72.2, 69.9, 69.8, 69.2, 68.3, 68.2, 37.1, 22.0, 20.2; HRMS (FAB) $C_{15}H_{18}O_2Fe$ + H^+ calcd 286.0656, found 286.0656.

(*R*)-2-Acetoxybutylferrocene, (+)-2b. The DKR was carried out using the same procedure described for the resolution of (+)-**2a**. Yield 95%; $[\alpha]_D^{25}$ +54.9 (*c* 4.0, CH_2Cl_2, >99% ee); ^{1}H NMR 4.77 (m, 1H), 4.07 (m, 9H), 2.60 (m, 2H), 2.02 (s, 3H), 1.53 (m, 4H), 0.87 (t, *J* = 7.41 Hz, 3H); ^{13}C NMR 171.4, 84.3, 76.7, 69.9, 69.8, 69.3, 68.3, 68.2, 35.0, 27.0, 22.0, 10.3; HRMS (FAB) $C_{16}H_{20}O_2Fe$ + H^+ calcd 300.0813, found 300.0813; HPLC analysis, Whelk-O1, *n*-hexane/2-propanol = 99/1, flow rate = 0.5 mL/min, UV 217 nm.

(*R,R*)-1,1'-Bis(2-acetoxypropy)ferrocene, (+)-4a. The same procedure as described for the resolution of (+)-**2a** was applied using the mixture of **3a** (30 mg, 0.1 mmol), Ru(II) catalyst **5** (17.4 mg, 0.016 mmol), LPS-D (24 mg) and *p*-chlorophenyl acetate (51.3 μL, 0.3 mmol) in dry toluene (0.5 mL). Yield 90%; $[\alpha]_D^{25}$ +103.6 (*c* 2.15, CH_2Cl_2, >99% ee, >99% de); ^{1}H NMR 4.86 (m, 2H), 3.99 (m, 9H), 2.64 (dd, *J* = 6.23, 14.1 Hz, 2H), 2.50 (dd, *J* = 6.23, 14.1 Hz, 2H), 2.01 (s, 6H), 1.15 (d, *J* = 6.30 Hz, 6H); ^{13}C NMR 171.2, 84.2, 72.2, 70.5, 70.4, 69.1, 69.0, 36.9, 22.1, 20.1; HRMS (FAB) $C_{20}H_{26}O_4Fe$ + H^+ calcd 386.1180, found 386.1181; HPLC analysis, Whelk-O1, *n*-hexane/2-propanol = 99/1, flow rate = 1.0 mL/min, UV 217 nm.

(*R,R*)-1,1'-Bis(2-acetoxybutyl)ferrocene, (+)-4b. The same procedure as described for the resolution of (+)-**4a** was applied. Yield 95%; $[\alpha]_D^{25}$ +68.7 (*c* 2.5, CH_2Cl_2, >99% ee, >99% de); ^{1}H NMR 4.75 (m, 2H), 3.98 (m, 9H), 3.85 (m, 4H), 2.02 (s, 6H), 1.52 (m, 4H), 0.86 (t, *J* = 7.35 Hz, 6H); ^{13}C NMR 171.1, 84.0, 76.4, 70.2, 70.1, 68.8, 68.7, 34.5, 26.7, 21.7, 10.0; HRMS (FAB) $C_{22}H_{30}O_4Fe$ + H^+ calcd 414.1493, found 414.1494; HPLC analysis, Whelk-O1, *n*-hexane/2-propanol = 99/1, flow rate = 1.0 mL/min, UV 217 nm.

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