Lipase/Ruthenium-Catalyzed Dynamic Kinetic Resolution of Hydroxy Acids, Diols, and Hydroxy Aldehydes Protected with a Bulky Group

Mahn-Joo Kim,* Yoon Kyung Choi, Min Young Choi, Mi Jung Kim, and Jaiwook Park*

National Research Laboratory of Chirotechnology, Department of Chemistry, Division of Molecular and Life Sciences, Pohang University of Science and Technology, San 31 Hyojadong, Pohang, Kyungbuk 790-784, Korea

mjkim@postech.ac.kr

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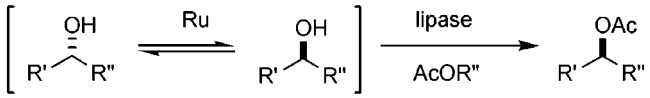
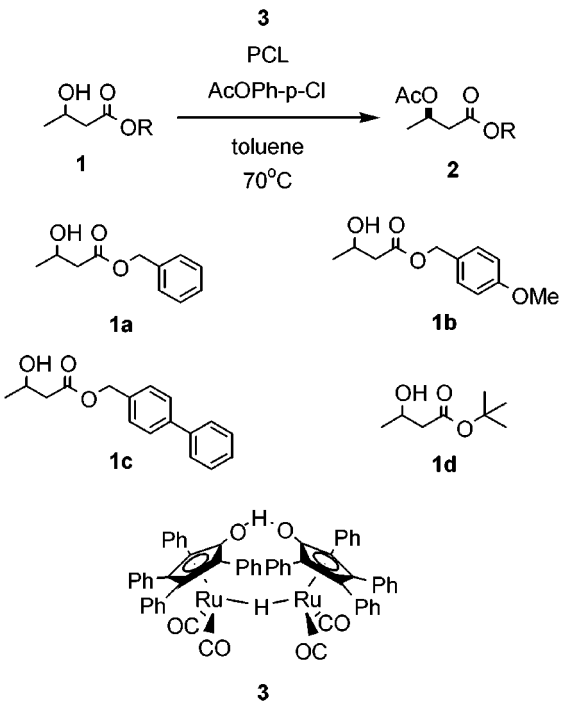
Kinetic resolutions of racemic mixtures based on lipase catalysis provide a useful methodology for the synthesis of optically active compounds such as chiral alcohols, acids, and their esters.[1] However, the enzymatic kinetic resolutions often suffer from two major problems: unsatisfactory enantioselectivity and low yield (the theoretical maximum yield is 50%). One of the useful strategies for enhancing the enzyme enantioselectivity is the use of structurally modified substrates.[2,3] The counterpart for improving the yield is the dynamic kinetic resolution (DKR),[4] allowing for the complete transformation of racemic mixtures to single enantiomers. In this work, these two strategies have been combined for the efficient resolution of versatile difunctional molecules such as hydroxy acids, diols, and hydroxy aldehydes. The racemic substrates were modified with a bulky protecting group[5] and then subjected to the lipase/ruthenium-catalyzed DKR (Scheme 1).[6,7] In most cases, both optical purities and yields of products reached a satisfactory level.

Scheme 1



Scheme 2



The first series of illustrative examples is the DKRs of protected *β*-hydroxybutyrates **1a**−**d**[8] (Scheme 2), in which the carboxy functionality is protected with four different bulky groups including benzyl (**1a**), (*p*-methoxyphenyl)methyl (**1b**), biphenylmethyl (**1c**), and *tert*-butyl (**1d**). Initially, the DKR of **1a** were examined with *Candida antarctica* lipase B (CALB, immobilized; trade name, Novozym-435[9]), which gave poor enantiomeric excesses. However, the DKR tested with *Pseudomonas cepacia* lipase (PCL, immobilized; trade name, Lipase PS-D[10]) provided better optical purity. Accordingly, the further DKR reactions were carried out with PCL. In the reactions of **1a**−**c**, a significant amount (15 mol %) of ruthenium catalysts were used with small amounts (0.05 mass equiv) of enzymes to get higher ee's. The reaction

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(4) Ward, R. S. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1475.

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(8) The protected substrates except commercially available **1d** were readily prepared by the enzymatic reactions of diketene with the corresponding alcohols followed by reduction in the presence of **3** and 2,6-dimethyl-4-heptanol.

(9) Provided by Novo Nordisk Korea.

(10) Provided by Amano, Japan.

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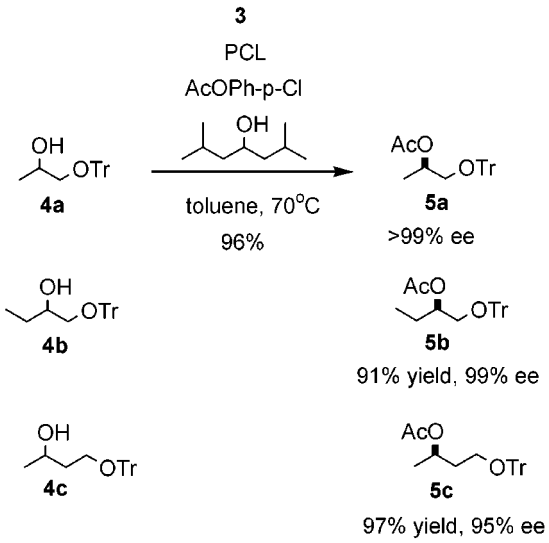
Table 1. DKR of Protected β-Hydoxybutyrates

substrate	time, d	convn,[a] %	yield,[b] %	ee,[c] %
1a	5	>99	88	86
1b	5	97	91	93
1c	4.5	>99	92	94
1d	4	>99	88	>99

[a] Percent conversion based on the consumed substrate. [b] Isolated yield. [c] Determined on the basis of the HPLC using a chiral column (Whelko-O1). Analytical conditions: **2a**, hexane/2-propanol = 99/1, flow rate = 1.0 mL/min, UV 217 nm; **2b**, hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV 217 nm; **2c**, hexane/2-propanol = 95/5, flow rate = 0.5 mL/min, UV 254 nm; **2d**, deacetylated (K_2CO_3 in 4:1 MeOH−H_2O) and then benzoylated (DMAP, Et_3N, BzCl) before analysis: hexane/2-propanol = 99/1, flow rate = 0.3 mL/min, UV 232 nm.

Scheme 3

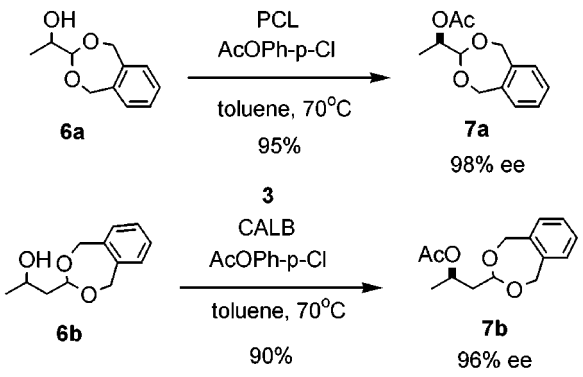


of **1d** was done with less ruthenium catalysts (10 mol %) and more enzymes (0.5 mass equiv) since the enzyme enantioselectivity was high in this case.[2a] In typical experiments, the reactions were run on a 0.3 mmol scale in a suspension containing substrate, PCL, ruthenium complex **3**, *p*-chlorophenyl acetate[11] (1.7 equiv), and toluene (1 mL) under an argon atmosphere (Scheme 1). After the reaction was complete (4−5 d), the enzymes were removed and the organic solution was concentrated. The resulting residue was subjected to silica gel chromatography to give the acetylated products. The optical purities were determined by chiral HPLC. The results are summarized in Table 1.

All the reactions required rather long reaction times (4−5 days) for complete transformations and good yields (88−92%). The enantiomeric excess was the lowest (86%) in the reaction of **1a** and increased up to >99% in the case of **1d**. Accordingly, these results clearly indicate that the *tert*-butyl group is the best protecting group as the steric auxiliary for the efficient DKR of β-hydroxybutyrate.

The second is the DKRs of monoprotected 1,2-diols **4a**−**c** (Scheme 3), in which the primary alcohols were protected with the trityl group.[2c] The DKR reactions were

Scheme 4



carried out on a 0.2 mmol scale with PCL (2 mg/mg of substrate) in the presence of **3** (15 mol %) and 2,6-dimethyl-4-heptanol (0.5 equiv). The alcohol additive acts as a reductant to depress the formation of ketone, the oxidized byproduct, without interfering the enzymatic acylation step. In its absence, a significant amount (10−15%) of ketone was observed.[12] These reactions required more enzymes and longer reaction times (6−8 days) due to the lower activities of enzymes toward the substrates. In all the cases, however, high ee's (95−99%)[13] were realized with high yields (91−97%), indicating that the trityl group is a good protecting group for the efficient DKR of diols.

The third is the DKRs of protected hydroxy aldehydes **6a**,**b**, in which 1,2-benzenedimethanol was employed for the protection of the aldehyde functionality[2d] (Scheme 4). The DKR of **6a** was performed on a 0.2 mmol scale with PCL (1 mass equiv) in the presence of a reduced amount (5 mol %) of the ruthenium catalyst **3**. The reaction for 3 days provided 95% yield and 98% ee. The DKR of **6b** under the similar conditions, however, resulted in a low optical purity (35% ee). Interestingly, the optical purity increased to 96% ee when PCL was replaced by CALB.[14]

All of the results clearly indicate that the DKRs of diols, hydroxy aldehydes, and hydroxy acids carrying a bulky group as the steric auxiliary proceed with high enantioselectivity to provide excellent ee's with good yields. In all the cases, the DKR reactions should provide the products of *R* configuration as suggested by the Kazlauskas rule.[5a] The absolute configuration of the product obtained from the DKR reaction of **1d** was confirmed as *R* by comparison of the optical rotation of its deacetylated form with that reported in the literature.[15] This work thus has demonstrated that two major problems of enzymatic kinetic resolutions, undesirable eantioselectivity and low yield, can be overcome at the same time by combining the substrate modification strategy with the DKR approach using enzyme/metal bicatalysis. It should be noted that the chiral compounds

(11) In the DKR reactions, *p*-chlorophenyl acetate serves better as the acyl donor than vinyl and isopropenyl acetates typically used in the enzymatic kinetic resolution. The use of the latter usually results in reduced yields since substrates are significantly oxidized by acetaldehyde or acetone formed from the latter in the acylation step. See ref 6a for more detail.

(12) Practically no oxidized byproducts are formed in the DKR reactions of hydroxy esters **1a**−**d** and acetals **6a**,**b**.

(13) For the determination of enantiomeric excesses, **5a**−**c** were hydrolyzed (K_2CO_3 in 4:1 MeOH−H_2O) to the alcohol forms **4a**−**c**. HPLC conditions: chiral stationary phase Chiracel OD, *n*-hexane/2-propanol = 99/1 (**4a**,**b**) or 90/10 (**4c**), flow rate = 0.5 mL/min, UV 232 nm.

(14) For the determination of enantiomeric excesses, **7a**,**b** were hydrolyzed (K_2CO_3 in 4: 1 MeOH−H_2O) to the alcohol forms **6a**,**b**. HPLC conditions: chiral stationary phase Chiracel OD, *n*-hexane/2-propanol = 95/5 (**5a**) or 90/10 (**4c**), flow rate = 0.5 mL/min, UV 260 nm.

resolved in this work can be used as C_3-C_4 synthons in the enantioselective synthesis of a wide range of more complex molecules.

Experimental Section

General Procedure for DKR. The DKR of **1d** is described as a representative procedure. A suspension containing **1d** (48.1 mg, 0.3 mmol), **3** (28 mg, 0.03 mmol), PCL (24 mg), and *p*-ClPhOAc (8.7 mg, 2.0 mmol) in toluene (1 mL) was stirred at 70 °C under argon atmosphere. After 4 days, the enzymes 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 to provide **2d** (53.7 mg, 0.264 mmol, 88%): $[\alpha]^{25}_D$ +7.59° (c = 1.0, $CHCl_3$, >99% ee); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 5.23 (m, 1 H), 2.47 (dd, J = 7.63, 15.5 Hz), 2.39 (dd, J = 5.73, 15.5 Hz, 1 H), 1.99 (s, 3 H), 1.41 (s, 9 H), 1.24 (d, J = 6.32 Hz, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 170.6, 169.9, 81.2, 68.0, 42.6, 28.4, 21.6, 20.2; HRMS (FAB) $C_{10}H_{18}O_4 + H^+$ calcd 203.1283, found 203.1279. For the determination of the enantiomeric excess, **2d** was hydrolyzed (K_2CO_3, MeOH−H_2O (4:1) and then benzoylated (DMAP, Et_3N, BzCl). The HPLC analysis of the benzoyl derivative was done using a chiral stationary phase (Whelk-O1, hexane/2-propanol = 99/1, flow rate = 0.3 mL/min, UV 232 nm).

(15) The optical rotation of deacetylated **2d**: $[\alpha]^{25}_D$ −16.1° (c = 1.0, MeOH) (lit. $[\alpha]^{rt}_D$ −16.1 (c = 1.01, MeOH) Bachmann, B. M.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2430). The optical rotations of other acetylated and deacetylated products: **2b**, $[\alpha]^{25}_D$ +2.42 (c = 1.0, $CHCl_3$); **2c**, $[\alpha]^{25}_D$ +3.35 (c = 1.0, $CHCl_3$); **2d**, $[\alpha]^{25}_D$ +7.59 (c = 1.0, $CHCl_3$); **5a**-deacetylated, $[\alpha]^{25}_D$ −16.3 (c = 1.0, $CHCl_3$); **5b**-deacetylated, $[\alpha]^{25}_D$ +2.63 (c = 1.0, $CHCl_3$); **5c**-deacetylated, $[\alpha]^{25}_D$ −12.1 (c = 1.0, $CHCl_3$); **7a**-deacetylated, $[\alpha]^{25}_D$ +2.03 (c = 1.0, $CHCl_3$); **7b**-deacetylated, $[\alpha]^{25}_D$ +6.40 (c = 1.0, $CHCl_3$).

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