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Asymmetric Transformations of Acyloxyphenyl Ketones by Enzyme−Metal Multicatalysis

Mahn-Joo Kim,* Min Young Choi, Min Young Han, Yoon Kyung Choi, Jae Kwan Lee, and Jaiwook Park*,[1]

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

mjkim@postech.ac.kr

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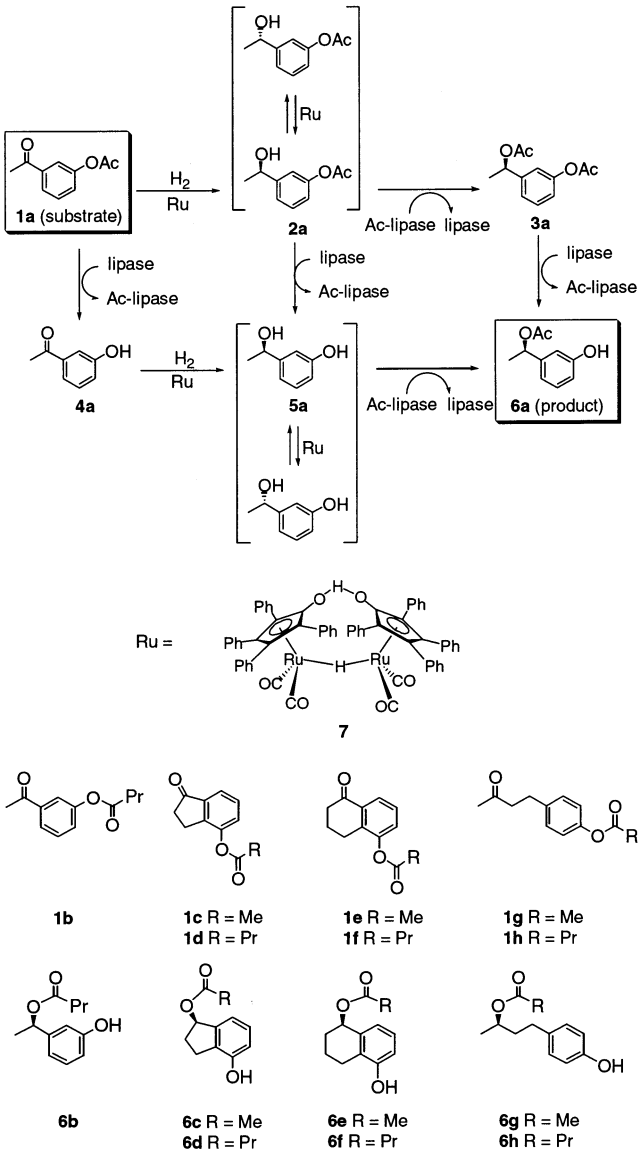
Abstract: A multipathway process comprising several enzyme- and metal-catalyzed reactions has been explored for the asymmetric transformations of acyloxyphenyl ketones to optically active hydroxyphenyl alcohols in the ester forms. The process comprises nine component reactions in three pathways, all of which take place by the catalytic actions of only two catalysts, a lipase and a ruthenium complex. The synthetic reactions were carried out on 0.2−0.6 mmol scales for eight different substrates under an atmosphere of hydrogen (1 atm) in toluene at 70 °C for 3 days. In most cases, the yields were high (92−96%) and the optical purities were excellent (96−98% ee), This work thus has demonstrated that enzyme−metal multicatalysis has great potential as a new methodology for asymmetric transformations.

Development of methods for the catalytic asymmetric transformations of prochiral molecules is one of the intensive research areas in synthetic organic chemistry.[2] Most of the procedures reported so far are based on transformations employing either a metal complex or an enzyme as the catalyst. Recently, we became interested in new approaches using an enzyme and a metal complex together for the enantioselective catalytic reactions. It has been demonstrated that the enzyme−metal combinations such as lipase/ruthenium or lipase/palladium are useful as the catalytic systems for the dynamic kinetic resolution (DKR) of secondary alcohols,[3] allylic acetates,[4] and amines[5] as well as for the asymmetric transformations of simple ketones,[6] enol acetates,[6] and ketoximes.[7]

SCHEME 1. Plausible Reaction Pathway for the Asymmetric Transformation of 3′-Acetoxyacetophenone (1a)



We now wish to report the use of the enzyme−metal combination as the catalyst system for a multipathway process, in which prochiral substrates are converted by the cooperative catalytic actions of an enzyme and a metal complex via several pathways to optically active chiral products.

A lipase/ruthenium-catalyzed multipathway process proposed for the asymmetric conversion of 3′-acetoxyacetophenone (**1a**) to (*R*)-1-(3-hydroxyphenyl)ethyl acetate (**6a**) is described in Scheme 1. In this scheme, the prochiral substrate is converted to the chiral product via three pathways. In the first pathway (**1a** → **2a** → **3a** → **6a**), the starting material is reduced through Ru-

(1) Email: pjw@postech.ac.kr.

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catalyzed hydrogenation to yield racemic alcohol **2a**, which is then resolved dynamically by two coupled reactions, Ru-catalyzed racemization and lipase-catalyzed enantioselective acylation, to give optically active diacetate **3a**. The lipase-catalyzed regioselective deacylation of **3a** affords monoacetate **6a** as the final product. In the second (**1a** → **4a** → **5a** → **6a**), the substrate is first deacylated by lipase and then reduced by the ruthenium catalyst to racemic alcohol **5a**. The racemic **5a** is then resolved dynamically by two coupled reactions, Ru-catalyzed racemization and lipase-catalyzed regio-/enantioselective acylation, to give the final product **6a**. In the third (**1a** → **2a** → **5a** → **6a**), the monoacetate **2a** in the first pathway is converted by lipase-catalyzed deacylation to **5a** in the second pathway. Overall, the substrate is converted to the product via nine catalytic steps: two Ru-catalyzed reductions, two Ru-catalyzed racemizations,[8] three lipase-catalyzed deacylations, and two lipase-catalyzed acylations. It is noteworthy that the DKRs take place at two stages for the conversions of racemic **2a** and **5a** to single enantiomers **3a** and **6a**, respectively. The overall reaction corresponds to the asymmetric reductive acyl migration, in which the acyl group moves from an aryl OH to an OH group at the stereogenic center of the reduced side chain.

According to the scheme, the reactions of **1a**[9] were explored with a ruthenium complex **7** and an immobilized lipase. A single reaction was carried out with a solution containing **1a** (0.56 mmol), **7**[10] (4 mol %), and lipase PS-D[11] (0.25 mass equiv) in toluene (1.4 mL) under an atmosphere of hydrogen (1 atm) at 70 °C. The ^{1}H NMR analysis[12] of the reaction mixture at an early stage (3 h) indicated that all the intermediates (**2a**, 16%; **3a**, 24%; **4a**, 17%; **5a**, 8%) proposed in the scheme are present together with substrate (18%) and product (17%). The qualitative analysis by TLC (*n*-hexane:EtOAc = 4:1) also supported this observation clearly: R_f = 0.06, 0.18, 0.25, 0.27, 0.43, 0.44 for **5a**, **2a**, **4a**, **6a**, **1a**, and **3a**, respectively. After 24 h, all substrate was consumed and the yield of product reached about 90% with negligible or small amounts of intermediates (**2a**, < 1%; **3a**, < 5%; **4a**, < 1%; **5a**, <5%). The further reaction for additional 48 h provided **6a** almost exclusively (95% isolated yield) with excellent optical purity (98% ee).

The good results from the asymmetric transformation of **1a** encouraged us to examine additional compounds **1b**−**h** as the substrates for lipase−ruthenium multicatalysis. Each of their reactions was carried out on a smaller scale with a substrate (0.2 mmol), a lipase (0.1−0.25 mass equiv), and **7** (2−4 mol %) in toluene (0.5 mL) at 70 °C under hydrogen gas (1 atm) for 3 days. After the reaction was complete, the catalysts were filtered off. The filtrate was concentrated and then subjected to a column chromatography to fractionate the desired products. The optical purities were determined by HPLC using a chiral column. The results are given together with those from the reaction of **1a** in Table 1.

TABLE 1. Lipase/Ruthenium-Catalyzed Asymmetric Transformations of Acyloxyphenyl Ketones (1a−h).[a]

entry	substrate	product	% yield	% ee[b]	entry	substrate	product	% yield	% ee[b]
1	**1a**	**6a**	95	98	5	**1e**	**6e**	88	89
2	**1b**	**6b**	96	98	6	**1f**	**6f**	88	98
3	**1c**	**6c**	94	93	7	**1g**	**6g**	92	96
4	**1d**	**6d**	93	96	8	**1h**	**6h**	89	98

[a] Lipases employed: lipase PS-D (entries 1−6), lipase PS-TN[13] (entries 7 and 8). [b] On the basis of the analyses by HPLC using a chiral column. The ee values of **6c**−**f** were determined in the deacylated forms, which were obtained by hydrolysis (K_2CO_3, MeOH/H_2O). Analytical conditions: Whelk-O1, hexane/2-propanol = 90/10 (**6a**,**b**,**h**), 95/5 (**6c**−**f**,**g**), flow rate = 1.0 (**6a**,**b**,**g**,**h**), 0.5 mL/min (**6c**−**f**), UV 217 nm.

The reaction of the 3′-butanoyloxyacetophenone **1b** gave **6b** in high yield (96%) and excellent ee (98%) (entry 2). The slightly reduced yields (93−94%) and ee values (93−96%) were obtained from the transformation of indanone derivatives **1c** and **1d** to **6c** and **6d**, respectively (entries 3 and 4). The reactions of tetralone derivatives **1e** and **1f** afforded **6e** and **6f** in good yields (88%) but substantially different optical purities, 89% and 98%, respectively (entries 5 and 6). Two acyl derivatives of 4-(4-hydroxyphenyl)-2-butanone, **1g** and **1h**, were transformed to **6g** and **6h**, respectively, with the almost same level of high enantioselectivity (96−98% ee) and good yields (89−92%) (entries 7 and 8). In general, the butanoylated substrates gave higher ee values compared to the acetylated substrates. All of these results thus prove that all the substrates examined were converted successfully to the optically active products by lipase/ruthenium multicatalysis.

In conclusion, this work has demonstrated for the first time that a multipathway transformation takes place efficiently by the cooperative action of only two distinct catalysts, a lipase and a ruthenium complex, to produce chiral products of high optical purity in good yield. It is notable that the chiral products obtained are useful as intermediates for the synthesis of chiral drugs such as rivastigmine (trade name Exelon) and its analogues for the treatment of Alzheimer's disease.[14] Now enzyme−metal multicatalysis offers new opportunity for asymmetric synthesis and its scope will expand with efforts to find proper combinations between enzymes and metal catalysts for new applications.

Experimental Section

General Procedure. The procedure for the synthesis of **6a** is described as representative. Substrate (**1a**, 100 mg, 0.56 mmol), **7** (24 mg, 0.022 mmol), and lipase PS-D (25 mg) were

(8) The Ru-catalyzed racemization takes place via oxiation−reduction by hydrogen transfer. For detailed a mechanism, see: Laxmi, Y. R. S.; Bäckvall, J.-E. *Chem. Commun.* **2000**, 611; also ref 3a.

(9) The substrates were prepared readily by the reaction of phenolic ketones with Ac_2O in the presence of DMAP and Et_3N in CH_2Cl_2.

(10) For the synthesis of **7**, see: (a) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885. (b) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090..

(11) Lipase PS-D is a trade name for *Pseudomonas cepacia* lipase immobilized on earth, which is available from Amano, Japan.

(12) Some characteristic ^{1}H NMR peaks for **1a**−**6a** are as follows: **1a**, singlet at 2.60 ppm, C*H*$_3$COPhOAc; **2a**, multiplet at 4.90 ppm, CH$_3$C*H*(OH)PhOAc; **3a**, quartet at 2.07 ppm, CH$_3$C*H*(OAc)PhOAc; **4a**, singlet at 2.57 ppm, C*H*$_3$COPhOH.; **5a**, multiplet at 4.84 ppm, CH$_3$C*H*(OH)PhOH.; **6a**, quartet at 5.81 ppm, CH$_3$C*H*(OAc)PhOH.

(13) *Pseudomonas cepacia* lipase immobilized on Toyonite. For its preparation, see: Kamori, M.; Hori, T.; Yamashita, Y.; Horose, Y.; Naoshima, Y. *J. Mol. Catal. B: Enzym.* **2000**, *9*, 269.

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added to a flask equipped with a grease-free high-vacuum stopcock. The flask was then degassed under vacuum and charged with argon, followed by the addition of toluene (1.4 mL). The reaction flask was subject to degassing under vacuum for the removal of argon, charged with hydrogen, and then heated at 70 °C for 3 days. The reaction mixture was cooled to room temperature, and the catalysts were filtered off. The resulting filtrate was concentrated and then subjected to flash column chromatography (silica gel, ethyl acetate/*n*-hexane = 1/ 6) to obtain **6a** (96 mg, 0.53 mmol, 95% yield, 98%ee). The optical purity was determined by HPLC using a chiral column (Whelk-O1) under the following conditions: hexane/2-propanol = 90/ 10, flow rate 1.0 mL/min, UV 217 nm.

(*R*)-1-Acetoxy-1-(3-hydroxyphenyl)ethane (6a): $[\alpha]^{20}_D$ = +108.2° (*c* = 1.0, MeOH, 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.20 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 6.82 (s, 1H), 6.72 (dd, J_1 = 7.9 Hz, J_2 = 2.5 Hz, 1H), 5.81(q, *J* = 6.5 Hz, 1H), 2.07 (s, 3H), 1.50 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 170.8, 155.5, 142.8, 129.3, 117.6, 114.5, 112.7, 72.1, 21.7, 21.0; HRMS (EI+) $C_{10}H_{12}O_3$ calcd 180.0786, found 180.0784.

(*R*)-1-Butanoyloxy-1-(3-hydroxyphenyl)ethane (6b): $[\alpha]^{20}_D$ = +90.7° (*c* = 2.0, $CHCl_3$, 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.20 (t, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.82 (s, 1H), 6.76 (dd, J_1 = 1.7 Hz, J_2 = 5.5 Hz, 1H), 5.83 (q, *J* = 6.6 Hz, 1H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.70−1.62 (m, 2H), 1.51 (d, *J* = 6.6 Hz, 3H), 0.94 (q, *J* = 7.3 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 174.1, 156.5, 144.2, 130.5, 118.8, 115.5, 113.8, 72.7, 37.3, 22.9, 19.1, 14.3; HRMS (EI+) $C_{12}H_{16}O_3$ calcd 208.1099, found 208.1101.

(*R*)-1-Acetoxy-4-hydroxyindane (6c): $[\alpha]^{20}_D$ = +92.7° (*c* = 1.0, MeOH, 93% ee); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.13 (t, *J* = 6.7 Hz, 1H), 7.00 (d, *J* = 6.6 Hz, 1H), 6.76 (d, *J* = 6.7 Hz, 1H), 6.20 (q, *J* = 3.3 Hz, 1H), 3.20−3.00 (m, 1H), 3.00−2.71 (m, 1H), 2.52−2.35 (m, 1H), 2.22−2.01 (m, 1H), 2.08 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 172.2, 152.7, 143.5, 131.0, 128.9, 118.1, 115.7, 78.6, 32.5, 26.9, 21.8; HRMS (EI+) $C_{11}H_{12}O_3$ calcd 192.0786, found 192.0789.

(*R*)-1-Butanoyloxy-4-hydroxyindane (6d): $[\alpha]^{20}_D$ = +79.8° (*c* = 2.0, $CHCl_3$, 96% ee); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.12 (t, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.22 (q, *J* = 3.2 Hz, 1H), 3.09−2.99 (m, 1H), 2.88−2.79 (m, 1H), 2.60−2.47 (m, 1H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.15−2.05 (m, 1H), 1.72−1.60 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 174.8, 152.9, 144.0, 130.8, 129.1, 118.3, 115.8, 79.1, 37.1, 32.8, 27.1, 19.2, 14.3; HRMS (EI+) $C_{13}H_{16}O_3$ calcd 220.1099, found 220.1102.

(*R*)-5-Acetoxy-5,6,7,8-tetrahydro-1-naphthol (6e): $[\alpha]^{20}_D$ = +123.2° (*c* = 2.0, $CHCl_3$, 89% ee); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.21−7.01 (m, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 7.8 Hz 1H), 5.98 (q, *J* = 3.8 Hz, 1H), 2.87−2.61 (m, 1H), 2.65−2.41 (m, 1H), 2.09 (s, 3H), 2.01−1.84 (m, 2H), 1.84−1.58 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 171.7, 154.0, 136.7, 127.3, 125.2, 122.4, 115.0, 70.7, 29.2, 23.1, 22.2, 18.6; HRMS (EI+) $C_{12}H_{14}O_3$ calcd 206.0943, found 206.0942.

(*R*)-5-Butanoyloxy-5,6,7,8-tetrahydro-1-naphthol (6f): $[\alpha]^{20}_D$ = +103.7° (*c* = 2.0, $CHCl_3$, 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.08 (t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 7.9 Hz 1H), 6.02−5.99 (m, 1H), 2.84−2.75 (m, 1H), 2.61−2.51 (m, 1H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.98−1.87 (m, 4H), 1.75−1.68 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 174.4, 154.0, 136.8, 127.2, 125.3, 122.2, 114.9, 70.5, 37.4, 29.3, 23.2, 19.3, 18.7, 14.3; HRMS (EI+) $C_{14}H_{18}O_3$ calcd 234.1256, found 234.1252.

(*R*)-2-Acetoxy-4-(4-hydroxyphenyl)butane (6 g): $[\alpha]^{20}_D$ = +6.13° (*c* = 2.0, $CHCl_3$, 96% ee); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.03 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 4.95−4.89 (m, 1H), 2.61−2.49 (m, 2H), 2.04 (s, 3H), 1.97−1.82 (m, 1H), 1.81−1.73 (m, 1H) 1.24 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 171.9, 154.7, 134.0, 130.0, 116.0, 71.5, 38.4, 31.5, 22.0, 20.7; HRMS (EI+) $C_{12}H_{16}O_3$ calcd 208.1099, found 208.1098.

(*R*)-2-Butanoyloxy-4-(4-hydroxyphenyl)butane (6h): $[\alpha]^{20}_D$ = +2.40° (*c* = 2.0, $CHCl_3$, 98% ee); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.02 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 4.99−4.88 (m, 1H), 2.65−2.50 (m, 2H), 2.28 (t, *J* = 7.4 Hz, 3H), 1.97−1.82 (m, 1H), 1.81−1.66 (m, 1H), 1.73−1.60 (m, 2H), 1.24 (d, *J* = 6.2, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 174.2, 154.5, 134.3, 130.1, 115.9, 70.9, 38.6, 37.3, 31.6, 20.8, 19.3, 14.4; HRMS (EI+) $C_{14}H_{20}O_3$ calcd 236.1412, found 236.1413.

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