(*S*)-Selective Dynamic Kinetic Resolution of Allylic Alcohols by Enzyme-Metal Bicatalysis†

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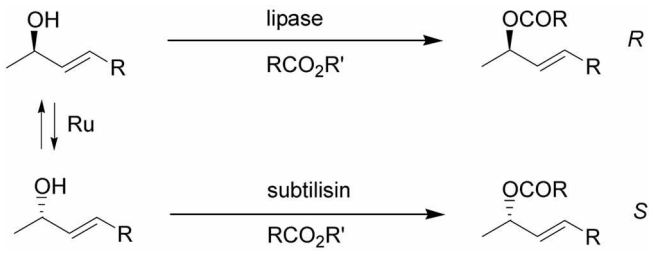
Key Words : Dynamic kinetic resolution, Allylic alcohol, Subtilisin, Ruthenium, Enzyme-metal combination

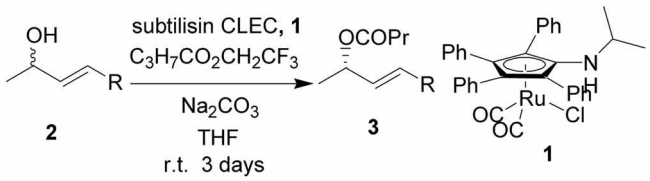
Dynamic kinetic resolution (DKR) provides a useful methodology for the conversion of racemic substrates to single enantiomeric products. In the last decade, a new approach for DKR has been intensively explored, in which an enzyme as the resolution catalyst is combined with a metal or metal complex as the racemization catalyst.[1] Several enzyme-metal combinations have been developed for the DKR of alcohols. Among them, lipase-ruthenium combinations are particularly useful for the (*R*)-selective DKR of secondary alcohols.[2] A wide range of simple and functionalized secondary alcohols have been transformed to enantiomerically-enriched forms with them. In many cases, high yields and enantiomeric excesses approaching 100% were realized. The (*S*)-selective DKR of secondary alcohols, however, has been much less intensively explored compared to its counterpart. We reported for the first time the use of a subtilisin-ruthenium combination for such DKR, which was applied to a limited number of simple secondary alcohols.[3] As our continuous efforts in this area, we now wish to report an application of subtilisin-ruthenium combination in the DKR of functionalized alcohols such as allylic alcohols.

Chiral allylic alcohols in optically pure forms are synthetically important synthons which can be transformed to a wide range of more complex molecules.[4] Previously we reported a procedure based on a lipase-ruthenium combination for the (*R*)-selective DKR of allylic alcohols.[5] Accordingly, we became interested in developing a complementary procedure for the synthesis of opposite enantiomers, which would be realized by using subtilisin as the resolution catalyst in the presence of a ruthenium-based racemization catalyst (Scheme 1).



Scheme 1. DKR of allylic alcohols by enzyme-metal combination.

†This paper is dedicated to Professor Sang Chul Shim on the occasion of his honorable retirement.

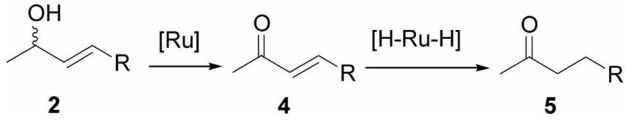


Scheme 2. (*S*)-Selective DKR of allylic alcohols.

For the (*S*)-selective DKRs of allylic alcohols, 10 different compounds **2a-j** were examined as substrates with a commercial enzyme (subtilisin CLEC) and a ruthenium complex **1** as the catalysts (Scheme 2). In a typical procedure, the reaction was performed for 3 days at room temperature with a mixture of substrate (0.3 mmol), subtilisin CLEC (15 mg/mmol of substrate), **1** (4 mol%, preactivated with potassium *t*-butoxide), and trifluoroethyl butyrate (5.1 mmol) as an acyl donor in THF. The acylated products were isolated by silica gel chromatography and their optical purities were analyzed by chiral HPLC.

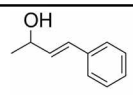
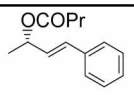
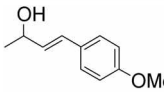
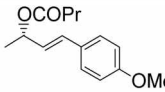
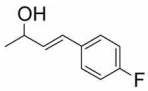
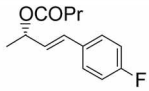
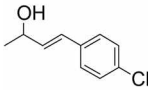
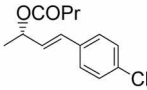
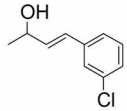
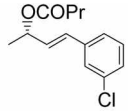
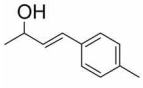
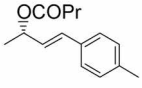
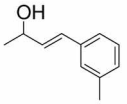
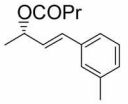
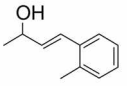
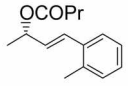
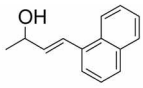
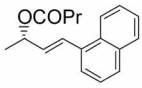
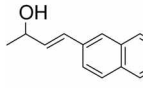
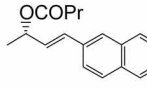
The data from Table 1 indicate that satisfactory resolution has been accomplished in all the cases. The isolated yields ranged from 73 to 92% and the enantiomeric excesses reached 96% or greater. It was observed that the yields were lowered by side reactions such as oxidation and isomerization,[6] leading to the formation of ketones such as **4** and **5** (Scheme 3). The yields of byproducts ranged from 5 to 9%. The *S*-configuration of the acylated products was confirmed by comparing the optical rotation (−23.1 for c = 1, $CHCl_3$, >99% ee) of allylic alcohol (*S*)-**2d** obtained from the hydrolytic deacylation of **3d** with the literature value (−25.4 for c = 1, $CHCl_3$, >99% ee).[7]

In summary, we have demonstrated that the (*S*)-selective DKR of allylic alcohols has been successfully achieved by combining subtilisin CLEC with an aminocyclopentadienylruthenium complex as the catalysts. The reactions are straightforward and give satisfactory yields and high optical purities in most cases. This work thus has established a



Scheme 3. Ru-catalyzed oxidation and isomerization of allylic alcohols.

Table 1. (*S*)-Selective DKR of allylic alcohols

entry	substrate	product	yield (%)[a]	ee (%)[b]
1	 **2a**	 **3a**	80	97
2	 **2b**	 **3b**	73	98
3	 **2c**	 **3c**	82	96
4	 **2d**	 **3d**	92	99
5	 **2e**	 **3e**	79	99
6	 **2f**	 **3f**	76	98
7	 **2g**	 **3g**	80	99
8	 **2h**	 **3h**	80	99
9	 **2i**	 **3i**	74	>99
10	 **2j**	 **3j**	88	99

[a]Isolated yield. [b]Determined by HPLC using a chiral column.

complementary procedure for the DKR of allylic alcohols, which should find use in asymmetric synthesis of bioactive molecules such as pharmaceuticals.[8]

Experimental Section

General procedure for (*S*)-selective DKR. The procedure for the DKR of **2a** is described as a representative. To a Schlenk-type flask was added a solution of potassium *tert*-butoxide (1.0 M in THF, 17 μL, 0.015 mmol) under argon, followed by the addition of ruthenium complex **1** (0.012 mmol, 7.44 mg). The resulting mixture was dried in vacuo to remove THF and the flask was filled with argon. Then, subtilisin CLEC (purchased from Altus; 4.5 mg, 15 mg/mmol) and sodium carbonate (63.6 mg, 0.6 mmol) were added under argon. The resulting mixture was dried again in vacuo, followed by the addition of a solution of substrate (44.6 mg, 0.3 mmol) in anhydrous THF (0.5 mL) and acyl donor (2,2,2-trifluoroethylbutyrate, 0.51 mmol, 78 μL). The resulting red-brown mixture was stirred at 25 °C. After the reaction was complete (3 days), the solid materials were filtered off and the filtrate was concentrated. The residue was subjected to flash column chromatography (*n*-hexane/Et_2O = 15/1) to afford **3a** (52 mg, 0.24 mmol, 80%). The enantiopurity of **3a** was determined by chiral HPLC (Whelk-O1, *n*-hexane/2-propanol = 98/2, flow rate = 1.0 mL/min, UV = 257 nm).

3a: 97% ee; $[\alpha]_D^{25} = -111.3$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.39-7.22 (m, 5H), 6.60 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 15.9, 6.7 Hz, 1H), 5.59-5.49 (m, 1H), 2.30 (t, J = 7.4 Hz, 2H), 1.73-1.61 (m, 2H), 1.41 (d, J = 6.5 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.1, 137.5, 131.6, 129.1, 128.7, 128.0, 126.7, 70.8, 36.7, 20.6, 18.6, 13.8; HRMS (EI+) $C_{14}H_{18}O_2$ calcd 218.1307, found 218.1303.

3b (73%, 54.6 mg, 0.22 mmol): 98% ee by HPLC (Whelk-O1, *n*-hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV = 257 nm); $[\alpha]_D^{25} = -104.6$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.33-7.29 (m, 2H), 6.87-6.83 (m, 2H), 6.54 (d, J = 15.9 Hz, 1H), 6.05 (dd, J = 15.9, 6.9 Hz, 1H), 5.56-5.47 (m, 1H), 3.81 (s, 3H), 2.29 (t, J = 7.4 Hz, 2H), 1.77-1.60 (m, 2H), 1.39 (d, J = 6.5 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.1, 159.6, 131.2, 129.2, 127.9, 126.9, 114.1, 71.1, 55.4, 36.7, 20.6, 18.6, 13.8; HRMS (EI+) $C_{15}H_{20}O_3$ calcd 248.1412, found 248.1417.

3c (82%, 58.1 mg, 0.246 mmol): 96% ee by HPLC (Whelk-O1, *n*-hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV = 257 nm); $[\alpha]_D^{25} = -82.4$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.37-7.31 (m, 2H), 7.04-6.97 (m, 2H), 6.56 (d, J = 16.0 Hz, 1H), 6.10 (dd, J = 15.9, 6.7 Hz, 1H), 5.57-5.48 (m, 1H), 2.30 (t, J = 7.4 Hz, 2H), 1.73-1.60 (m, 2H), 1.40 (d, J = 6.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.1, 164.2, 161.0, 145.0, 132.7, 132.7, 130.4, 128.9, 128.3, 128.2, 115.7, 115.5, 70.8, 36.7, 20.5, 18.6, 13.8; HRMS (EI+) $C_{14}H_{17}O_2F$ calcd 236.1213, found 236.1215.

3d (92%, 69.8 mg, 0.276 mmol): 99% ee by HPLC (Whelk-O1, *n*-hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV = 257 nm); $[\alpha]_D^{25} = -106.8$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.32-7.26 (m, 4H), 6.54 (d, J = 15.9 Hz, 1H), 6.15 (dd, J = 15.9, 6.9 Hz, 1H), 5.54-5.50 (m, 1H), 2.30 (t, J = 7.4 Hz, 2H), 1.70-1.63 (m, 2H), 1.40 (d, J = 6.5 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.1, 135.8, 133.6, 130.3, 129.8, 128.9, 127.9, 70.6, 36.7, 20.5, 18.6, 13.8; HRMS (EI+) $C_{14}H_{17}O_2Cl$ calcd 252.0917, found 252.0914.

3e (79%, 60 mg, 0.237 mmol) : 99% ee by HPLC (Whelk-O1, *n*-hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV = 257 nm); $[\alpha]_D^{25} = -103.4$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.37 (s, 1H), 7.26-7.23 (m, 3H), 6.53 (d, J = 16.0 Hz, 1H), 6.19 (dd, J = 15.9, 6.5 Hz, 1H), 5.55-5.50 (m, 1H), 2.31 (t, J = 7.4 Hz, 2H), 1.71-1.61 (m, 2H), 1.40 (d, J = 6.5 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 172.4, 137.8, 134.0, 130.1, 129.4, 129.3, 127.3, 125.9, 124.3, 69.8, 36.0, 19.8, 18.0, 13.1; HRMS (EI+) $C_{14}H_{17}O_2Cl$ calcd 252.0917, found 252.0919.

3f (76%, 52.6 mg, 0.226 mmol): 98% ee by HPLC (Whelk-O1, *n*-hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV = 257 nm); $[\alpha]_D^{25} = -115.9$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.29-7.23 (m, 2H), 7.13-7.06 (m, 2H), 6.56 (d, J = 15.9 Hz, 1H), 6.13 (dd, J = 15.9, 6.7 Hz, 1H), 5.57-5.48 (m, 1H), 2.33 (s, 3H), 2.30 (t, J = 7.4 Hz, 2H), 1.73-1.60 (m, 2H), 1.40 (d, J = 6.5 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.1, 137.9, 133.7, 131.5, 129.4, 128.1, 126.6, 70.9, 36.7, 21.4, 20.6, 18.7, 13.8; HRMS (EI+) $C_{15}H_{20}O_2$ calcd 232.1463, found 232.1461.

3g (80%, 56 mg, 0.241 mmol) : 99% ee by HPLC (Whelk-O1, *n*-hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV = 257 nm); $[\alpha]_D^{25} = -104.9$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.25-7.04 (m, 4H), 6.56 (d, J = 15.9 Hz, 1H), 6.17 (dd, J = 15.9, 6.7 Hz, 1H), 5.55-5.51 (m, 1H), 2.34 (s, 3H), 2.30 (t, J = 7.4 Hz, 2H), 1.71-1.63 (m, 2H), 1.39 (d, J = 6.4 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.1, 138.3, 136.5, 131.6, 128.9, 128.8, 128.6, 127.4, 123.9, 70.9, 36.7, 21.5, 20.6, 18.6, 13.8; HRMS (EI+) $C_{15}H_{20}O_2$ calcd 232.1463, found 232.1465.

3h (80%, 55.8 mg, 0.241 mmol): 99% ee by HPLC (Whelk-O1, *n*-hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV = 257 nm); $[\alpha]_D^{25} = -102.5$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.43-7.11 (m, 4H), 6.81 (dd, J = 15.7, 0.6 Hz, 1H), 6.06 (dd, J = 15.8, 6.7 Hz, 1H), 5.60-5.51 (m, 1H), 2.33 (s, 3H), 2.30 (t, J = 7.4 Hz, 2H), 1.74-1.61 (m, 2H), 1.41 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.1, 135.8, 135.7, 130.5, 130.4, 129.4, 127.9, 126.2, 125.8, 71.1, 36.7, 20.7, 19.9, 18.7, 13.8; HRMS (EI+) $C_{15}H_{20}O_2$ calcd 232.1463, found 232.1464.

3i (74%, 59.2 mg, 0.221 mmol): >99.5% ee by HPLC (Whelk-O1, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV = 257 nm); $[\alpha]_D^{25} = -53.2$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 8.07-7.33 (m, 8H), 6.21 (dd, J = 15.7, 6.6 Hz, 1H), 5.71-5.62 (m, 1H), 2.34 (t, J = 7.4 Hz, 2H), 1.76-1.54 (m, 2H), 1.48 (d, J = 6.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.2, 134.4, 133.7, 132.4, 131.4 128.9, 128.7, 128.3, 126.3, 126.0, 125.7, 124.1, 123.9, 71.0, 36.8, 20.7, 18.7, 13.9; HRMS (EI+) $C_{18}H_{20}O_2$ calcd 268.1463, found 268.1465.

3j (88%, 71.1 mg, 0.265 mmol): 99% ee by HPLC (Whelk-O1, *n*-hexane/2-propanol = 97/3, flow rate = 1.0 mL/min, UV = 257 nm); $[\alpha]_D^{25} = -108.3$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm) 7.81-7.77 (m, 4H), 7.60-7.57 (m, 1H), 7.47-7.32 (m, 2H), 6.76 (d, J = 16.5 Hz, 1H), 6.32 (dd, J = 15.9, 6.6 Hz, 1H), 5.62-5.57 (m, 1H), 2.33 (t, J = 7.4 Hz, 2H), 1.73-1.65 (m, 2H), 1.45 (d, J = 6.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 173.1, 134.0, 133.7, 133.3, 131.6, 129.5, 128.3, 128.1, 127.8, 126.8, 126.4, 126.1, 123.6, 70.8, 36.7, 20.6, 18.6, 13.8; HRMS (EI+) $C_{18}H_{20}O_2$ calcd 268.1463, found 268.1465.

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