ORGANIC LETTERS

2008
Vol. 10, No. 6
1295−1298

Highly Enantioselective Dynamic Kinetic Resolution of 1,2–Diarylethanols by a Lipase–Ruthenium Couple

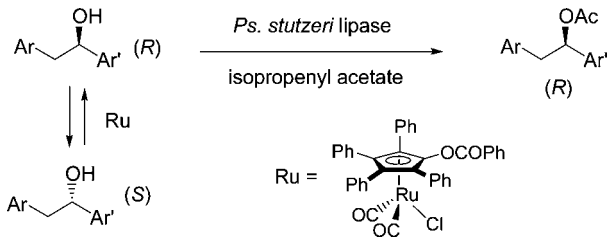
Mahn-Joo Kim,* Yoon Kyung Choi, Sol Kim, Daeho Kim, Kiwon Han, Soo-Byung Ko, and Jaiwook Park*

Department of Chemistry, Pohang University of Science and Technology (POSTECH), San-31 Hyojadong, Pohang 790-784, Korea

mjkim@postech.ac.kr; pjw@postech.ac.kr

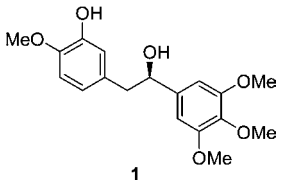
Received January 23, 2008

ABSTRACT



A practical procedure has been developed for the dynamic kinetic resolution of 1,2-diarylethanols. This procedure employs a highly enantioselective lipase from *Pseudomonas stutzeri* (trade name, lipase TL) as the resolution catalyst and a ruthenium complex as the racemization catalyst. Sixteen 1,2-diarylethanols have been efficiently resolved to provide their acetyl derivatives with good yields (95–97%) and high enantiomeric excesses (96–99%).

Optically pure 1,2-diarylethanols are pharmaceutically interesting as a result of the great potential of combretastatin (**1**) and analogs as anti-cancer agents.[1] We herein wish to report a novel procedure for their enantioselective synthesis, in which their racemic forms are converted to desirable single enantiomers via enzyme/metal-catalyzed dynamic kinetic resolution.



1

Figure 1. Structure of combretastatin.

Dynamic kinetic resolution (DKR) provides a practical method for the conversion of racemic substrates to single enantiomeric products. In the past decade, we and others have developed a new approach using two different types of catalyst systems, enzyme and metal, in combination for efficient DKR.[2] For example, the DKR of racemic secondary alcohols can be accomplished with lipase−Ru combinations.[3,4] Here, lipase acts as an enantioselective resolution catalyst and Ru complex as a racemization catalyst for the

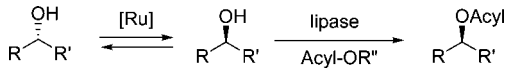
(1) (a) Petit, G. R.; Cragg, G. M.; Herald, D. L.; Schmidt, J. M.; Lohavanijaya, P. *Can. J. Chem.* **1982**, *60*, 1374−1376. (b) Petit, G. R.; Singh, S. B.; Cragg, G. M. *J. Org. Chem.* **1985**, *50*, 3404−3406. (c) Ramacciotti, A.; Fiaschi, R.; Napolitano, E. *Tetrahedron: Asymmetry* **1996**, *7*, 1101−1104. (d) Cirla, A.; Mann, J. *Nat. Prod. Rep.* **2003**, *20*, 558−564.

(2) For reviews, see: (a) Kim, M.-J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578−587. (b) Pamies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247−3262. (c) Kim, M.-J.; Ahn, Y.; Park, J. *Bull. Kor. Chem. Soc.* **2005**, *26*, 515−522. (d) Kim, M.−J.; Park, J.; Ahn, Y. In *Biocatalysis in the Pharmaceutical and Biotechnology Industries*; Patel, R. N., Ed.; CRC Press: Boca Raton, FL, 2007; pp 249−272. (e) Martín-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226−232.

10.1021/ol800163z CCC: $40.75
Published on Web 02/28/2008

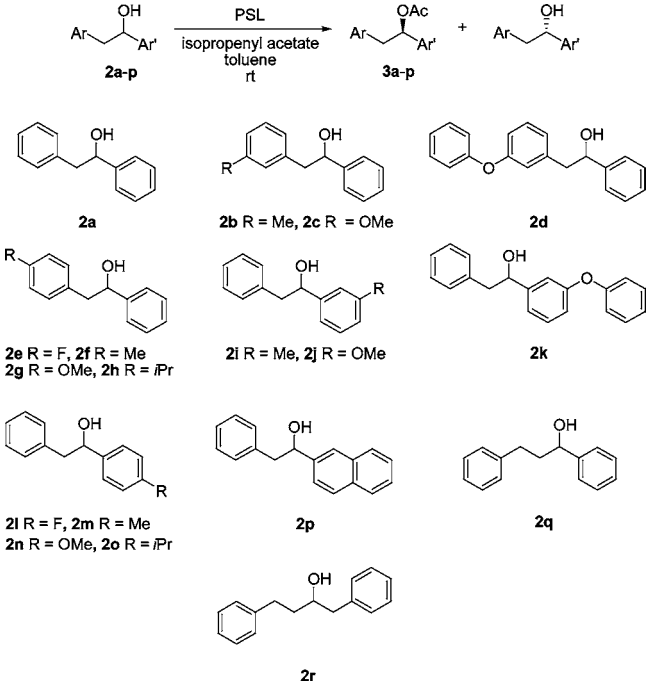
complete conversion of racemic alcohols to single enantiomeric acyl derivatives (Scheme 1). To date, most studies have been done to find efficient racemization catalysts, while few studies have been done to find highly enantioselective enzymes for new applications. The enzyme most frequently employed in the previous DKR processes is *Candida antarctica* lipase B (CALB; trade name, Novozym-435), which accepts a limited range of secondary alcohols carrying one small (up to three carbon unit) and one significantly larger substituent at the hydroxymethine center with high enantioselectivity.[5] Accordingly, the enzyme is inapplicable to 1,2-diarylethanols with two bulky substituents at the hydroxymethine center.

Scheme 1. Dynamic Kinetic Resolution of Secondary Alcohols



Through screening experiments, we found that *Pseudomonas stutzeri* lipase (PSL; trade name,[6] lipase TL) is highly enantioselective toward 1,2-diarylethanols.[7] In the transesterification reactions carried out in the presence of isopropenyl acetate in toluene at room temperature (Scheme 2), this enzyme displayed a high enantioselectivity ($E > 200$) toward 1,2-diphenylethanol **2a**.[8]

Scheme 2. PSL-Catalyzed Transesterification of 1,2-Diarylethanols



Such a high level of enantioselectivity was also observed with its analogues **2b**−**o**, in which one of two phenyl rings is monosubstituted at the *meta* or *para* position (entries 2−15, Table 1). The ring substituent varies from a small (F, Me, OMe, and *i*Pr) to a significantly larger group (OPh). Interestingly, the change in the size and position of the

Table 1. Enantioselectivity in PSL-Catalyzed Transesterification

entry	alcohol	E^a	entry	alcohol	E^a
1	**2a**	>200	10	**2j**	>200
2	**2b**	>200	11	**2k**	>200
3	**2c**	>200	12	**2l**	>200
4	**2d**	>200	13	**2m**	>200
5	**2e**	200	14	**2n**	>200
6	**2f**	>200	15	**2o**	>200
7	**2g**	>200	16	**2p**	166
8	**2h**	>200	17	**2q**	38
9	**2i**	164	18	**2r**	8

[a] The E values indicating the enantioselectivity, the ratio in reactivity between two enantiomers of alcohol, are obtained using the equation: $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$, where $c = ee_s/(ee_s + ee_p)$.[10]

(3) (a) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373−2376. (b) Kim, M.-J.; Chung, Y. I.; Choi, Y. K.; Lee, H. K.; Kim, D.; Park, J. *J. Am. Chem. Soc.* **2003**, *125*, 11494−11495. (c) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972−1977. (d) Akai, S.; Tanimoto, K.; Kita, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 1407−1410. (e) Martín-Matute, B.; Edin, M.; Bogár, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535−6539. (f) Kim, M.-J.; Kim, H. M.; Kim, D. H.; Park, J. *Green Chem.* **2004**, *6*, 471−474. (g) Kim, N.; Ko, S.-B.; Kwon, M. S.; Kim, M.-J.; Park, J. *Org. Lett.* **2005**, *7*, 4523−4526. (h) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817−8825. (i) Ko, S.-B.; Baburaj, B.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2007**, *72*, 6860−6864. (j) Kim, M.-J.; Lee, H. K.; Park, J. *Bull. Kor. Chem. Soc.* **2007**, *28*, 2096−2098. (k) Bogár, K.; Vidal, P. H.; León, A. R. A.; Bäckvall, J.-E. *Org. Lett.* **2007**, *9*, 3401−3404.

(4) For DKR of secondary alcohols with other enzyme-metal couples, see: (a) Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J.; Harris, W. *Tetrahedron Lett.* **1996**, *37*, 7623−7626. (b) Wuyts, S.; De Temmerman, K.; De Vos, D. E.; Jacobs, P. A. *Chem. Eur. J.* **2005**, *11*, 386−397. (c) Akai, S.; Tanimoto, K.; Kanao, Y.; Egi, M.; Yamamoto, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 2592−2595, (d) Berkessel, A.; Sebastian-Ibarz, M. L.; Müller, T. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6567−6570. (e) Wuyts, S.; Wahlen, F. J.; Jacobs, P. A.; De Vos, D. E. *Green Chem.* **2007**, *9*, 1104−1108.

(5) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656−2665.

(6) Commercially available from Meito Sangyo, Japan (MW, 27000; specific activity, ca. 650 U/g for *p*-nitrophenyl acetate).

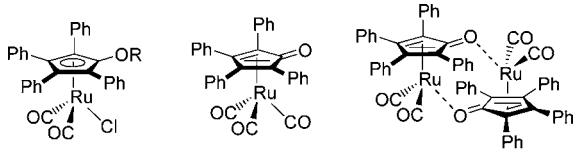
(7) For recent studies on PSL-catalyzed resolution of secondary alcohols, see: (a) Aoyagi, Y.; Agata, N.; Shibata, N.; Horiguchi, M.; Williams, R. M. *Tetrahedron Lett.* **2000**, *41*, 10159−10162. (b) Aoyagi, Y.; Iijima, A.; Williams, R. M. *J. Org. Chem.* **2001**, *66*, 8010−8014. (c) Aoyagi, Y.; Saitoh, Y.; Ueno, T.; Horiguchi, M.; Takeya, K.; Williams, R. M. *J. Org. Chem.* **2003**, *68*, 6899−6904. (d) Demir, A. S.; Findik, H.; Köse, E. *Tetrahedron: Asymmetry* **2004**, *15*, 777−781. (e) Kato, K.; Gong, Y.; Saito, T.; Yokogawa, Y. *J. Mol. Catal. B: Enzym.* **2004**, *30*, 61−68. (f) Moore, B. D.; Stevenson, L.; Watt, A.; Flitsch, S.; Turner, N. J.; Cassidy, C.; Grahan, D. *Nat. Biotechnol.* **2004**, *22*, 1133−1138. (g) Gill, I. I.; Das, J.; Patel, R. N. *Tetrahedron: Asymmetry* **2007**, *18*, 1330−1337. (h) Martínez, I.; Markovits, A.; Chamy, R.; Markovits, A. *Appl. Biochem. Biotechnol.* **2004**, *112*, 55−62. (i) Shoji, M.; Kishida, S.; Takeda, M.; Kakeya, H.; Osada, H.; Hayashi, Y. *Tetrahedron Lett.* **2002**, *43*, 9155−9158.

(8) To the best of our knowledge, this is the highest enantioselectivity of a lipase so far reported with **2a**. A low enantioselectivity ($E = 6$) toward **2a** was previously reported for lipase PS. Ema, T.; Kageyama, M.; Korenaga, T.; Sakai, T. *Tetrahedron: Asymmetry* **2003**, *14*, 3943−3947.

substituent did not affect the enantioselectivity seriously. For example, compare **2b**−**d** with **2i**−**k** (entries 2−4 and 9−11) and **2e**−**h** with **2l**−**o** (entries 5−8 and 12−15). All of them except **2i** were accepted with the same level of high enantioselectivity ($E > 200$). A slightly lower but still high level of enantioselectivity was observed for **2i** ($E = 164$). The replacement of a phenyl ring by another aromatic ring in **2a** was acceptable for high enantioselectivity as observed for **2p** ($E = 166$, entry 16).

On the contrary, the enzymatic enantioselectivity was dramatically reduced toward 1,3-diphenyl-1-propanol **2q** ($E = 38$) and further reduced toward 1,4-diphenyl-2-butanol **2r** ($E = 8$) (entries 17 and 18). These results indicate that proper positioning of each aromatic ring around the hydroxymethine center is essential for high enantioselectivity. Overall, all of the observations clearly indicate that PSL could serve as the efficient resolution catalyst for the DKR of 1,2-diarylethanols.[9]

As the racemization catalyst for DKR, we initially tested air-stable **4**, which had previously showed a good performance in the DKR with Novozym-435,[3g] but later we found its new analogue **5** was similarly good in both activity and air stability but more practical to synthesize. The synthesis of **5** was achieved by two different methods. The first method is the reaction of **6** with benzoyl chloride in toluene at 80 °C, which was completed in 6 h with 95% yield.[10] The second is the reaction of **7** with benzoyl chloride in toluene at room temperature, which reached completion within only 2 h to afford 92% yield.[11] In contrast to these methods, the synthesis of **4** required a long reaction time (5 days) even at high reaction temperature (110 °C) for a moderate yield (65%).[3g]



4: R = CH_2Ph
5: R = COPh

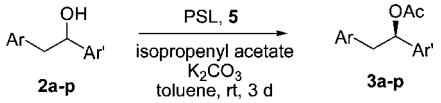
6

7

Figure 2. Ru complexes.

The DKR reactions with PSL and **5** were carried out under the conditions optimized for **2a**: substrate (0.2 mmol, 0.3 M), PSL (24 mg, 120 mg/mmol of substrate), **5** (0.016 mmol), isopropenyl acetate (0.3 mmol), K_2CO_3 (0.2 mmol), toluene (0.65 mL), room temperature, 3 days. The results are given in Table 2. In all cases, almost quantitative yields

Table 2. DKR of 1,2-Diarylethanols with PSL and **5**[a]



2a-p **3a-p**

entry	alcohol	isolated yield (%)	optical purity (% ee)[b]
1	**2a**	98	98
2	**2b**	96	98
3	**2c**	97	97
4	**2d**	99	96
5	**2e**	98	97
6	**2f**	97	97
7	**2g**	96	99
8	**2h**	95	99
9	**2i**	95	98
10	**2j**	96	98
11	**2k**	99	99
12	**2l**	96	98
13	**2m**	98	98
14	**2n**	95	96
15	**2o**	97	99
16	**2p**	97	98

[a] Reaction conditions: alcohol (0.2 mmol, 0.3 M), enzyme (24 mg, 120 mg/mmol of substrate), **5** (0.016 mmol), isopropenyl acetate (0.3 mmol), K_2CO_3 (0.2 mmol), toluene (0.65 mL), room temperature, 3 days. [b] Optical purities were determined by HPLC using a chiral column ((*R*,*R*) Whelk-O1).

(95−99%) were obtained with excellent enantiomeric excesses (96−99% ee). The patterns of HPLC chromatograms taken for measuring the ee values of the products suggested that all of the products should have the same absolute configuration. We have assigned it as *R* by comparing the optical rotation of an acetylated product **3a** with the literature value.[12] These results thus indicate that all the DKR reactions proceeded efficiently to give desirable single enantiomeric products.

The conversion of the acetylated products to the corresponding optically active alcohols can be readily achieved by basic hydrolysis. As a representative example, **3a** (98% ee) was deacetylated with K_2CO_3 in MeOH−H_2O to give (*R*)-**2a** quantitatively without loss in enantiomeric excess.[13]

In summary, we have demonstrated for the first time that 1,2-diarylethanols are efficiently resolved by PSL in kinetic and dynamic kinetic resolutions. Their DKR reactions by the combination of PSL and **5** are straightforward and

(9) Lately, a group from Spain reported the use of PSL (lipase TL) in the DKR of benzoins. (a) Hoyos, P.; Fernández, M.; Sinisterra, J. V.; Alcántara, A. *J. Org. Chem.* **2006**, *71*, 7632−7637. (b) Hoyos, P.; Buthe, A.; Ansorge-Schumacher, M. B.; Sinisterra, J. V.; Alcántara, A. R. *J. Mol. Catal. B: Enzym.* **2007**, in press (doi:10.1016/j.molcatb.2007.10.009).

(10) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294−7299.

(11) Ruthenium complexes **6** and **7** were prepared according to the known procedures. (a) Mays, M. J.; Morris, M. J.; Raithby, P. R.; Shvo, Y.; Czarkie, D. *Organometallics* **1989**, *8*, 1162−1167. (b) Blum, Y.; Czarkle, D.; Rahamlm, Y.; Shvo, Y. *Organometallics* **1985**, *4*, 1459−1461. (c) Kim, N. Studies on Recyclable Racemization Catalysts for Dynamic Kinetic Resolution of Secondary Alcohols, Ph.D. Thesis, Pohang University of Science and Technology, Pohang, 2005.

(12) $[\alpha]^{25}_D = +21.8$ (*c* 1.0, $CHCl_3$, 98% ee), (lit.[8] $[\alpha]^{15}_D = +14.0$ (*c* 0.5, $CHCl_3$, 66% ee).

(13) (*R*)-**2a** (white solid, 98% yield, 98% ee): mp 69−70 °C (lit.[14] 66−70 °C); $[\alpha]^{25}_D = -53.8$ (*c* 1.0, EtOH) (lit.[14] $[\alpha]^{23}_D = -52.9$ (*c* 1.0, EtOH, >98% ee).

(14) David, C.; Paul, H.; Julian, P. H.; Ian, C. L.; Graham, M.; Paul, M.; Christopher, J. P.; James, A. R.; Simon, W.; Antonio, Z.-G. *Org. Proc. Res. Dev.* **2003**, *7*, 89−94.

provide high yields and excellent optical purities, both approaching 100%. The procedure thus can serve as a protocol for the synthesis of a wide range of enantiopure 1,2-diarylethanols. Further studies for the application of this protocol to **1** and close analogues are in progress.

Acknowledgment. This work was supported by the Korean Ministry and Science and Technology through KOSEF (Center for Integrated Molecular System and R01-2006-000-10696-0) and by the Korean Ministry of Education and Human Resources through KRF (BK21 program and KRF-2006-311-C00089).

Supporting Information Available: Experimental procedures for kinetic and dynamic kinetic resolution and analytical data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800163Z