Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5471–5474

# High-yielding metalloenzymatic dynamic kinetic resolution of fluorinated aryl alcohols

Krisztián Bogár and Jan-E. Bäckvall*

*Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden*

Received 26 April 2007; revised 21 May 2007; accepted 31 May 2007
Available online 6 June 2007

**Abstract**—Dynamic kinetic resolution (DKR) of various fluorinated aryl alcohols by a combination of lipase-catalyzed enzymatic resolution with in situ ruthenium-catalyzed alcohol racemization is described. (*R*)-Selective *Candida antarctica* lipase B (CALB) was employed for transesterification of different fluoroaryl alcohols in DKR reactions delivering the corresponding acetates in high yield (⩾97%) with excellent enantiomeric excess (⩾98%).


## 1. Introduction

The asymmetric synthesis of chiral fluoroorganic compounds plays an important role in the development of medicines, agrochemicals and materials due to the influence of fluorine's unique properties.[1] There are many ways to fluorinate organic compounds and it is well known that the introduction of fluorine atom(s) into organic molecules greatly enhances or dramatically changes their biological activities.[1d] Chiral fluorinated alcohols are versatile intermediates for the synthesis of pharmaceuticals,[2] agrochemicals, and ferroelectric and antiferroelectric liquid crystals.[3] Besides conventional methodologies,[4] catalytic transformations[5] and organocatalysis,[6] which use very special and/or expensive chemicals, the use of biocatalysts (for instance lipases) for highly chemo-, regio- and stereoselective transformations in preparative organic chemistry has become increasingly important in recent years.[7] Enantiomerically enriched fluorinated aryl alcohols and their esters can be prepared by enzymatic kinetic resolution, but this method has a limitation of a maximum yield of 50%. Dynamic kinetic resolution (DKR) is a powerful tool to prepare enantiomerically enriched compounds in high yields that overcomes the limitation of kinetic resolution. Recently, we developed a highly efficient DKR protocol for secondary alcohols in which traditional enzymatic resolution is combined with an in situ racemization of the substrate using a ruthenium-based room temperature racemization catalyst.[8]

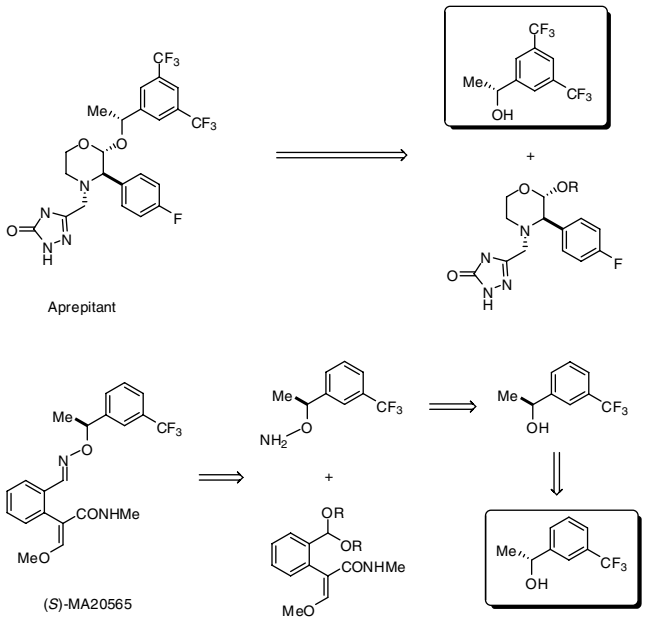
Optically active 1-(phenyl)ethanol and its substituted analogues are widely used as building blocks in asymmetric syntheses, and fluorinated derivatives thereof are structural elements in pharmaceutical[2] and agrochemical products.[9] These fluorinated alcohols have also been used in mechanistic enzymology research.[10] For instance, in the pharmaceutical area, (*R*)-1-(3,5-bis-trifluoromethylphenyl)-ethanol is a valuable intermediate in the synthesis of neurokinin receptor (NK-1) antagonists (Scheme 1).[11] We were interested in extending our ongoing research program on metalloenzymatic dynamic kinetic resolution (DKR) of secondary alcohols to fluorinated examples. Herein we report a high-yielding chemoenzymatic DKR of fluorinated aryl alcohols at room temperature.

## 2. Results and discussion

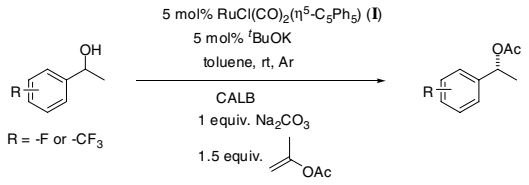
As we have previously described, racemic functionalized and nonfunctionalized secondary alcohols can be transformed into their (*R*)-acetates in high yields with excellent ee's via chemoenzymatic dynamic kinetic resolution (DKR) under ambient conditions.[8a,b] It is known that when a lipase is immobilized on a solid carrier, the activity and the stability of the enzyme are improved. *Candida antarctica* lipase B (CALB) is a very robust enzyme and one of the most effective catalysts for resolution of alcohols in organic solvents giving high

* Corresponding author. Tel.: +46 8 6747178; fax: +46 8 154908; e-mail: jeb@organ.su.se

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.175




**Scheme 1.** Retrosynthetic analysis of aprepitant and (*S*)-MA20565.



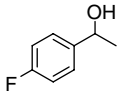
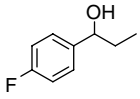
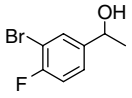
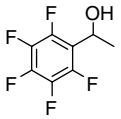
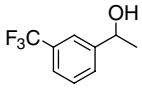
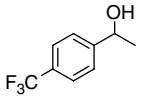
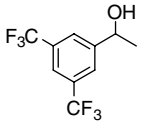

**Scheme 2.** (*R*)-Selective dynamic kinetic resolution of various fluorinated aryl alcohols.

enantioselectivity.[12] In our study, two groups surround the alcohol moiety: one is the larger fluorinated aryl group and the other is the smaller alkyl group. This composition determines the stereochemical outcome of the product in the lipase-catalyzed transesterification reactions (Scheme 2), and the enantioselectivity follows Kazlauskas' rule.[13]

In preliminary studies we found that 5 mol % of Ru-catalyst (**I**) and CALB in the presence of $Na_2CO_3$ in toluene with isopropenyl acetate as acylating agent resulted in the DKR of (*rac*)-1-(4-trifluoromethylphenyl)ethanol (**6**) and (*rac*)-1-(1,2,3,4,5-pentafluorophenyl) ethanol (**4**).[8b] In the present study, the same reaction conditions were employed for the DKR of various fluoro-substituted aryl alcohols. The results are summarized in Table 1. The substrate choice was motivated by (i) the increased demand for enantiopure fluoroalcohols, and (ii) the substrate structure requirements of the employed CALB, described above, to provide high stereochemical outcome in the DKR reactions.

All fluoro-substituted alcohols **1**–**7** are electron deficient, and except for 1-(4-trifluoromethylphenyl)ethanol (**6**) (Table 1, entry 6), which was transformed into product in 24 h, they all required 72 h reaction time. The long reaction time is due to a slow transition metal-catalyzed redox racemization at room temperature. Employing the optimized amount of CALB, these reactions proceeded with very high enantioselectivity: for 1-(3-bromo-4-fluorophenyl)ethanol (**3**) the ee was 98% (entry 3) and for all other cases ⩾99% ee was obtained (entries 1–2 and 4–7). For many cases, such as 1-(4-fluorophenyl)ethanol (**1**), 1-(4-fluorophenyl)propanol (**2**), 1-(2,3,4,5,6-pentafluorophenyl)ethanol (**4**), 1-(4-trifluoromethylphenyl)-ethanol (**6**) and 1-(3,5-*bis*-trifluoromethylphenyl)ethanol (**7**), the corresponding acetates were isolated in excellent yields (⩾97%).

**Table 1.** Dynamic kinetic resolution of various fluorinated alcohols[a]

| Entry | Substrate | Time (h) | Yield (%) of (*R*)-acetate[b,c] | ee[b] (%) |
|---|---|---|---|---|
| 1 |  **1** | 72 | >99 (99) | 99 |
| 2[d] |  **2** | 72 | 99 (>97) | >99 |
| 3 |  **3** | 72 | >99 | 98 |
| 4 |  **4** | 72 | 98 (97) | >99 |
| 5 |  **5** | 72 | 98 | >99 |
| 6 |  **6** | 24 | >98 (98) | >99 |
| 7 |  **7** | 72 | >99 (>98) | >99 |

[a] Unless otherwise noted, Ru-catalyst **I** (5 mol %), CALB (3 mg), $Na_2CO_3$ (0.5 mmol), and $^t$BuOK (5 mol %) were stirred in toluene (1 mL) for 6 min before adding the alcohol (0.5 mmol). After 4 min, isopropenyl acetate (0.75 mmol) was added and the mixture was stirred under an argon atmosphere at rt.

[b] Determined by chiral GC using a CP-Chirasil-Dex CB (25 m × 0.32 mm × 0.25 μm) capillary chiral column.

[c] Isolated yield in parentheses.

[d] 3 mmol scale.

In conclusion, we have reported on a high-yielding chemoenzymatic DKR of fluorinated aryl alcohols at room temperature. Under optimized conditions a variety of fluorinated benzylic secondary alcohols were

subjected to DKR reaction and the corresponding acetates with *R*-configuration were obtained in 97–99% yields with 98–99% ee's, indicating the high efficiency of our catalytic system.

## 3. Experimental

Racemic 1-(1,2,3,4,5-pentafluorophenyl)ethanol (**4**) is commercially available. Other racemic alcohols were prepared by standard $NaBH_4$ reduction of the corresponding commercially available ketone in methanol.

### 3.1. Typical experimental procedure for DKR of secondary alcohols

A solution of $^t$BuOK (0.5 M in THF; 50 μL, 0.025 mmol) was added to a mixture of RuCl-$(CO)_2(\eta^5\text{-}C_5Ph_5)$ (**I**)[8b] (16 mg, 0.025 mmol), CALB (3 mg) and $Na_2CO_3$ (53 mg, 0.5 mmol) in dry toluene (1 mL) in a 10 mL flame-dried Schlenk tube and the mixture was stirred for 6 min under argon at room temperature. Then the substrate alcohol (0.5 mmol) was added, and after 4 min, isopropenyl acetate (88 μL, 0.75 mmol) was added and the reaction mixture was stirred at room temperature. The reaction was followed by GC. At the end of the reaction, the reaction mixture was passed through a silica pad and concentrated. Purification by column chromatography afforded the corresponding acetates as colourless oils.

### 3.2. Selected spectral data for substrates and acylated products

**1-(4-Fluorophenyl)-1-propanol (entry 2).** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.33–7.29 (m, 2H), 7.06–7.01 (m, 2H), 4.59 (t, $J = 6.6$ Hz, 1H), 1.86–1.67 (m, 3H, $CH_2$ and O*H*), 0.91 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 127.60, 127.53, 115.29, 115.08, 75.37, 32.00, 10.04.

**(*R*)-1-Acetoxy-1-(4-fluorophenyl)propane (entry 2).** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.31–7.28 (m, 2H), 7.05–7.00 (m, 2H), 5.63 (t, $J = 6.9$ Hz, 1H), 2.06 (s, 3H), 1.97–1.86 (m, 1H), 1.83–1.73 (m, 1H), 0.87 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 170.35, 163.52, 136.31, 128.36, 128.28, 115.35, 115.14, 29.23, 21.21, 9.84.

**1-(3-Bromo-4-fluorophenyl)ethanol (entry 3).** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.59 (dd, $J = 2.2$, 6.6 Hz, 1H), 7.30–7.26 (m, 1H), 7.09 (t, $J = 8.6$ Hz, 1H). 4.87 (q, $J = 6.4$ Hz, 1H), 1.78 (br s, 1H), 1.47 (d, $J = 6.1$ Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 130.59, 125.99, 125.91, 116.48, 116.26, 69.23, 25.40.

**(*R*)-1-Acetoxy-1-(3-bromo-4-fluorophenyl)ethane (entry 3).** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.55 (dd, $J = 2.4$, 6.6 Hz, 1H), 7.26 (ddd, $J = 8.4$, 4.8, 2.4 Hz, 1H), 7.09 (t, $J = 8.4$ Hz, 1H), 5.81 (q, $J = 7.6$ Hz, 1H), 2.07 (s, 3H), 1.51 (d, $J = 5.6$ Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 170.11, 131.31, 126.90, 126.82, 116.54, 116.320, 70.93, 22.18, 21.24.

**(*R*)-1-Acetoxy-1-(4-trifluoromethylphenyl)ethane (entry 6).** $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.61 (d, $J = 8.0$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 5.90 (q, $J = 6.0$ Hz, 1H), 2.09 (s, 3H), 1.54 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 170.13, 145.72, 126.29, 125.83, 125.51, 71.59, 22.24, 21.19 (one carbon is missing due to overlapping signals).

## Acknowledgements

This work was financially supported by the Swedish Foundation for Strategic Research and the Swedish Research Council.

## References and notes

1. (a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Hayashi, T., Soloshonok, V. A., Eds.; *Tetrahedron: Asymmetry* **1994**, *5*, 955–1126 (special issue); (b) *Organofluorine Chemistry—Principle and Commercial Application*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994; (c) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds, Stereochemical Challenges and Biomedical Targets*; Soloshonok, V. A., Ed.; Wiley: New York, 1999; (d) *Organofluorine Chemistry—Chemistry and Applications*; Hiyama, T., Ed.; Springer: Berlin, 2000; (e) *Modern Organofluorine Chemistry*; Kirsch, P., Ed.; Wiley: Weinheim, 2004.
2. For fluorinated drugs, see, for example: (a) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27; (b) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029.
3. (a) Suzuki, Y.; Nonaka, O.; Koide, Y.; Okabe, N.; Hagiwara, T.; Kawamura, I.; Yamamoto, N.; Yamada, Y.; Kitazume, T. *Ferroelectrics* **1993**, *147*, 109; (b) Koden, M.; Kaneko, T.; Tamai, K.; Takeda, H.; Miyoshi, S.; Wada, T.; Takeda, M.; Itoh, K.; Yamazaki, T.; Kitazume, T. *Jpn. J. Appl. Phys.* **1994**, *33*, 1096; (c) Itoh, K.; Takeda, M.; Namekawa, M.; Nayuri, S.; Murayama, Y.; Yamazaki, T.; Kitazume, T. *Chem. Lett.* **1994**, 839; (d) Itoh, K.; Takeda, M.; Namekawa, M.; Nayuri, S.; Murayama, Y.; Yamazaki, T.; Kitazume, T. *Chem. Lett.* **1995**, 641.
4. (a) Welch, J. T.; Eswarakrishnan, S. *J. Am. Chem. Soc.* **1987**, *109*, 6716; (b) Welch, J. T.; Seper, K. W. *J. Org. Chem.* **1988**, *53*, 2991; (c) Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1995**, *60*, 6563; (d) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2002**, 2609; (e) Ferreira, S. B. *Synlett* **2006**, 1130; (f) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827.
5. Catalytic asymmetric synthesis of fluoroorganic compounds, see, for instance: (a) Mikami, K.; Yajima, T.; Takasaki, T.; Matsukawa, S.; Terada, M.; Uchimaru, T.; Maruta, M. *Tetrahedron* **1996**, *52*, 85; (b) Soloshonok, V. A.; Kacharov, A. D.; Hayashi, T. *Tetrahedron* **1996**, *52*, 245.
6. For a recent publication in the area of organocatalytic fluorination, see: Brandes, S.; Niess, B.; Bella, M.; Pietro, A.; Overgaard, J.; Jørgensen, K. A. *Chem. Eur. J.* **2006**, *12*, 6039.
7. Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis, Regio- and Stereoselective Biotransformations*; Wiley: Weinheim, 1999.
8. (a) Martín-Matute, B.; Edin, M.; Bogár, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535; (b) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817; (c) Borén, L.;

Martin-Matute, B.; Xu, Y.; Cordova, A.; Bäckvall, J.-E. *Chem. Eur. J.* **2006**, *12*, 225.
9. For instance, optically pure 1-(3-trifluoromethylphenyl)-ethanol is a precursor for the (*S*)-MA20565 fungicide, see: Tanaka, K.; Katsurada, M.; Ohno, F.; Shiga, Y.; Oda, M. *J. Org. Chem.* **2000**, *65*, 432.
10. Rzepa, H. S.; O'Hagan, D. *Chem. Commun.* **1997**, 645.
11. For a recent article on the synthesis of an $NK_1$ receptor antagonist, see: Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N.; McNamara, J. M.; Reider, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 2129.
12. Rotticci, D.; Ottosson, J.; Norin, T.; Hult, K. *Methods Biotechnol.* **2001**, *15*, 261.
13. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.