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Chemoenzymatic Synthesis of Rivastigmine via Dynamic Kinetic Resolution as a Key Step

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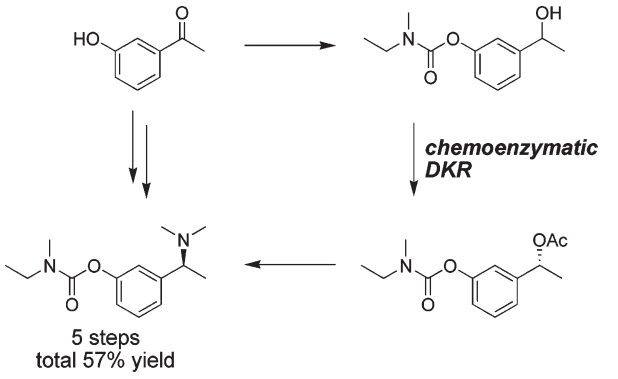
Received December 31, 2009



A practical and efficient procedure for the synthesis of rivastigmine was developed. This procedure includes dynamic kinetic resolution using a polymer-bound ruthenium complex and a lipase in combination as a key step. Enantiopure (−)-rivastigmine was obtained from commercially available 3′-hydroxyacetophenone via five steps in overall 57% yield.

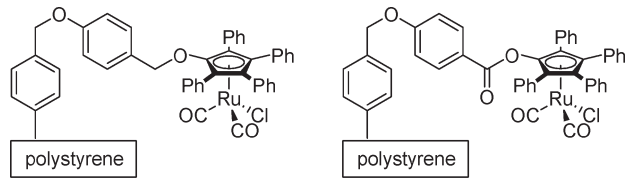
Rivastigmine (**1**) is an acetylcholinesterase inhibitor of the carbamate type, which is selective in the brain region and has a long duration of action.[1] It improves cognition, participation in daily activities, and global evaluation of patients with mild to moderate Alzheimer's disease.[2] In addition, it is supposed to be effective in the treatment of dementia caused by Parkinson's disease[3] and Lewy body.[4] Now, its tartrate salt is marketed under brand name Exelon. Rivastigmine was first synthesized by resolution of the racemic rivastigmine using (+)-di-*O*,*O*′-*p*-toluoyl tartaric acid monohydrate in 1987.[5] Later, asymmetric syntheses of rivastigmine were reported.[6] Herein, we wish to report an alternative asymmetric synthetic procedure for rivastigmine, which includes the dynamic kinetic resolution of a secondary alcohol intermediate as a key step.

Dynamic kinetic resolution (DKR), in which in situ metal-catalyzed racemization is coupled with enzymatic resolution, is an attractive strategy to obtain enantiomerically enriched products from racemic substrates with high yields and excellent enantiomeric excesses, both approaching 100%.[7] Several groups including ours have developed racemization catalysts that are compatible with the enzymatic systems for the DKR of secondary alcohols.[8] However, most of them are soluble in the reaction medium so that recovering them is not easy after the reaction is complete. Recently, we reported the use of a polymer-bound racemization catalyst (**2**) in the DKR of alcohols (Figure 1).[9,10] In this work, we used its modified analogue **3** which was more practical to prepare.[11]

The polymer-bound racemization catalyst **3** was prepared by heating a mixture of polystyrene-attached benzoyl chloride (**4**) and $[Ph_4(\eta^4\text{-}C_4CO)]Ru(CO)_3$ (**5**) in toluene for 1 d (Scheme 1). Ruthenium content in **3** was estimated to 4.25 wt % by ICP analysis. The activity and reusability of **3** were examined in the racemization of optically active 1-phenylethanol ((*S*)-**6**, >99% ee) (Table 1). The racemization of (*S*)-**6** in the presence

(1) Polinsky, R. J. *Clin. Ther.* **1998**, *20*, 634–647.
(2) Rosler, M.; Anand, R.; Cicin-Sain, A.; Gauthier, S.; Agid, Y.; Dal-Bianco, P.; Stahelin, H. B.; Hartman, R.; Gharabawi, M. *Brit. Med. J.* **1999**, *318*, 633–638.
(3) Reading, P. J.; Luce, A. K.; McKeith, I. G. *Movement Disord.* **2001**, *16*, 1171–1174.
(4) McKeith, I.; Del Ser, T.; Spano, P.; Emre, M.; Wesnes, K.; Anand, R.; Cicin-Sain, A.; Ferrara, R.; Spiegel, R. *Lancet* **2000**, *356*, 2031–2036.
(5) Enz, A. GB 2203040A, **1987**.
(6) (a) Boezio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260–14261. (b) Mangas-Sánchez, J.; Rodríguez-Mata, M.; Busto, E.; Gotor-Fernández, V.; Gotor, V. *J. Org. Chem.* **2009**, *74*, 5304–5310. (c) Hu, M.; Zhang, F.-L.; Xie, M.-H. *Synth. Commun.* **2009**, *39*, 1527–1533.
(7) (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. Korean 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, 2007; pp 249−272. (e) Martín-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226–232.
(8) (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) Martín-Matute, B.; Edin, M.; Bogár, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535–6539. (d) Kim, M.-J.; Kim, H. M.; Kim, D. H.; Park, J. *Green Chem.* **2004**, *6*, 471–474. (e) Martín-Matute, B.; Edin, M.; Bogár, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825. (f) Hilker, I.; Rabani, G.; Verzijl, G. K. M.; Palmans, A. R. A.; Heise, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 2130–2132. (g) Akai, S.; Tanimoto, K.; Kanao, Y.; Egi, M.; Yanamoto, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 2592–2595. (h) Eckert, M.; Brethon, A.; Li, Y. X.; Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2007**, *349*, 2603–2609. (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. Korean 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. (l) Kim, M.-J.; Choi, Y. K.; Kim, S.; Kim, D.; Han, K.; Ko, S.-B.; Park, J. *Org. Lett.* **2008**, *10*, 1295–1298. (m) Haak, R. M.; Berthiol, F.; Jerphagnon, T.; Gayet, A. J. A.; Tarabiono, C.; Postema, C. P; Ritleng, V.; Pfeffer, M.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Am. Chem. Soc.* **2008**, *130*, 13508–13509.
(9) Kim, N.; Ko, S.-B.; Kwon, M. S.; Kim, M.-J.; Park, J. *Org. Lett.* **2005**, *7*, 4523–4526.
(10) For the DKRs of secondary alcohols using other heterogeneous racemization catalysts, see: (a) Wuyts, S.; De Temmerman, K.; De Vos, D. E.; Jacobs, P. A. *Chem.—Eur. J.* **2005**, *11*, 386–397. (b) Wuyts, S.; Wahlen, J.; Jacobs, P. A.; De Vos, D. E. *Green Chem.* **2007**, *9*, 1104–1108. (c) Zhu, Y. Z.; Fow, K. L.; Chuah, G. K.; Jaenicke, S. *Chem.—Eur. J.* **2007**, *13*, 541–547.
(11) The synthesis of **2** required a long reaction time (5 days), while the synthesis of **3** was complete within 1 day because the polymer-attached benzoyl chloride (**4**) was more reactive than its benzyl chloride counterpart.

DOI: 10.1021/jo9027374 Published on Web 03/26/2010



2 3

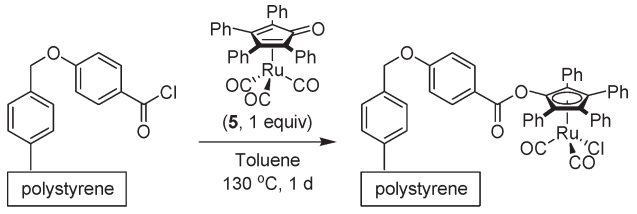
FIGURE 1. Polymer-supported ruthenium catalysts.

TABLE 1. Recycling of 3 in the Racemization of (*S*)-6[a]

run	reaction time (h)	% ee of **6**[b]
1	8	2
2	8	5
3	8	1
4	8	0
5	8	2

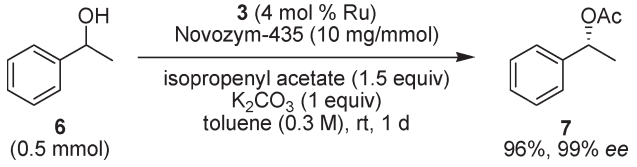
[a]Reaction condition: (*S*)-**6** (0.15 mmol), **3** (4 mol % Ru), K_2CO_3 (1 equiv), toluene (0.5 mL), rt. [b]Determined by HPLC.

SCHEME 1. Preparation of Polymer-Bound Ruthenium Complex 3



4 3

SCHEME 2. DKR of 6



of 4 mol % of **3** and 1 equiv of K_2CO_3 at room temperature was complete within 8 h. The racemization activity remains unaltered even after five repeated use of **3** and K_2CO_3.

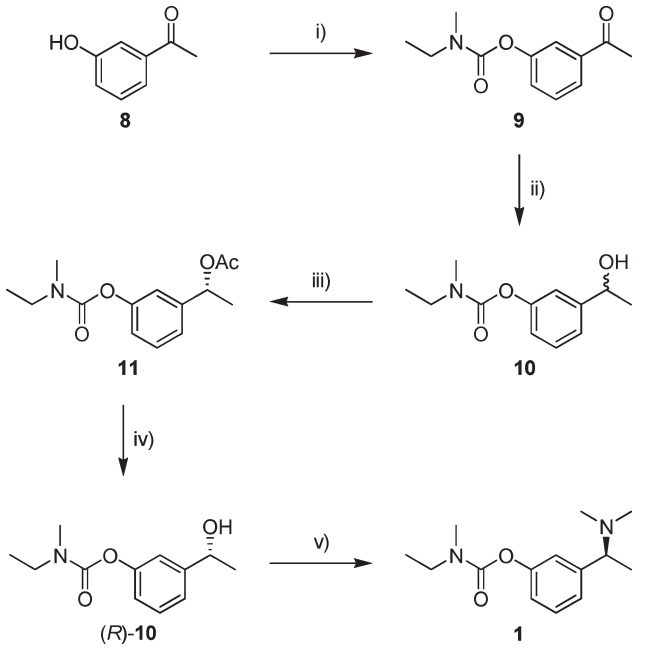
We then explored the DKR of racemic **6** with recycling **3** and a commercial lipase (*Candida antarctica* lipase B immobilized on polyacrylic resin; trade name, Novozym-435). The first run for the DKR of **6** was carried out with a solution containing isopropenyl acetate (1.5 equiv) as acyl donor, **3** (4 mol %), Novozym-435 (10 mg/mmol of substrate), and potassium carbonate (1 equiv) in toluene at room temperature for 1 day (Scheme 2). The first DKR reaction proceeded smoothly to afford the acetate **7** in good isolated yield (96%) and high optical purity (99% ee). Then, the DKR reaction was repeated four times with the recycling of both **3** and lipase. After each run, the solid mixture containing catalysts and K_2CO_3 was separated from the reaction mixture, washed 3 times with dry toluene, and then reused. In the fourth run, the conversion was only 61% after 1 day, but the catalytic activity was resumed by the addition of 1 equiv of fresh potassium carbonate in the fifth run (Table 2). These results

TABLE 2. Recycling of Catalysts in the DKR of 6[a]

run	conv (%)[b]	ee_p[c] (%)
1	> 97	> 99
2	> 97	> 99
3	96	> 99
4	61	> 99
5[d]	> 97	> 99

[a]Reaction conditions: **6** (0.50 mmol), **3** (4 mol % Ru), Novozym-435 (10 mg/mmol), isopropenyl acetate (1.5 equiv), K_2CO_3 (1 equiv), toluene (0.5 mL), rt, 1 d. [b]Measured by ^1H NMR. [c]Measured by HPLC with a chiral column. [d]1 equiv of fresh K_2CO_3 was added.

SCHEME 3. Asymmetric Synthesis of Rivastigmine[a]



[a]Reaction conditions: (i) Et(Me)NCOCl (2 equiv), NaH (2 equiv), CH_2Cl_2 (0.3 M), rt, 4 h, 85%; (ii) $NaBH_4$ (1 equiv), MeOH (1 M), 0 °C, 10 min, 99%; (iii) **3** (4 mol % Ru), Novozym-435 (30 mg/mmol), isopropenyl acetate (1.5 equiv), K_2CO_3 (1 equiv), toluene (0.3 M), rt, 1 d, 96%, 99% ee; (iv) K_2CO_3 (2 equiv), MeOH/H_2O (v/v = 4/1, 0.3 M), rt, 2 h, 92%, 99% ee; (v) $MeSO_2Cl$ (1.3 equiv), Et_3N (3 equiv), CH_2Cl_2 (0.2 M), 0 °C, 30 min, and then Me_2NH in THF (4 equiv), rt, 2 d, 77%.

clearly indicate that the catalysts (**3** and lipase) are recyclable several times without losing their activities.[12]

The application of DKR using **3** in the synthesis of rivastigmine is described in Scheme 3. Alcohol intermediate **10** for DKR was prepared in two steps from commercially available starting material **8**. The reaction of **8** with *N*-ethyl-*N*-methylcarbamoyl chloride afforded **9** (85% yield) which in turn was reduced with $NaBH_4$ to give **10** quantitatively.[13] Before the DKR of **10**, its enzymatic kinetic resolution (EKR) was examined to see if it is resolved with a satisfactory enantioselectivity. The EKR of **10** (0.3 mmol) was carried out in the presence of isopropenyl acetate as acyl donor with Novozym-435 (30 mg/mmol of substrate) in toluene at room temperature. The reaction proceeded to 50% completion in

(12) The removal of potassium carbonate from the polymer-attached catalysts and the separation between the latter were not tried because they were not readily separable.

(13) *N*-Ethyl-*N*-methylcarbamoyl chloride was prepared from triphosgene and ethylmethylamine in the presence of sodium bicarbonate in methylene chloride.

12 h to give enantiomerically enriched substrate and product ((*S*)-**10**, >99% ee; **11**, 99% ee), indicating that the enzymatic enantioselectivity for the resolution is excellent ($E = >400$). The DKR of **10** (1 mmol) was then carried out with **3** (4 mol %), Novozym-435 (30 mg/mmol), isopropenyl acetate (1.5 equiv), and K_2CO_3 (1 equiv) in toluene at room temperature for 1 day. The acylated product **11** was obtained in 96% isolated yield and 99% ee. The DKR reaction was repeated with **3**, lipase, and K_2CO_3, all of which were recovered from the first reaction, under identical conditions to give **11** with similarly good results (94% isolated yield, 99% ee). Ester **11** was hydrolyzed under alkaline conditions (K_2CO_3/MeOH/H_2O) at room temperature for 2 h to give (*R*)-**10** (92% isolated yield, 99% ee) without loss in optical purity. Finally, (*R*)-**10** was transformed into target compound **1** (77% isolated yield and 97% ee)[14] via a mesylated intermediate according to the known procedure.[15] The overall yield was 57% from **8**.

In summary, we have demonstrated a highly efficient synthesis of rivastigmine via chemoenzymatic DKR using a recyclable enzyme and a polymer-bound racemization catalyst. This synthesis presents an illustrative application of enzyme−metal cocatalysis for asymmetric synthesis of chiral drugs.

Experimental Section

Preparation of Polystyrene Containing Benzoyl Chloride (4). A solution of methyl 4-hydroxybenzoate (685 mg, 4.5 mmol) in *N*,*N*-dimethylformamide (20 mL) was added dropwise to a suspension of chloromethyl polystyrene (882 mg, 3.0 mmol; susbstitution: 3.4 mmol/g), cesium carbonate (1.47 g, 4.5 mmol), and sodium iodide (135 mg, 0.9 mmol) in *N*,*N*-dimethylformamide (10 mL) at room temperature. The mixture was stirred at room temperature. After 1 day, the result solid was filtered, washed with water (20 mL), acetone (20 mL) and CH_2Cl_2 (20 mL), and dried under vacuum to give polystyrene containing methyl benzoate (**12**) of yellow solid (1.23 g, 100% yield; FT-IR, 1718 cm^{-1}). A mixture of tetrahydrofuran and water (v/v = 2: 1, 30 mL) was added to solid mixture of **12** (1.23 g, 3.0 mmol) and sodium hydroxide (240 mg, 6.0 mmol) at room temperature. The mixture was stirred at room temperature. After 1 day, the result solid was filtered, washed with water (20 mL), acetone (20 mL), and CH_2Cl_2 (20 mL), and dried under vacuum to give polystyrene containing benzoic acid (**13**) of pale yellow solid (1.15 g, 97% yield; FT-IR, 1723 cm^{-1}). A solution of thionyl chloride (436 μL, 6.0 mmol) in dry toluene (10 mL) was added dropwise to a suspension of **13** (1.15 g, 2.9 mmol) in dry toluene (20 mL) at 120 °C and refluxed for 1 day. The reaction mixture was cooled to room temperature and filtered. The result solid was washed with CH_2Cl_2 (20 mL) twice, and dried under vacuum to give **4** of brown solid (1.09 g, overall 88% yield; FT-IR, 1717 cm^{-1}).

Synthesis of Polymer-Supported Ruthenium Catalyst (3). In a 50-mL flask equipped with a grease-free high-vacuum stopcock were placed **4** (414 mg, 1.0 mmol), η^4-(C_4Ph_4CO)($CO)_3$Ru (**5**) (570 mg, 1.0 mmol), and dry toluene (20 mL) under argon atmosphere. The mixture was stirred at 130 °C for 1 day. The reaction mixture was cooled to room temperature and filtered. The result solid was washed with acetone (10 mL) and CH_2Cl_2 (10 mL) and dried under vacuum to give **3** of orange solid (466 mg, 49% yield). The solid with 4.25 wt % of ruthenium was identified by ICP mass. The product's molecular weight was 2381 g/mol in accordance with the result of ICP mass. FT-IR (cm^{-1}): 2043, 1990, 1715.

General Procedure for Recycling of 3 in the Racemization of Optically Active 1-Phenylethanol ((*S*)-6). A suspension containing K_2CO_3 (21 mg, 0.15 mmol), **3** (14 mg, 6 μmol), and (*S*)-**6** (17 μL, 0.15 mmol) in dry and degassed toluene (500 μL) was stirred at room temperature under argon atmosphere in a 50 mL Schlenk flask. After 8 h, the solution was removed, and the solid catalysts were washed with dry and degassed toluene (3 × 500 μL). Immediately, 1-phenylethanol (17 μL, 0.15 mmol) and toluene (500 μL) were added, and the mixture was stirred for 8 h. These procedures were repeated four times.

DKR of 6. A suspension containing K_2CO_3 (69 mg, 0.5 mmol), **3** (48 mg, 20 μmol), Novozym-435 (5 mg, 10 mg/mmol), isopropenyl acetate (83 μL, 0.75 mmol), and **6** (55 μL, 0.5 mmol) in dry and degassed toluene (1.7 mL) was stirred at room temperature under argon atmosphere in a 50 mL Schlenk flask. After 24 h, the reaction mixture was filtered. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel to give (*R*)-ester (**7**) (96% yield, 99% ee).

Recycling of the Catalytic System in DKR of 6. A suspension containing K_2CO_3 (21 mg, 0.15 mmol), **3** (14 mg, 6 μmol), Novozym-435 (1.5 mg, 10 mg/mmol), isopropenyl acetate (25 μL, 0.23 mmol), and **6** (17 μL, 0.5 mmol) in dry and degassed toluene (500 μL) was stirred at room temperature under argon in a 25 mL Schlenk flask. After 24 h, the solution was removed, and the solid residue was washed with dry and degassed toluene (3 × 500 μL). Immediately, **6** (17 μL, 0.15 mmol), isopropenyl acetate (25 μL, 0.23 mmol), and toluene (500 μL) were added, and the solution was stirred for 24 h. These procedures were repeated 5 times. In the fifth recycling reaction, 1 equiv of fresh K_2CO_3 was added before **6**, isopropenyl acetate, and toluene were added.

Synthesis of 3-Acetylphenyl Ethyl(methyl)carbamates (9). To a suspension containing 3′-hydroxyacetophenone (**8**, 1.12 g, 8.3 mmol) in dry CH_2Cl_2 (15 mL) were added NaH (60%, dispersion in mineral oil, 660 mg, 16.6 mmol) and *N*-ethyl-*N*-methylcarbamoyl chloride (2 g, 16.5 mmol) at 0 °C under argon atmosphere, and the resultant mixture was stirred for 4 h. The reaction was quenched by addition of H_2O (5 mL). The reaction mixture was extracted with CH_2Cl_2/H_2O, and the organic layer was combined, dried over Na_2SO_4, and evaporated to obtain crude product. The residue was purified with column chromatography (silica gel, MeOH/CH_2Cl_2 = 1/10) to provide oily **9** (1.55 g, 85% yield): ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.81−7.77 (m, 1H), 7.70 (s, 1H), 7.48−7.43 (m, 1H), 7.36−7.33 (m, 1H), 3.53−3.39 (m, 2H), 3.05 (d, J = 25.12 Hz, 3H), 2.60 (s, 3H), 1.29−1.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 197.3, 154.3, 151.8, 138.4, 129.4, 126.7, 125.1, 121.7, 44.2, 34.3, 33.9, 26.7, 13.3, 12.4; HRMS (EI) $C_{12}H_{15}NO_3$ calcd 221.1052 (M^+), found 221.1050.

Synthesis of 3-(1-Hydroxyethyl)phenyl Ethyl(methyl)carbamates (10). To a solution of **9** (1 g, 4.52 mmol) in dry methanol (3.5 mL) was added added sodium borohydride (171 mg, 4.52 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 10 min. After completion of the reaction was confirmed by TLC, the reaction was quenched by careful addition of H_2O (1 mL), and methanol was evaporated. The residue was extracted with CH_2Cl_2/H_2O, and the organic layers were combined and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to provide **10** as a colorless oil (1 g, 99% yield): ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.33 (t, J = 7.83 Hz, 1H), 7.20−7.15 (m, 2H), 7.02 (d, J = 7.77 Hz, 1H), 4.89 (q, J = 6.48 Hz, 1H), 3.51−3.38 (m, 2H), 3.03 (d, J = 23.25 Hz, 3H), 1.49 (d, J = 6.45 Hz, 3H), 1.27−1.17 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 154.7, 151.7, 147.6, 129.2, 122.2,

(14) $[\alpha]^{25}_D = -32.8$ (c = 1.3, EtOH) (lit.[5] $[\alpha]^{20}_D = -32.1$ (c = 5, EtOH)). The ee value was determined by modifying the HPLC method reported in the literature: Srinivasu, M. K.; Rao, B. M.; Reddy, B. S.; Kumar, P. R.; Chandrasekhar, K. B.; Mohakhud, P. K. *J. Pharm. Biom. Anal.* **2005**, *38*, 320–325.

(15) Fieldhouse, R. PCT WO 2005/058804 A1, **2005**. In this reference, mesyl anhydride was used as mesylating agent. In our case, we employed mesyl chloride instead of mesyl anhydride.

120.6, 118.8, 69.9, 44.1, 34.2, 33.8, 25.0, 13.2, 12.5; HPLC (Chiracel-OD, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV 217 nm) (*S*)-**10** = 17.27 min, (*R*)-**10** = 20.13 min; HRMS (EI) $C_{12}H_{17}NO_3$ calcd 223.1208 (M^+), found 223.1206.

Typical Procedure for Enzymatic KR of 10. To a solution of **10** (22 mg, 0.1 mmol) and isopropenyl acetate (15 μL, 0.15 mmol) in anhydrous toluene (300 μL, 0.3 M) was added Novozym-435 (3 mg, 30 mg/mmol) under an argon atmosphere. The mixture was stirred at room temperature for 12 h. The enzyme was removed from the reaction mixture by filtration through a Celite. The solvent was evaporated under reduced pressure to give an oily mixture. For determination of optical purities (ee_p and ee_s), the mixture was dissolved in 2-propanol without further purification and then subjected to the analysis by HPLC with a chiral column (condition: Chiracel-OD, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV 217 nm (*R*)-**11** = 10.70 min, (*S*)-**11** = 12.64 min, (*S*)-**10** = 17.27 min, (*R*)-**10** = 20.13 min.).

DKR of 10. A suspension containing K_2CO_3 (140 mg, 1 mmol), **3** (95 mg, 40 μmol Ru), Novozym-435 (30 mg, 30 mg/mmol of substrate), isopropenyl acetate (150 μL, 1.5 mmol), and **10** (223 mg, 1 mmol) in dry and degassed toluene (2.5 mL) was stirred at room temperature under argon atmosphere in a 50 mL Schlenk flask. After 24 h, the reaction mixture was filtered. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 1/1) to give (*R*)-ester (**11**) as a colorless liquid (254 mg; 96% yield, 99% ee): ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ 7.33 (t, J = 7.83 Hz, 1H), 7.20−7.15 (m, 2H), 7.02 (d, J = 7.77 Hz, 1H), 4.92−4.86 (m, 1H), 3.51−3.38 (m, 2H), 3.03 (d, J = 23.25 Hz, 3H), 1.49 (d, J = 6.45 Hz, 3H), 1.27−1.17 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ 170.3, 154.5, 151.6, 143.0, 129.3, 122.9, 121.3, 119.5, 71.8, 44.1, 34.3, 33.8, 22.1, 21.3, 13.2, 12.5; HPLC (Chiracel-OD, *n*-hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, UV 217 nm) (*R*)-**11** = 10.70 min, (*S*)-**11** = 12.64 min; $[\alpha]^{25}_D$ = +68.2 (c = 1.1, $CHCl_3$, 99% ee); HRMS (EI) $C_{14}H_{19}NO_4$ calcd 265.1314 (M^+), found 265.1310.

Hydrolysis of 11. To a solution of **11** (133 mg, 0.5 mmol) in methanol (1.6 mL) were added potassium carbonate (138 mg, 1 mmol) and H_2O (0.4 mL). The reaction mixture was stirred at room temperature for 2 h. Methanol was removed by evaporation, and the aqueous solution was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by a column chromatography (silica gel, *n*-hexane/EtOAc = 1/1) to give oily (*R*)-**10** (101 mg; 92% yield, 99% ee). ^{1}H and ^{13}C NMR and HRMS were that same as the data of **10**: $[\alpha]^{24}_D$ = +25.3 (c = 1.1, $CHCl_3$, 99% ee).

Synthesis of Rivastigmine (1). To a solution of (*R*)-**10** (100 mg, 0.45 mmol) in dry CH_2Cl_2 (1.6 mL) was added distilled triethylamine (200 μL, 1.35 mmol) at 0 °C under argon atmosphere in a 25 mL Schlenk flask, and the reaction solution was stirred for 10 min. Methanesulfonyl chloride dissolved in dry CH_2Cl_2 (v/v 10%, 500 μL, 0.59 mmol) was added to the cold reaction mixture dropwise over 30 min at 0 °C. The reaction solution was stirred at 0 °C for 1 h, dimethylamine (2 M solution in THF, 1 mL) was added, and the reaction mixture was stirred at room temperature for 2 d. After completion of the reaction was confirmed by TLC, the reaction mixture was poured in 1 M HCl and extracted with CH_2Cl_2 and the organic layer was extracted again with 1 M HCl. Both aqueous layers were combined and neutralized with 2 M NaOH until the pH was above 10 and then extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and evaporated under reduced pressure to provide oily **1** (96 mg, 77% yield): $[\alpha]^{25}_D$ = −32.8 (c = 1.3, EtOH) (lit.[5] $[\alpha]^{20}_D$ = −32.1 (c = 5, EtOH)); HRMS (EI) $C_{14}H_{22}N_2O_2$ calcd 250.1681 (M^+), found 250.1683. ^{1}H and ^{13}C NMR data are in good agreement with those reported in the literature.[6] For determining the enantiopurity of **1**, a small amount of **1** was mixed with one equivalent of (*R*,*R*)−tartaric acid in ethanol and the resulting mixture was then analyzed by HPLC[14](Chiracel-OD, *n*-hexane/2-propanol/trifluoroacetic acid = 80/20/0.3, flow rate = 1.5 mL/min, UV 220 nm): (*R*)-**1** = 10.91 min, (*S*)-**1** = 14.00 min; 97% *ee*.

Acknowledgment. This work was supported by National Research Foundation of Korea (2009-0087801). We thank the Korean Goverment for supporting our graduate program (BK21 Program).

Supporting Information Available: Copies for ^{1}H and ^{13}C NMR spectra and HPLC chromatographs of products. This material is available free of charge via the Internet at http://pubs.acs.org.