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Chemoenzymatic Synthesis of Rivastigmine Based on Lipase-Catalyzed Processes

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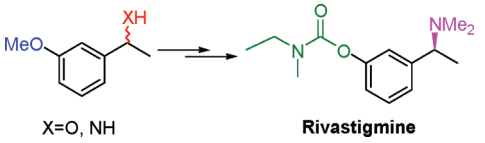

A straightforward chemoenzymatic synthesis of enantiomerically pure rivastigmine has been efficiently carried out under mild reaction conditions, with *Candida antarctica* lipase B responsible for the stereoselective acetylation of the corresponding (*R*)-alcohol or amine. An exhaustive enzymatic study has been developed exploring the possibilities of carry out enzyme recycling, scaling up the enzymatic process and development of a dynamic kinetic resolution procedure for the production of adequate enantiomerically pure precursors of rivastigmine. Total chemoenzymatic synthesis of this pharmaceutical has been performed in good overall yield from commercially available 3-methoxyacetophenone.

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Introduction

The development of stereoselective synthetic methods for the production of chiral organic compounds in nonracemic form has dramatically increased in recent years due to the necessity of producing enantiomerically pure compounds for the fine chemical industry.[1] This fact occurs because chirality has a pivotal role in both efficiency and safety of many drugs. Moved by the high demand for environmentally friendly synthetic routes, biocatalysis has emerged in the last decades as a powerful and recognized tool for the development of chemo-, regio-, and stereoselective processes. In this manner, many biocatalytic reactions have already been implemented for industrial development, being the preparation of single enantiomers a great challenge for organic chemists using mainly lipases, oxidoreductases, transaminases, lyases, and oxygenases in combination with chemical catalysis.[2]

In particular, lipases show high enantioselectivities toward a wide range of secondary alcohols and primary amines, which are interesting intermediates for the preparation of pharmaceuticals.[3] This type of biocatalyst works under mild reaction conditions (room temperature, atmospheric pressure, etc.), and their immobilized forms are highly stable in organic solvents, allowing an easy isolation of enantiomerically enriched compounds and the possibility of enzyme reuse that is always interesting in economical terms.[4]

In our ongoing project toward the synthesis of interesting high added value compounds in optically pure form, we have focused our research attention in the chemoenzymatic stereoselective synthesis of adequate building blocks for the total synthesis of rivastigmine [3-[1-(dimethylamino)-ethyl]phenyl ethyl(methyl)carbamate, **1a**] or miotine (**1b**, Figure 1). The activity of these drugs mostly resides in their (*S*)-enantiomers. Thus, (*S*)-rivastigmine is described for the

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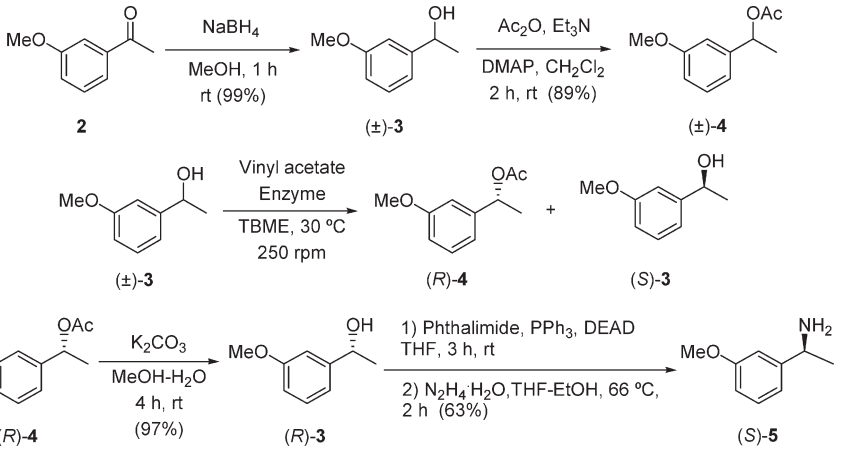
SCHEME 1. Chemical Synthesis and Lipase-Catalyzed Acetylation of (±)-3 Using Vinyl Acetate As Acyl Donor for the Production of Amine (*S*)-5



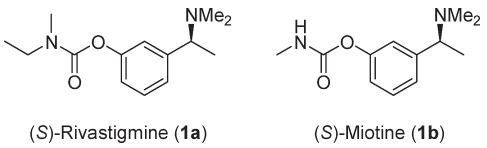


FIGURE 1. Rivastigmine and miotine structures.

treatment of mild to moderate dementia of the Alzheimer's type, and its tartrate salt is marketed under brand name Exelon.[5] Rivastigmine tartrate is included in the cholinesterase inhibitor group, improving mental function by increasing the amount of acetylcholine in brain, allowing better responses for memory, attention, and learning skills. Meanwhile, miotine is an cholinesterase inhibitor which has been used in therapy only as a miotic and which is relatively unstable at physiologic pH.[6]

Previous synthetic procedures have been developed for the production of racemic or optically active rivastigmine, but as far as we know, none of them imply the use of biocatalysts,[7] although some biotransformations have been used for the preparation of some intermediates using alcohol dehydrogenases[8] or feruloyl esterase from *Humicola insolens*.[9] Herein, we report a practical chemoenzymatic approach for the synthesis of adequate intermediates in the preparation of optically active rivastigmine or miotine to later carry out the total synthesis of (*S*)-rivastigmine.

Results and Discussion

First, we looked for possible chiral compounds which are susceptible to the introduction of chirality in the moiety. In this manner, (±)-1-(3-methoxyphenyl)ethanol (**3**) was selected and successfully prepared as a racemate by chemical reduction of commercially available 3-methoxyacetophenone (**2**) using sodium borohydride in methanol (99%, Scheme 1). Prior to the lipase-catalyzed transesterification assays, compound (±)-**3** was completely transformed into the acetate (±)-**4** (89%) by reaction in dry dichloromethane with acetic anhydride in the presence of triethylamine and 4-(*N*,*N*)-dimethylaminopyridine (DMAP), in order to establish robust analytical methods for the HPLC separation of the two enantiomers and the measurement of the enantiomeric excesses in the biocatalyzed reactions. Then enzymatic processes were carried out and the reaction courses regularly followed by chiral HPLC.[10]

The enzymatic kinetic resolution of (±)-**3** was initially attempted using *Candida antarctica* lipase type B (CAL-B) and *Pseudomonas cepacia* lipase (PS-C I) using 2 equiv of vinyl acetate as acyl donor and *tert*-butyl methyl ether (TBME) as solvent at 30 °C. Reactions were carried out at 0.1 M substrate concentration, showing both biocatalysts excellent enantioselectivities in the acetylation of (*R*)-**3** (Table 1). In addition, short reaction times (less than 2 h, entries 1−2) were necessary to reach 50% conversion values. Absolute configurations of substrate and product were in accordance with the empirical Kazlauskas rule (see the Experimental Section for further details regarding optical rotation values).[11] As expected, when a lower amount of lipase was used, slower reactions were observed (entries 3−4), and both substrate and product in enantiopure form were recovered if CAL-B was employed in the enzymatic kinetic resolution process.

In order to extend the applicability of this enzymatic approach, we decided to explore three important factors for the application of this protocol in the industrial sector: enzyme recycling, reaction scale up, and dynamic kinetic resolution possibility. As shown in Table 2, the reuse of the immobilized CAL-B led to almost the same enantioselectivity and enzyme activity after five reaction cycles, when racemic alcohol was treated with CAL-B (1:0.5 ratio in weight) and 2 equiv of vinyl acetate during 3.5 h in TBME

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TABLE 1. Enzymatic Kinetic Resolution of (±)-3 using 2 equiv of Vinyl Acetate in TBME at 30 °C and 250 rpm

entry	enzyme	ratio[a]	time (h)	ee_P (%)[b]	ee_S (%)[b]	c (%)[c]	E[d]
1	CAL-B	1:1	1.5	98.5	>99	50	>200
2	PS-C I	1:1	1.5	92	>99	52	179
3	CAL-B	1:0.5	4	>99 (43)	>99 (49)	50	>200
4	PS-C I	1:0.5	4	96.5	>99	51	>200

[a]Ratio substrate vs enzyme in weight. [b]Determined by HPLC. Isolated yields in parentheses. [c]$c = ee_S/(ee_S + ee_P)$. [d]$E = \ln[(1 - c)(1-ee_S)]/\ln[(1 - c)(1 + ee_P)]$.

TABLE 2. Study of Enzyme Recycling for the Enzymatic Kinetic Resolution of (±)-3 with CAL-B

cycle no.	ee_P[a] (%)	ee_S[a] (%)	c[b] (%)	E[c]
1	>99	98.6	49.7	>200
2	>99	98.2	49.6	>200
3	>99	98.0	49.5	>200
4	>99	97.9	49.5	>200
5	>99	97.7	49.5	>200
6	>99	96.0	49.0	>200

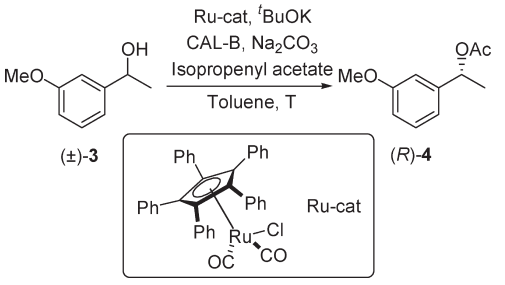
[a]Determined by HPLC. [b]$c = ee_S/(ee_S + ee_P)$. [c]$E = \ln[(1-c)(1 - ee_S)]/\ln[(1 - c)(1 + ee_P)]$.

TABLE 3. Dynamic Kinetic Resolution of Racemic 3 with CAL-B and a Ruthenium Complex Using 1.5 equiv of Isopropenyl Acetate As Acyl Donor and Toluene as Solvent after 24 h

entry	T (°C)	CAL-B[a]	c[b] (%)	ee_P[c] (%)
1	30	25	85	>99
2	50	25	>97	98
3	50	15	95 (91)	>99
4	50	50	>97	97

[a]Ratio referred to mg of CAL-B vs mmol of (±)-alcohol **3**. [b]Determined by ^{1}H NMR of the reaction crude. Isolated yields in parentheses after flash chromatography on silica gel. [c]Determined by GC.

SCHEME 2. Dynamic Kinetic Resolution of Alcohol (±)-3 Catalyzed by CAL-B and a Ruthenium Complex Using Isopropenyl Acetate As Acyl Donor and Toluene as Solvent



at 30 °C. These data highlight the utilization of a well-known biocatalyst as CAL-B for the synthesis of the desired optically active intermediate in the synthesis of rivastigmine.

At the same time, the reaction was scaled up using 1.5 g of starting material and only 75 mg of enzyme (1:0.05 ratio in weight), isolating both acetate (*R*)-**4** and alcohol (*S*)-**3** in enantiopure form after 24 h at 30 °C and 250 rpm. This issue is critical for the development of a highly economic process at industrial scale.

Dynamic kinetic resolution (DKR) is a powerful tool for the production of optically active compounds. The DKR approach, based on the combination of resolution mediated by a lipase and in situ racemization operated by a metal catalyst, allows a theoretical 100% conversion value, overcoming the limitation of the maximum 50% yield in a kinetic resolution process.[12] In this manner, we tested the possibilities of combining the best biocatalyst found in the lipase-mediated kinetic resolution of 1-(3-methoxyphenyl)ethanol (CAL-B) with the use of a well-known metal complex catalyst such as chlorodicarbonyl(1,2,3,4,5-pentaphenylcyclopentadienyl)ruthenium(II), which in the presence of sodium carbonate and potassium *tert*-butoxide form the corresponding alkoxide complex responsible of the racemization process (Scheme 2).[13] Results are described in Table 3.

Because of the short reaction time and mild conditions required for the kinetic resolution of racemic alcohol **3**, dynamic kinetic resolution processes were initially run at 30 °C using isopropenyl acetate as acyl donor, yielding the (*R*)-acetate **4** in enantiopure form at a 85% conversion after 24 h (entry 1). Isopropenyl acetate was selected instead of vinyl acetate because side reactions occur when using vinyl acetate due to the formation of acetaldehyde. The temperature was increased to 50 °C in order to facilitate the racemization step reaching an excellent conversion and the acetate in nearly enantiopure form (98% ee, entry 2). The influence of the enzyme loading was analyzed by trying to recover the product as a single enantiomer and observing the best results when the amount of CAL-B decreased from 25 to 15 mg of enzyme/mmol of alcohol **3** (entry 3). In this manner, acetate (*R*)-**4** was obtained in 91% isolated yield and >99% ee. However, an increase in the amount of biocatalyst to 50 mg/mmol of substrate had little influence on the proccess (entry 4). Therefore, the efficiency of biotransformations, which have made possible access to an enantiomerically pure compound in excellent yield from the corresponding racemate in just one reaction step, has been proven.

Because targeted rivastigmine possesses an (*S*)-configuration, it was mandatory to perform a stereoinversion in the chiral center of the (*R*)-acetate **4** to prepare the amino precursor (*S*)-**5**, an adequate building block for the total synthesis of rivastigmine. At this point, we first carried out the deprotection of the ester (*R*)-**4** by using potassium carbonate in a mixture of methanol and water at room temperature. This process occurred in nearly quantitative yield (97% isolated yield). Then the configuration of alcohol (*R*)-**3** was inverted after reaction with phthalimide, triphenylphosphine, and diethyl azodicarboxylate (DEAD) in dry tetrahydrofuran (THF), obtaining the corresponding protected amine that was subsequently deprotected employing hydrazine in a mixture of ethanol and THF at 66 °C. This chemical route led to the amine (*S*)-**5** in a combined 63% yield of the last two steps.

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SCHEME 3. Chemical Synthesis of Racemic Amine 5 and Later Enzymatic Kinetic Resolution

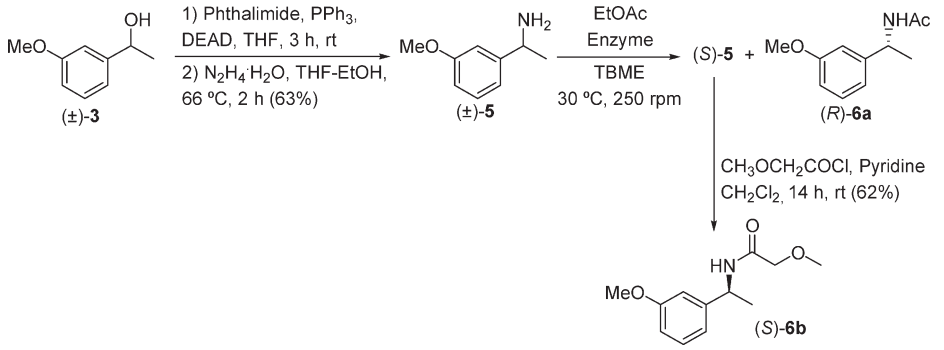

TABLE 4. Lipase-Catalyzed Kinetic Resolution of (±)-5 Using EtOAc as Acyl Donor and TBME as Solvent at 250 rpm

entry	enzyme	T (°C)	time (h)	ee_P[a] (%)	ee_S[a] (%)	c[b] (%)	E[c]
1	CAL-B	30	27	>99	93.5	48.5	>200
2	PS-C I	30	120	90	7.5	8	21
3	CAL-B	45	19	>99 (43)	97.5 (34)	49.5	>200

[a]Determined by HPLC. Isolated yields in parentheses. [b]$c = ee_S/(ee_S + ee_P)$. [c]$E = \ln[(1 - c)(1 - ee_S)]/\ln[(1 - c)(1 + ee_P)]$.

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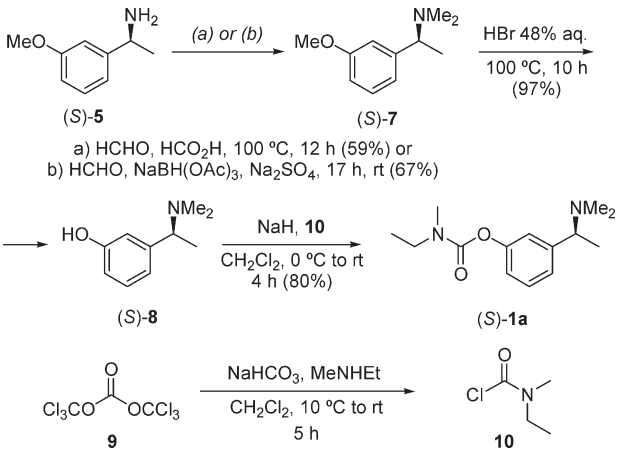
Alternative methods were considered at this time, such as the synthesis and later enzymatic resolution of racemic amine **5**. Enzymatic aminolysis processes are less studied than the analogous transesterification procedures, but lipases have shown excellent potential in this class of biotransformations.[14] In fact, CAL-B is considered an ideal catalyst for the production of nitrogenated organic compounds.[15] Thus, 1-(3-methoxyphenyl)ethanamine was prepared under conditions analogous to those previously used for the isolation of enantiomerically pure (*S*)-**5** using Mitsunobu reaction conditions and a deprotection step from racemic alcohol **3** (Scheme 3).

Then, different reaction parameters that have an influence on the lipase-catalyzed aminolysis processes were assayed as type of biocatalyst, reaction time, or temperature. The results have been collected in Table 4. Again, CAL-B and PS-C I were chosen as enzymes, using a double amount of enzyme vs starting material (weight ratio); meanwhile, TBME was used as solvent and EtOAc as acyl donor. Aliquots were regularly taken, converting in situ the nonreacting optically active amine of the lipase-mediated process in the corresponding methoxyacetamide **6b**, which was previously prepared in racemic form in order to find reliable techniques for the separation of its two enantiomers (see the Supporting Information for analytical data).

Conversely to the reaction that occurred with the alcohol derivative, remarkable differences were observed for CAL-B and PS-C I at 30 °C (entries 1 and 2). CAL-B stereoselectively acetylated the (*R*)-enantiomer, yielding the acetamide in enantiomerically pure form and the remaining (*S*)-amine **5** in very high optical purity after 27 h of reaction. Best values were achieved by increasing the temperature to 45 °C (entry 3) and obtaining both product and substrate in almost enantiopure form after 19 h. In addition, longer reaction times led to a decrease in the enzyme enantiopreference (data not shown).

SCHEME 4. Chemical Synthesis of (*S*)-Rivastigmine from (*S*)-5



Finally, our attention was focused on the chemical preparation of rivastigmine from enantiopure amine (*S*)-**5** following a straightforward chemical route consisting of three steps (Scheme 4). First, the dimethylation of the amino group was carried out using formic acid and formaldehyde at 100 °C obtaining (*S*)-**7** in 59% isolated yield. Alternatively, a slightly better result was obtained when the amine was treated with the 37% aqueous solution of formaldehyde in water followed by a small amount of sodium sulfate and sodium triacetoxyborohydride [$NaBH(OAc)_3$], as this route led to (*S*)-**7** in 67% yield.

Next, the cleavage of the *O*-methyl bond occurred in nearly quantitative yield using a 48% solution of HBr in water.[16] Finally, *N*-ethyl-*N*-methylcarbamoyl chloride (**10**) was generated in situ from triphosgene (**9**) and *N*-ethyl-*N*-methylamine in the presence of sodium bicarbonate in CH_2Cl_2, and the mentioned compound allowed the

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carbamoylation of alcohol (*S*)-**8** in the presence of sodium hydride using CH_2Cl_2 as solvent at room temperature, isolating enantiomerically pure (*S*)-rivastigmine in 80% yield.

Conclusions

In summary, a novel practical chemoenzymatic strategy has been developed for the preparation of enantiopure (*S*)-rivastigmine, where the stereoselective synthetic step has been performed by using a lipase as catalyst in contrast with traditional synthetic routes that usually employ diasteromeric salts. Lipase-catalyzed acetylation processes of 1-(3-methoxyphenyl)ethanol have been carried out and parameters that have influence in the enzymatic processes optimized, focusing attention on the lipase recycling and scale-up of the kinetic resolution process. In addition, performing a dynamic kinetic resolution reaction using a complementary metal complex has been successfully achieved for the production of (*R*)-1-(3-methoxyphenyl)ethyl acetate. An alternative synthetic route involving the preparation and enzymatic kinetic resolution of racemic 1-(3-methoxyphenyl)ethanamine has been also considered observing lower kinetics for this amino compound in comparison with the alcohol analogue. Finally, we have completed the total synthesis of (*S*)-rivastigmine in a practical and efficient chemical way from 3-methoxyacetophenone in seven steps and a global 29% isolated yield.

Experimental Section

Synthesis of 1-(3-Methoxyphenyl)ethanol (3). To a solution of ketone **2** (3.0 g, 20 mmol) in dry MeOH (77 mL) under nitrogen atmosphere was added $NaBH_4$ (1.14 g, 30 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. Unreacted excess hydride was destroyed by careful addition of water (5 mL), and MeOH was then evaporated. The mixture was basified with NaOH 3 N (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The reaction crude was purified by flash chromatography on silica gel (40% EtOAc/hexane) to afford racemic alcohol **3** as a colorless oil (99% isolated yield): R_f (40% EtOAc/hexane) 0.37; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.48 (d, 3H, $^3J_{HH}$ = 6.5 Hz, H_1), 1.87 (s, 1H, H_{10}), 3.82 (s, 3H, H_9), 4.86 (q, 1H, $^3J_{HH}$ = 6.4, H_2), 6.81 (ddd, 1H, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 2.6 Hz, $^4J_{HH}$ = 1.1 Hz, H_6), 6.94 (m, 2H, $H_4 + H_8$) and 7.26 (t, 1H, $^3J_{HH}$ = 8.1 Hz, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.6 (C_1), 55.7 (C_9), 70.7 (C_2), 111.4 (C_4), 113.3 (C_5), 118.2 (C_8), 130.0 (C_7), 148.1 (C_3), 160.2 (C_5).

Synthesis of 1-(3-Methoxyphenyl)ethyl Acetate (4). To a solution of alcohol **3** (100 mg, 0.66 mmol) in dry CH_2Cl_2 (10 mL) were successively added Et_3N (280 μL, 2.0 mmol), DMAP (25.6 mg, 0.20 mmol), and Ac_2O (128 μL, 1.32 mmol) under nitrogen atmosphere. The reaction was stirred at room temperature for 2 h and stopped by addition of water (30 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), and the organic layers were combined and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the reaction crude purified by flash chromatography on silica gel (20% EtOAc/hexane), affording acetate **4** as a clear yellow oil (89% isolated yield): R_f (20% EtOAc/hexane) 0.30; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.52 (d, 3H, J_{HH} = 6.6, H_1), 2.07 (s, 3H, H_8), 3.81 (s, 3H, H_7), 5.85 (q, 1H, $^3J_{HH}$ = 6.6, H_2), 6.81 (ddd, 1H, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 2.3 Hz, $^4J_{HH}$ = 0.8 Hz, H_6), 6.91 (m, 2H, $H_4 + H_8$), 7.26 (t, 1H, $^3J_{HH}$ = 8.1 Hz, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.2 (C_1), 22.1 (C_{11}), 55.0 (C_9), 72.0 (C_2), 111.7 (C_4), 112.9 (C_6), 118.2 (C_8), 129.4 (C_7), 143.2 (C_3), 159.6 (C_5), 170.3 (C_{10}).

Typical Procedure for the Enzymatic Kinetic Resolution of 1-(3-Methoxyphenyl)Ethanol. To a suspension of racemic alcohol **3** (50 mg, 0.33 mmol) and CAL-B (25 mg) in dry TBME (3.3 mL) was added vinyl acetate (60.6 μL, 0.66 mmol) under nitrogen atmosphere. The reaction was shaken at 30 °C and 250 rpm, and regular aliquots were taken and analyzed by HPLC until around 50% conversion was reached (4 h). The reaction was then stopped and the enzyme filtered with CH_2Cl_2 (3 × 5 mL). The solvent was evaporated and the crude of the reaction purified by flash chromatography on silica gel (10−30% EtOAc/hexane), affording (*R*)-(+)-**4** [43% isolated yield and >99% ee, $[\alpha]^{20}_D$ = +93.6 (c = 1.0, CH_2Cl_2)] and (*S*)-(−)-**3** [49% isolated yield and >99% ee, $[\alpha]^{20}_D$ = −29.5 (c = 1.0, CH_2Cl_2)].[17] See Tables 1 and 2.

Dynamic Kinetic Resolution of 1-(3-Methoxyphenyl)ethanol. Over a solution of chlorodicarbonyl(1,2,3,4,5-pentaphenylcyclopentadienyl)ruthenium(II) (0.020 mmol, 13 mg) in dry toluene (0.4 mL) under N_2 atmosphere was added a 0.5 M solution of KO^{t}Bu in THF (48 μL, 0.024 mmol). The mixture was stirred for 6 min at room temperature, and after this time, racemic 3-methoxy-1-phenylethanol (60 mg, 0.40 mmol) in toluene (0.4 mL) was added. The solution was stirred at room temperature for an additional 4 min, and after this time, Na_2CO_3 (42 mg, 0.4 mmol), CAL-B (10 mg), and isopropenyl acetate (72 μL, 0.60 mmol) were added, and the mixture was at 50 °C for 24 h. The reaction was filtered and the solvent evaporated under reduced pressure. Purification by column chromatography on silica gel (15% EtOAc/hexane) afforded 70 mg of (*R*)-3-methoxy-1-phenylethanol as a colorless oil (91% isolated yield and >99% ee). See Table 3.

Chemical Hydrolysis of 1-(3-Methoxyphenyl)ethyl Acetate (4). To a solution of (*R*)-**4** (750 mg, 3.86 mmol) in MeOH (18.8 mL) were added K_2CO_3 (1.07 g, 7.72 mmol) and H_2O (18.8 mL). The mixture was stirred at room temperature for 4 h until complete consumption of the starting material. Then MeOH was evaporated under reduced pressure, and the resulting aqueous solution was extracted with EtOAc (3 × 15 mL). The organic layers were combined and dried over Na_2SO_4, and the solvent was evaporated. The reaction crude was later purified by flash chromatography on silica gel (30% EtOAc/hexane), affording alcohol (*R*)-**3** (97% isolated yield).

Synthesis of 1-(3-Methoxyphenyl)ethanamine (5). To a solution of **3** (568 mg, 3.73 mmol) in dry THF (19 mL) were successively added PPh_3 (1.15 g, 4.37 mmol) and phthalimide (550 mg, 3.73 mmol) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C, and DEAD (687 μL, 4.37 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 3 h until no starting material was detected by TLC analysis. The organic solvent was evaporated under reduced pressure, and the deprotection reaction was carried out without further purification. The mixture was dissolved in THF (50 mL) and EtOH (8.7 mL), and then hydrazine monohydrate (1.36 mL, 28.01 mmol) was added dropwise. The mixture was stirred at 66 °C under reflux for 2 h. The white suspension formed after this time was filtered and washed with THF, and then the organic solvent was evaporated under reduced pressure. At this point, HCl 3 N was added to the mixture, and the solution was extracted with CH_2Cl_2 (3 × 15 mL), discarding the organic layer. Then, the aqueous phase was basified with NaOH 3 N and extracted with CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Finally, the crude was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 96/4/0.4), affording the amine **5** as a clear oil (63% isolated

(17) (a) Pastor, I. M.; Vastila, P.; Adolfsson, H. *Chem. Eur. J.* **2003**, *9*, 4031–4045: $[\alpha]^{20}_D$ = −30.9 (c = 0.85, MeOH) . (b) Morris, D. J.; Hayes, A. M.; Wills, M. *J. Org. Chem.* **2006**, *71*, 7035–7044: $[\alpha]^{20}_D$ = −30.9 (c = 1.0, MeOH) .

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yield): R_f (CH_2Cl_2/MeOH/NH_3 96/4/0.4) 0.17; ^{1}H NMR (MeOD, 300.13 MHz) δ 1.41 (d, 3H, $^3J_{HH}$ = 6.8 Hz, H_1), 3.81 (s, 3H, H_9), 4.04 (q, 1H, $^3J_{HH}$ = 6.8 Hz, H_2), 6.82 (ddd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2.3 Hz, $^4J_{HH}$ = 1.0 Hz, H_6), 6.94−6.97 (m, 2H, H_4+H_8), 7.26 (t, 1H, $^3J_{HH}$ = 8.3 Hz, H_7); ^{13}C NMR (MeOD, 75.5 MHz) δ 25.6 (C_1), 52.7 (C_2), 56.1 (C_9), 113.0 (C_4), 113.9 (C_6), 119.6 (C_8), 131.1 (C_7), 150.0 (C_3), 161.8 (C_5); $[\alpha]^{20}_D$ = −13.6 (c = 0.74, MeOH) for >99% ee.

Synthesis of *N*-[1-(3-Methoxyphenyl)ethyl]acetamide (6a). To a solution of racemic amine **5** (37.2 mg, 0.25 mmol) in dry CH_2Cl_2 (1.6 mL) was added pyridine (24.8 μL, 0.31 mmol) under nitrogen atmosphere. The resulting solution was cooled to 0 °C, and acetyl chloride (43.8 μL, 0.62 mmol) was carefully added. The mixture was allowed to warm to room temperature and stirred for an additional 14 h until no starting material was detected by TLC analysis. The organic solvent was evaporated under reduced pressure and the reaction crude purified by flash chromatography on silica gel (80% EtOAc/hexane), isolating the amide (±)-**6a** as an orange oil (85% isolated yield): R_f (80% EtOAc/hexane) 0.26; ^{1}H NMR (MeOD, 300.13 MHz) δ 1.45 (d, $^3J_{HH}$ = 7.1 Hz, 3H, H_1), 1.99 (s, 3H, H_{11}), 3.82 (s, 3H, H_9), 5.00 (q, $^3J_{HH}$ = 7.1 Hz, 1H, H_2), 6.82 (ddd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.6 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, H_6), 6.93−6.91 (m, 2H, H_4 + H_8), 7.26 (t, $^3J_{HH}$ = 8.2 Hz, 1H, H_7); ^{13}C NMR (MeOD, 75.5 MHz) δ 22.9 (C_1), 23.1 (C_{11}), 50.6 (C_2), 56.1 (C_9), 113.5 (C_4), 113.8 (C_6), 119.8 (C_8), 131.0 (C_7), 147.3 (C_3), 161.8 (C_5), 172.0 (C_{10}).

Synthesis of 2-Methoxy-*N*-[1-(3-methoxyphenyl)ethyl]acetamide (6b). To a solution of racemic amine **5** (37.2 mg, 0.25 mmol) in dry CH_2Cl_2 (1.6 mL) was added pyridine (24.8 μL, 0.31 mmol) under nitrogen atmosphere. The resulting solution was cooled to 0 °C, and methoxyacetyl chloride (56.3 μL, 0.62 mmol) was carefully added. The mixture was allowed to warm to room temperature and stirred for an additional 4 h until no starting material was detected by TLC analysis. The organic solvent was evaporated under reduced pressure and the reaction crude purified by flash chromatography (80% EtOAc/hexane), isolating the corresponding amide (±)-**6b** as a pale yellow solid (62% isolated yield): R_f (80% EtOAc/hexane) 0.29; ^{1}H NMR (MeOD, 300.13 MHz) δ 1.51 (d, $^3J_{HH}$ = 7.1 Hz, 3H, H_1), 3.44 (s, 3H, H_{12}), 3.82 (s, 3H, H_9), 3.93 (d, $^2J_{HH}$ = 2.0 Hz, 2H, H_{11}), 5.09 (q, $^3J_{HH}$ = 7.1 Hz, 1H, H_2), 6.83 (ddd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 2.5 Hz, $^4J_{HH}$ = 0.8 Hz, 1H, H_6), 6.96−6.93 (m, 2H, H_4+H_8), 7.26 (t, $^3J_{HH}$ = 8.1 Hz, 1H, H_7); ^{13}C NMR (MeOD, 75.5 MHz) δ 22.6 (C_1), 50.2 (C_2), 56.1 (C_9), 60.0 (C_{12}), 73.2 (C_{11}), 113.5 (C_4), 114.0 (C_6), 119.9 (C_8), 131.1 (C_7), 147.0 (C_3), 161.9 (C_5), 172.0 (C_{10}).

Typical Procedure for the Enzymatic Kinetic Resolution of 1-(3-Methoxyphenyl)Ethanamine (±)-5. To a suspension of racemic amine **6** (50 mg, 0.33 mmol) and CAL-B (100 mg) in dry TBME (3.3 mL) was added ethyl acetate (97 μL, 0.99 mmol) under nitrogen atmosphere. The reaction was shaken at 30 or 45 °C and 250 rpm, taking regularly aliquots that were analyzed by HPLC until around 50% conversion was reached (19 h for 45 °C or 27 h for 30 °C). Then the reaction was stopped and the enzyme filtered with CH_2Cl_2 (5 × 1 mL). The solvent was evaporated and the crude of the reaction purified by flash chromatography (CH_2Cl_2/MeOH/NH_3 96/4/0.4) affording (*S*)-(−)-**5** [34% isolated yield and 97.5% ee, $[\alpha]^{20}_D$ = −13.6 (c = 0.74, MeOH)][18] and (*R*)-(+)-**6a** [43% isolated yield and >99% ee, $[\alpha]^{20}_D$ = +166.13 (c = 1, $CHCl_3$)]. See Table 3.

Synthesis of (*S*)-1-(3-Methoxyphenyl)-*N*,*N*-dimethylethanamine (7). Route A. To a solution of (*S*)-**5** (240 mg, 1.58 mmol) in formic acid (2.4 mL) was added a 37% solution of formaldehyde in water (1.84 mL, 22.22 mmol), and then the mixture was heated to 100 °C for 12 h. NaOH 3 N was added until basic pH and the mixture extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and dried under Na_2SO_4, and the solvent was evaporated under reduced pressure. The reaction crude was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 96/4/0.4), affording (*S*)-**8** as a yellow oil (59% isolated yield): R_f (CH_2Cl_2/MeOH/NH_3 96/4/0.4) 0.38; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.38 (d, 3H, $^3J_{HH}$ = 6.6 Hz, H_1), 2.22 (s, 6H, H_{10}), 3.24 (q, 1H, $^3J_{HH}$ = 6.6 Hz, H_2), 3.80 (s, 3H, H_9), 6.78 (ddd, 1H, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 2.4 Hz, $^3J_{HH}$ = 0.9 Hz, H_6), 6.89−6.87 (m, 2H, H_4 + H_8), 7.22 (t, 1H, $^3J_{HH}$ = 8.1 Hz, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.2 (C_1), 43.1 (C_{10}), 55.1 (C_9), 66.1 (C_2), 112.4 (C_4), 112.9 (C_6), 119.9 (C_8), 129.1 (C_7), 145.2 (C_3), 159.5 (C_5); $[\alpha]^{20}_D$ = −43.6 (c = 1, MeOH) for >99% ee.

Route B. To a solution of (*S*)-**5** (95.3 mg, 0.63 mmol) in CH_2Cl_2 (7.9 mL) were successively added a 37% aqueous solution of formaldehyde in water (142 μL, 1.89 mmol), Na_2SO_4 (30 mg), and sodium triacetoxyborohydride (802 mg, 3.78 mmol). The mixture was stirred during 17 h at room temperature until no starting material was detected by TLC analysis (CH_2Cl_2/MeOH/NH_3 96/4/0.4), a saturated aqueous solution of sodium bicarbonate was added until pH 8−9, and the mixture was extracted with CH_2Cl_2 (5 × 10 mL). The organic phases were combined and dried over Na_2SO_4, the desiccant agent was filtered off, and the solvent was evaporated under reduced pressure, obtaining a crude that was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 96/4/0.4), affording (*S*)-**7** as a yellow oil (67% isolated yield).

Synthesis of (*S*)-3-[1-(Dimethylamino)ethyl]phenol (8). A 48% solution of HBr in water was added over (*S*)-**7** (135 mg, 0.75 mmol) in a sealed tube. The reaction was heated at 100 °C for 10 h. After this time, HBr was evaporated, and an aqueous K_2CO_3 saturated solution was added until basic pH. The resulting mixture was extracted with EtOAc (3 × 15 mL), the organic layers were combined, filtered, and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude was finally purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_3 96/4/0.4), affording (*S*)-**8** (69% isolated yield): R_f (CH_2Cl_2/MeOH/NH_3 96/4/0.4) 0.15; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.40 (d, 3H, $^3J_{HH}$ = 6.8 Hz, H_1), 2.23 (s, 6H, H_{10}), 3.34 (c, 1H, $^3J_{HH}$ = 6.8, H_2), 6.74 (m, 3H, H_4 + H_6 + H_8), 7.12 (t, 1H, $^3J_{HH}$ = 7.9, H_7), 8.47 (s, 1H, H_9); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.5 (C_1), 45.0 (C_{10}), 68.1 (C_2), 117.6 (C_4), 117.8 (C_6), 121.8 (C_8), 131.8 (C_7), 145.4 (C_3), 159.6 (C_5); $[\alpha]^{20}_D$ = −36.1 (c = 1, EtOH) for >99% ee.

Synthesis of (*S*)-3-[1-(Dimethylamino)ethyl]phenyl Ethyl(methyl)carbamate (Rivastigmine, 1a). To a suspension of $NaHCO_3$ (1.31 g, 13.5 mmol) in dry CH_2Cl_2 (6 mL) under N_2 atmosphere was added triphosgene (1.33 g, 4.50 mmol), and the mixture was cooled to 10 °C under stirring. Then *N*-ethylmethylamine (580 μL, 6.80 mmol) was added at 10 °C over 2 h. The reaction was allowed to reach room temperature and was stirred for an additional 3 h. After this time, the reaction mixture was filtered to remove NaCl and the solvent of the reaction filtrate removed by distillation at reduced pressure to give 800 mg of *N*-ethyl-*N*-methylcarbamoyl chloride as a crude that was employed for the next step without further purification. Over a solution of (*S*)-(−)-3-[1-(dimethylamino)ethyl]phenol (33 mg, 0.20 mmol) in dry CH_2Cl_2 under N_2 atmosphere and at 0 °C were added sodium hydride (20 mg, 0.40 mmol) and *N*-ethyl-*N*-methylcarbamoyl chloride (49 mg, 0.40 mmol). The suspension was allowed to reach room temperature and was stirred for 4 h. After this time, the reaction was carefully stopped with H_2O (1 mL) and extracted with CH_2Cl_2 (3 × 5 mL), the organic phases were combined and dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford a crude that was purified by *flash* chromatography

(18) (a) Mereyala, H. B.; Koduru, S. R.; Cheemalapati, V. N. *Tetrahedron: Asymmetry* **2006**, *17*, 259–267: $[\alpha]^{20}_D$ = −18.1 (c = 2, MeOH) . (b) Hu, M.; Zhang, F.-L.; Xie, M.-H. *Lett. Org. Chem.* **2007**, *4*, 126–128: $[\alpha]^{20}_D$ = −18.8 (c = 1, EtOH) .

(CH_2Cl_2/MeOH/NH_3 96/4/0.4), affording 40 mg of (*S*)-(−)-rivastigmine as a colorless oil (80% isolated yield): R_f (CH_2Cl_2/MeOH/NH_3 96/4/0.4) 0.30; ^{1}H NMR ($CDCl_3$, 300.13 MHz) δ 1.17−1.27 (m, 3H, H_{12}, 2 rotamers), 1.37 (t, $^3J_{HH}$ = 6.6 Hz, 3H, H_1), 2.21 (s, 6H, H_9), 2.99−3.07 (m, 3H, H_{10}, 2 rotamers), 3.25 (q, $^3J_{HH}$ = 6.6 Hz, 1H, H_2), 3.38−3.51 (m, 2H, H_{11}, 2 rotamers), 7.00−7.14 (m, 3H, H_4 + H_6 + H_8), 7.29 (apparent t, $^3J_{HH}$ = 8.1 Hz, 1H, H_7); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.9 (C_{12}, rotamer 1), 13.6 (C_{12} rotamer 2), 20.3 (C_1), 34.2 (C_{10}, rotamer 1), 34.6 (C_{10}, rotamer 2), 43.4 (C_9), 44.4 (C_{11}), 66.0 (C_2), 120.8 (CH), 121.2 (CH), 124.7 (CH), 129.3 (CH), 145.4 (C), 151.9 (C), 155.0 (C); $[\alpha]^{20}_D$ = −28.5 (*c* = 1, CH_2Cl_2) for >99% ee.

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Supporting Information Available: Experimental procedures, chiral HPLC and GC conditions, characterization data for new compounds, and copies of ^{1}H NMR, ^{13}C NMR, and DEPT spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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