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A Novel Synthesis of Rasagiline via a Chemoenzymatic Dynamic Kinetic Resolution

Guozhen Ma,[†] Zhongqi Xu,[†] Pengfei Zhang,[†] Jinpo Liu,[†] Xilin Hao,[‡] Jingping Ouyang,[‡] Ping Liang,[†] Song You,*[,†] and Xian Jia*[,‡]

[†]School of Life Sciences & Biopharmaceutical Sciences, Shenyang Pharmaceutical University, 103 Wenhua Road, Shenyang, 110016, China

[‡]Key Laboratory of Structure-Based Drug Design and Discovery (Shenyang Pharmaceutical University), Ministry of Education, Shenyang 110016, China

Supporting Information

ABSTRACT: A novel synthetic route for preparing rasagiline mesylate is presented using a dynamic kinetic resolution (DKR) as the key step, catalyzed by Candida antarctica lipase B (CALB) and a Pd nanocatalyst. The chiral intermediate (*R*)-2,3-dihydro-1-indanamine was obtained through the DKR of the racemic aminoindan *rac*-1 in high yield (>90%) and excellent enantioselectivity (>99% ee). The process could be conducted on a 73 g scale at 200 g/L. Rasagiline mesylate was synthesized in 25% overall yield and excellent enantioselectivity (99.9% ee) over 7 steps.

INTRODUCTION

The demand of optically pure compounds is increasing in the pharmaceutical, fine chemicals, and agrochemical industries in recent years. Currently, the production of optically active intermediates is relying more and more on biocatalysis processes.[1] Of the conventional methods to synthesize enantiomerically pure molecules, kinetic resolution (KR) is one of the most practical ways in pharmaceutical industry; however, the one major limitation of this technique is that the maximum theoretical conversion cannot exceed 50%. Dynamic kinetic resolution (DKR), which combines KR with in situ racemization of the undesired enantiomer, has the potential to overcome this problem, and then theoretically 100% of the racemic mixture can be converted to one enantiomer. The DKR has been used in the synthesis of several chiral drugs, for instance, duloxetine,[2] odanacatib,[3] roxifiban,[4] and lamivudine,[5] et al.

Parkinson's disease (PD)—the most prevalent neurodegenerative disorder—affects 6.3 million people worldwide today. Rasagiline ((*R*)-*N*-propargyl-1-aminoindan, Figure 1) is an irreversible, selective monoamine oxidase (MAO) B inhibitor for the treatment of PD.[6] Several methods have been reported for the synthesis of rasagiline, and most of them introduced the chiral aminoindan motif via resolving the correct isomer from a racemic mixture[7] or by asymmetric synthetic methodologies.[8]

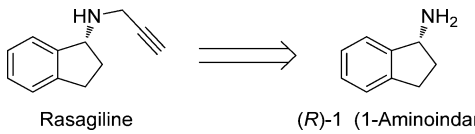

Figure 1. Structures of rasagiline and its chiral synthetic precursor (*R*)-1.

Allegrini et al.[7d] disclosed a process for preparation of rasagiline which involves an efficient two-step pathway to racemic *N*-propargyl-1-aminoindan and utilized a late-stage kinetic resolution with *L*-(+)-tartaric acid (Scheme 1A). Gutman et al.[7i] developed a pathway to rasagiline by using (*R*)-*N*-benzyl-1-indanamine intermediate resolved with *L*-(+)-tartaric acid (Scheme 1 B). Colyer et al.[8a] reported an asymmetric synthesis of the key chiral intermediate of rasagiline using a asymmetric induction (Scheme 1C). Some disadvantages of these existing methods are the 50% loss of yield due to the drawback of the kinetic resolution process, severe reaction conditions such as high-pressure catalytic hydrogenation, and the use of the costly chiral auxiliary reagents.

Recently, Kim et al.[9] disclosed a DKR process for primary benzyl amines with a Pd nanocatalyst in the presence of CALB; good chemical yields with high enantiomeric excess was achieved, and their excellent work inspired us. We were interested in exploring the possibility of improving upon the current state for the synthesis of rasagiline by taking advantage of the high selectivity of nano palladium-enzyme catalysis, which may bypassing the limitation of a classical kinetic resolution by converting the slow-reacting enantiomer to the fast reacting one.

Herein we report a practical process for the enantioselective synthesis of rasagiline via a DKR. The chemo-enzymatic DKR method was utilized in the enantio-determining step of the synthetic route, and this process could be conducted in a concentration of up to 200 g/L in lab which has the potential to scale up for a commercial process.

RESULTS AND DISCUSSION

Rac-1 was obtained starting from the readily available material 3-phenylpropionic acid through three steps: intramolecular Friedel−Crafts acylation, oxime formation, and catalytic hydrogenation (Scheme 2). *Rac*-1 was then reacted with butanedioic acid to give a salt, which is more stable and suitable for storage. *Rac*-1 was converted to the enantiomerically pure amide (*R*)-2 by

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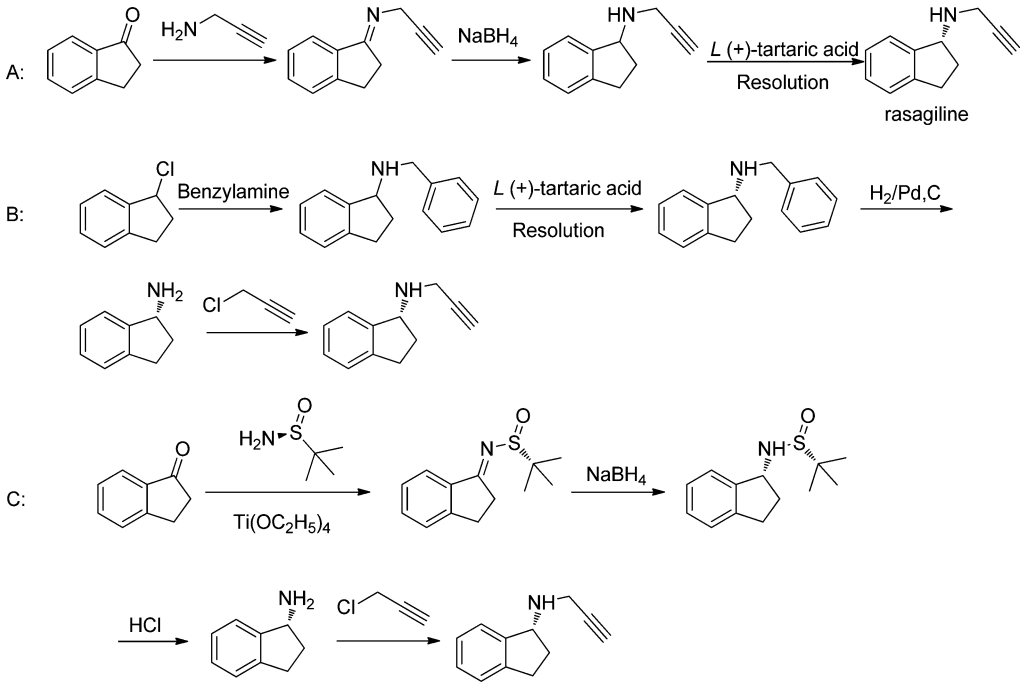
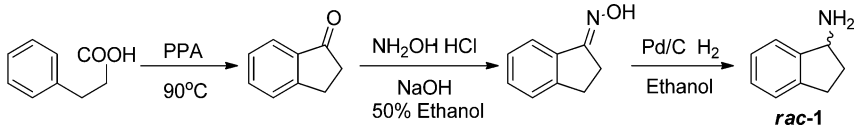
Scheme 1. Synthetic routes to rasagiline



Scheme 2. Synthesis of *rac*-1

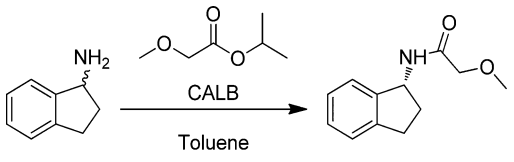


using our DKR process. The amide was hydrolyzed to give (*R*)-2,3-dihydro-1-indanamine ((*R*)-**1**), and finally, a propargyl group was introduced via a nucleophilic alkynylation to give rasagiline.

The lipase from *Candida antarctica* and the Pd nanocatalyst were picked as the chemo-enzymatic catalyst.[9,10] The *C. antarctica* lipase B (CALB) gene was cloned and overexpressed in methylotrophic yeast *Pichia pastoris*.[11] The crude enzymes were directly immobilized utilizing Lewatit VP OC 1600 resin without further purification. The activity and selectivity of the immobilized CALB toward the resolution of primary benzyl amines had been examined in the KR of (±)-1-phenylethylamine, which using isopropyl 2-methoxyacetate as an acyl donor.[12]

First, the enzymatic KR process toward *Rac*-1 was studied using isopropyl 2-methoxyacetate as an acyl donor (Scheme 3).

Scheme 3. KR of *rac*-1



This ester produced good results in our earlier experiments, and no other ester was examined. The effects of temperature and the ratio of enzyme to substrate were studied. The results demonstrated that the ee value decreased with the increase of the conversion. The best result occurred where the desired product was obtained at 43.4% yield with 97.5% ee (Table 1). We

Table 1. Kinetic resolution of 2,3-dihydro-1-indanamine[a]

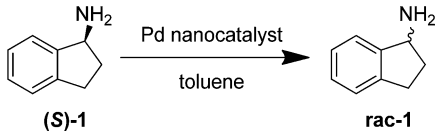
entry	temperature (°C)	enzyme:substrate	time (h)	conv.[b] (%)	ee[b] (%)	*E*
1	50	1:1.2	6	15.7	99.5	375
2	60	1:1.2	6	20.1	97.9	226
3	70	1:1.2	6	43.4	97.5	173
4	80	1:1.2	6	48.7	94.8	116
5	70	1:1.6	6	42.7	96.7	178
6	70	1:2.4	6	41.6	97.2	175
7	70	1:1.2	9	50.4	95.1	145

[a]Conditions: 2 mmol of (*rac*)-1, 2 mL of toluene, reacted under N_2 atmosphere. [b]Measured by chiral HPLC.

also observed that the conversion of substrate was increased with the elevation of temperature; however, the ee value deteriorated correspondingly, which we attribute to the effect of higher temperatures on the selectivity of the enzyme. When the reaction time was prolonged to 9 h, around 50% conversion of the substrate was observed; however, the ee decreased to 95.1%.

The Pd nanocatalyst, Pd/AlO(OH), was chosen as the racemising reagent for the amine which proceeds via an imine intermediate state (Scheme 4). Pd/AlO(OH) was prepared as

Scheme 4. Racemization of (*S*)-1



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palladium nanoparticles entrapped in aluminum hydroxide according to Kim's method.[9] The activity of the Pd nanocatalyst was monitored by the enantiomeric excess (ee) of (*S*)-2,3-dihydro-1-indanamine during the racemization procedure. This demonstrated the high activity of the Pd nanocatalyst. The racemization was completed in 3 h in the presence of 1 mol % of Pd in toluene at 70 °C (Table 2, entry 3), and when the temperature decreased, the racemization time was prolonged correspondingly.

Table 2. Racemization of (*S*)-2,3-dihydro-1-indanamine[a]

entry	amount of catalyst (mol %)	temperature (°C)	time (h)	ee[b] (%)
1	1	50	6	35
2	1	60	6	12
3	1	70	3	3
4	0.5	70	4	4
5	0.1	70	6	7

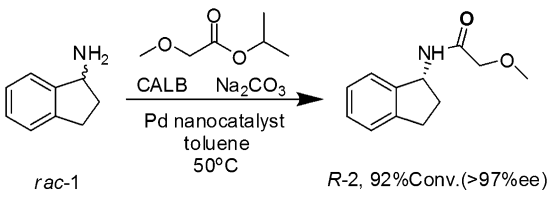
[a]Conditions: 2 mmol of (*S*)-1, 2 mL of toluene. [b]Measured by chiral HPLC.

The DKR efficiency for the desired enantiomer can be dramatically improved by the combination of a selective kinetic resolution process matched with a fast racemization.[13] We investigated the relationship between the amount of Pd nanocatalyst charged in the racemization and the reaction speed. We found that the racemization could completed in 4 h even using only 0.5 mol % of Pd in toluene at 70 °C (Table 2, entry 4), which is only half of the charge in the literature.[8] This suggests the rates of KR and racemization are compatible with each other, leading to a good DKR.

The above individual studies and data indicated that a DKR strategy may be suitable for the preparation of (*R*)-1. We supposed that the optimal condition for a successful DKR employing CALB and Pd nanocatalyst can be carried out at a temperature above 70 °C. However, the yield and the ee value of the amide decreased with time, and about 25% (calculated by peak area) of byproduct formed mainly due to the effect of the crude enzyme. Some miscellaneous proteins were generated during the course of overexpression. HPLC only poorly separates the byproducts, and we were unsuccessful in separating and identifying these by impurities. We believe they consist of miscellaneous proteins derived from the crude enzyme and byproducts caused by the reaction of the proteins with the imine intermediate during the racemization at the higher temperatures.

After the studies on the effects of the reaction temperature in our chemoenzymatic system, a modified DKR process was determined to be optimum (Scheme 5). The byproducts were kept to a minimum at 50 °C. Under the optimized reaction conditions, the conversion yield of *rac*-1 to the desired product was over 90% within 12 h, and only 5% HPLC A% of byproducts formed. The amide was isolated and recrystallized to give the desired product in 85% yield, and the ee of the product was improved to >99% through recrystallization.

Scheme 5. DKR of *rac*-1



The application of DKR to (±)-2,3-dihydro-1-indanamine (*rac*-1) has been investigated for the multigram scale as well under these optimized reaction conditions. When 40 g of *rac*-1 at a substrate concentration of 200 g/L was run, 87.5% conversion yield and 95.7% ee were obtained (Table 3, entry 2). This process was repeated on a scale of 73 g at the same concentration of 200 g/L. However, when the concentration was increased to 300 g/L, both the activity and the enantioselectivity of the catalyst were inhibited, and the yield dropped.

Table 3. Investigation of DKR on multigram scale for *rac*-1

entry	weight of *rac*-1 (g) [concentration/ of *rac*-1 (g·L^{-1})]	conv.[c] (%)	yield[d] (%)	ee[c,e] (%)
1[a]	30 (150)	88.2	81.6	97.6 (99)
2[a]	40 (200)	87.5	80.1	95.7 (98.9)
3[a]	60 (300)	70	62.3	94.1 (96.8)
4[b]	73 (200)	87.6	80.1	96.7 (99.2)

[a]Conditions: 10 g of CALB, 15 g of Pd nanocatalyst, 10 g of Na_2CO_3, 1.5 equiv of acyl donor, 50 °C for 12 h. [b]Conditions: 18.3 g of CALB, 27.5 g of Pd nanocatalyst, 18.3 g of Na_2CO_3, 1.5 equiv of acyl donor, 50 °C for 12 h. [c]Measured by chiral HPLC. [d]Calculated by weight. [e]Measured after purification.

We were pleased to observe that the activity of the chemoenzymic catalyst still maintained its relatively high activity and enantioselectivity even after 9−10 recycles (Table 4). However,

Table 4. Investigation of recycling times of immobilized CALB and Pd nanocatalyst[a]

entry	recycling times	conv.[b] (%)	yield[c] (%)	ee[b] (%)
1	1	98.9	90.6	99.1
2	2	98.8	90.4	98.9
3	3	98.9	90.5	99.0
4	4	98.7	89.7	98.8
5	5	97.1	88.2	98.1
6	6	96.2	86.6	97.3
7	7	94.1	85.3	96.4
8	8	91.7	83.6	95.8
9	9	88.8	82.1	95.1
10	10	85.7	79.0	93.3
11	11	83.2	76.8	91.0

[a]Conditions: 4 g of (*rac*)-1, 1 g of CALB, 1.5 g of Pd nanocatalyst, 1 g of Na_2CO_3, 1.5 equiv of acyl donor, 20 mL of toluene, 50 °C for 12 h. [b]Measured by chiral HPLC. [c]Calculated by weight.

for useful results, it appears that 5−6 recycles is a practical limit for acceptable quality product. The recovered catalyst should be used directly; otherwise, it should be stored under the protection of nitrogen gas. Since no significant change in the catalyst's appearance was observed, we strongly suggest the user should test the activity of the catalyst in a small scale of substrate after the catalyst has been reused 5 times.

The ee value of the amide could be upgraded through crystallization; over 99% ee could be obtained via crystallization from amide of 97−98% ee. For the amide of 95−97% ee, two recrystallizations were required.

By hydrolyzing the amide in triethanolamine with 40% NaOH, the aminoindan (*R*)-1 was formed in over 76.2% yield with 99% ee, followed by nucleophilic alkynylation with propargyl bromide

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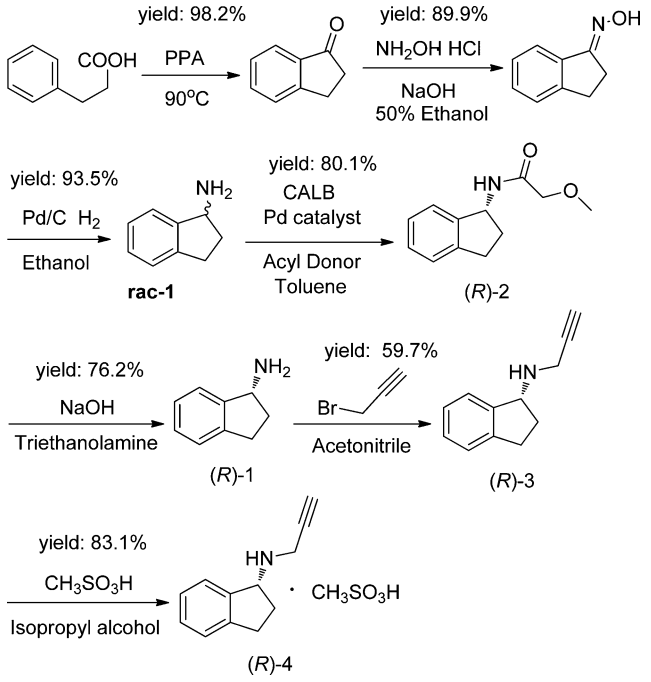
at 30 °C to give rasagiline (*R*)-3 in 99.5% (w/w) purity with 99.9% ee. The amount of double alkylation byproduct was decreased with the decrease in temperature; however, the reaction time was prolonged as well, and therefore, 30 °C was selected as the best compromise, and 59.7% yield was obtained. The product was purified by forming the salt with butanedioic acid.

CONCLUSION

In summary, we demonstrated a novel synthetic route for (*R*)-rasagiline mesylate (Scheme 6). It is noteworthy that this new

Scheme 6. Optimized synthesis of (*R*)-rasagiline mesylate



chemistry can be carried out under mild conditions and avoids the waste of the undesired enantiomer or the use of the expensive chiral auxiliary reagents. By employing the DKR method, (*R*)-1 was obtained in satisfactory yield and excellent enantioselectivity in the enantio-determining step. We conducted the DKR procedure of 2,3-dihydro-1-indanamine on a scale of 73 g in the concentration of 200 g/L, which is indicative of a potential commercial scale process once other aspects of the entire operation are optimized.

EXPERIMENTAL SECTION

General. KR, DKR, and racemization reactions were carried out under dry nitrogen atmosphere using a standard Schlenk technique.[14] Dry toluene was obtained via distillation.

High-performance liquid chromatography (HPLC) analyses were carried out with a JASCO LC-1500 system with a UV detector. The conversion and ee values were determined by chiral HPLC. For 2,3-dihydro-1-indanamine and its amide, a Chiralpak OD-H chiral column (4.6 × 250 mm, Daicel Chemical Industries) and a mobile phase of *n*-hexanes/isopropanol/diethylamine (97:3:0.1, v/v) were used; the flow rate was 0.8 mL/min, the column temperature was set at 30 °C, and the UV detection wavelength was 254 nm. The elution times were 9.3 min, 11.1 min, 12.6 min, and 21.1 min for (*S*)-1, (*R*)-1, (*R*)-2, and (*S*)-2, respectively. For rasagiline, a Chiralpak AD-H (4.6 × 250 mm, Daicel Chemical Industries) and a mobile phase of *n*-hexanes/isopropanol (99:1, v/v) were used; the flow rate was 0.8 mL/min, the column temperature was set at 30 °C, and the UV detection wavelength was 254 nm. The elution times were 13.0 min and 15.6 min for (*S*)-3 and (*R*)-3, respectively. ^{1}H NMR spectrum for (*rac*)-1 and HPLC, MS, IR, ^{1}H, and ^{13}C NMR spectra for (*R*)-2 and (*R*)-4 are shown in the Supporting Information.

Pd Nanocatalyst and CALB. Pd nanocatalyst was synthesized according to a literature procedure.[9] CALB was prepared according to ref 11, and Lewatit VP OC 1600 resin (30 g) was added to the crude enzyme supernatant (100 mL). After stirring at 28 °C for 24 h, the resin was filtered off, washed with deionized water, and dried under vacuum until constant weight.

2,3-Dihydro-1-indanamine (rac-1). Polyphosphoric acid (1000 g, 2.96 mol) was heated to 90 °C. 3-Phenylpropionic acid (100 g, 0.67 mol) was added in portions. After stirring at 90 °C for 30 min, the reaction mixture was added to 5000 mL of ice water under vigorous stirring conditions and was cooled to room temperature. The reaction mixture was extracted by dichloromethane (3000 mL/three times), and the combined organic phase was washed by saturated aqueous sodium chloride solution (2000 mL/two times), dried over anhydrous sodium sulfate (50 g), and filtered. The solvent was removed by evaporation at 30 °C under vacuum, leaving light-yellow crystals (86.4 g, yield: 98.2%).

To these crystals (86.4 g, 0.655 mol) were added 50% ethanol/water solution (400 mL) followed by a solution of hydroxylammonium chloride (69.0 g, 0.995 mol) in 50% ethanol/water (400 mL). The reaction mixture was heated to reflux, whereupon aqueous sodium hydroxide (43 g, 1.08 mol in 196 mL deionized water) was added over 15 min. After refluxing for 30 min, the reaction mixture was cooled to room temperature. The precipitated solid was filtered off, washed with deionized water (300 mL), and dried at 55 °C under vacuum until constant weight to afford white needles (86.5 g, yield: 89.9%).

To these needles (86.5 g, 0.588 mol) were added ethanol (865 mL), followed by 10% Pd/C (5.9 g). The reaction mixture was heated at 70 °C under H_2 atmosphere for 4 h. Pd/C was removed by vacuum filtration. The filtrate was concentrated to dryness at 40 °C under vacuum to afford a colorless oily liquid (73.2 g, yield: 93.5%). Bp 96−98 °C/8 mmHg. ^{1}H NMR (600 MHz, DMSO-d_6) (considering the stabilizing of the indanamine, proton NMR data was detected with a succinate form) 7.49 (d, J = 7.3 Hz, 1H), 7.32−7.22 (m, 3H), 4.60 (t, J = 6.9 Hz, 1H), 3.01 (ddd, J = 15.9, 8.7, 4.7 Hz, 1H), 2.83 (ddd, J = 15.8, 8.4, 7.1 Hz, 1H), 2.43 (dtd, J = 13.1, 8.1, 4.7 Hz, 1H), 2.27 (s, 4H), 1.89 (ddt, J = 13.2, 8.7, 6.7 Hz, 1H).

For the production of 1 kg of (*R*)-rasagiline mesylate, 1.65 kg of *rac*-1 was needed. Therefore, 123.8 L of deionized water, 67.6 L of dichloromethane, 45.1 L of saturated aqueous sodium chloride solution, 18.0 L of 50% ethanol/water solution, and 19.5 L of ethanol should be used in this step.

General Procedure for KR. CALB (100 mg) and Na_2CO_3 (100 mg) were added to a vial. *Rac*-1 (0.14 g, 1 mmol) dissolved in dry toluene (2 mL) was added to the vial, and the mixture was stirred. After a few minutes, isopropyl 2-methoxyacetate (0.16 g, 1.2 mmol) was added to the reaction mixture. Samples for HPLC analysis were collected with a syringe after 0.5, 2, 3, 4, 5, and 6 h.

General Procedure for Racemization. (*S*)-1 (13 mg, 0.10 mmol) was added to a suspension of Pd nanocatalyst (20 mg) in dry and degassed toluene (1 mL). The reaction mixture was stirred at 70 °C under nitrogen. After 1, 2, 3, 4, 5 and 6 h, the

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reaction mixture was cooled to room temperature and collected a sample for HPLC analysis.

General Procedure for DKR. CALB (100 mg), Na_2CO_3 (100 mg), and Pd nanocatalyst (200 mg) were added to a vial. *Rac*-1 (0.14 g, 1 mmol) dissolved in dry toluene (2 mL) was added to the vial, followed by isopropyl 2-methoxyacetate (0.16 g, 1.2 mmol). The reaction mixture was stirred under nitrogen atmosphere. Samples for HPLC analysis were collected with a syringe after 2, 4, 6, 8, 10, and 12 h.

Large-Scale DKR of 2,3-Dihydro-1-indanamine (rac-1). A solution containing *rac*-1 (73.2 g, 0.55 mol), Pd nanocatalyst (27.5 g), CALB (18.3 g), sodium carbonate (18.3 g), and isopropyl 2-methoxyacetate (108.9 g, 0.825 mol) in dry and degassed toluene (366 mL) was stirred at 50 °C under nitrogen atmosphere. After reacting for 12 h, the reaction mixture was cooled to room temperature and filtered using filter paper. The separated catalysts were washed with predried toluene. The catalyst may be directly used for the next reaction or dried in vacuum for 4 h under 50 °C and kept under nitrogen atmosphere. The filtrate was concentrated, and the mixture standing at 4 °C provided (*R*)-*N*-(2,3-dihydro-1*H*-inden-1-yl)-2-methoxyacetamide ((*R*)-2) (90.3 g, yield: 80.1%, ee >99%); ^{1}H NMR (600 MHz, $CDCl_3$) 7.29 (d, *J* = 7.2 Hz, 1H), 7.25 (s, 2H), 7.23 (dd, *J* = 8.8, 4.9 Hz, 1H), 6.73 (s, 1H), 5.54 (q, *J* = 7.9 Hz, 1H), 3.96 (s, 2H), 3.40 (s, 3H), 3.01 (m, 1H), 2.89 (m, 1H), 2.62 (m, 1H), 1.84 (m, 1H).

For the production of 1 kg of (*R*)-rasagiline mesylate, 2.03 kg of (*R*)-2 was needed. Therefore, 8.2 L of toluene should be used in this step.

(R)-2,3-Dihydro-1-Indanamine ((R)-1). (*R*)-*N*-(2,3-Dihydro-1*H*-inden-1-yl)-2-methoxyacetamide ((*R*)-2) (90.3 g, 0.44 mol, ee >99%) dissolved in triethanolamine (350 mL) was heated to 80 °C with stirring, whereupon 40% aqueous sodium hydroxide (220 mL) was added to the mixture over 15 min. The reaction mixture was heated at reflux for 6 h. After cooling to the room temperature, deionized water (2200 mL) was added to the suspension with stirring, whereupon the remaining solution was extracted by ethyl acetate (2400 mL/three times) and the organic phases were washed by saturated aqueous sodium chloride solution (1200 mL/two times), dried over anhydrous sodium sulfate (50 g), and filtered. The solvent was removed by evaporation at 30 °C under reduced pressure to leave an oily liquid. The remaining oily liquid was distilled under reduced pressure (9 mmHg). The distillation cut at 97−99 °C was collected (44.6 g, yield: 76.2%, ee >99%).

For the production of 1 kg of (*R*)-rasagiline mesylate, 1 kg of (*R*)-1 was needed. Therefore, 7.9 L of triethanolamine, 4.9 L of 40% aqueous sodium hydroxide, 49.6 L of deionized water, 54.1 L of ethyl acetate, and 27.0 L of saturated aqueous sodium chloride solution should be used in this step.

(R)-N-(Prop-2-yn-1-yl)-2,3-dihydro-1H-inden-1-amine ((R)-3). Potassium carbonate (46.3 g, 0.335 mol) was added to a solution of (*R*)-2,3-dihydro-1-indanamine (44.6 g, 0.335 mol, ee >99%) in acetonitrile (670 mL). Propargyl bromide (39.9 g, 0.335 mol) dissolved in acetonitrile (335 mL) was added to the reaction mixture with stirring at 30 °C. After stirring at 30 °C for 12 h, potassium carbonate was filtered off, whereupon acetonitrile was removed by evaporation at 30 °C under reduced pressure. After adding deionized water (1100 mL), the remaining phase was extracted by ethyl acetate (1200 mL/three times), and the organic phase was washed by saturated aqueous sodium chloride solution (600 mL/two times), dried over anhydrous sodium sulfate (25 g), and filtered. Butanedioic acid (39.5 g, 0.335 mol) dissolved in ethyl acetate (200 mL) was added to the filtrate to purify the product by forming a salt. After heating at reflux for 1 h, the mixture was cooled to room temperature and filtered. The residue was dissolved in deionized water (600 mL). The pH was adjusted to 10 by saturated aqueous sodium carbonate solution and extracted by ethyl acetate (600 mL/three times). The organic phases were washed by saturated aqueous sodium chloride solution (400 mL/two times), dried over anhydrous sodium sulfate (15 g), and filtered. The solvent was removed by evaporation at 30 °C under reduced pressure remaining an oily liquid (34.2 g, yield: 59.7%, ee >99.9%).

For the production of 1 kg of (*R*)-rasagiline mesylate, 0.77 kg of (*R*)-3 was needed. Therefore, 22.6 L of acetonitrile, 38.3 L of deionized water, 45.1 L of ethyl acetate, and 22.5 L of saturated aqueous sodium chloride solution should be used in this step.

(R)-N-(Prop-2-yn-1-yl)-2,3-dihydro-1H-inden-1-amine Mesylate ((R)-Rasagiline Mesylate, (R)-4). (*R*)-Rasagiline mesylate was prepared according to the procedure of Sathe.[15] Rasagiline (34.2 g, 0.2 mol) was dissolved in IPA (342 mL) under stirring. A solution of methanesulfonic acid (0.25 mol, 24.3 g) in IPA (48 mL) was added dropwise to the above cooled solution. After complete addition, the mixture was cooled to 5 °C and stirred for 30 min at 5−10 °C to get the white solid which was filtered and dried to furnish the product (*R*)-4. (44.38 g, yield: 83.1%, ee >99.9%) ^{1}H NMR (600 MHz, D_2O) 7.55 (d, *J* = 7.7 Hz, 1H), 7.52−7.41 (m, 2H), 7.36 (m, 1H), 5.01−4.93 (m, 1H), 3.97 (dd, *J* = 4.3, 2.6 Hz, 2H), 3.16 (m, 1H), 3.02 (m, 2H), 2.79 (d, *J* = 1.2 Hz, 3H), 2.63−2.52 (m, 1H), 2.27 (m, 1H). ^{13}C NMR (600 MHz, D_2O) 148.14, 138.67, 133.20, 130.00, 128.52, 128.29, 80.89, 76.15, 64.84, 41.32, 37.09, 32.48, 31.23.

For the production of 1 kg of (*R*)-rasagiline mesylate, 8.8 L of IPA should be used in this step.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectrum for (*rac*)-1; HPLC, MS, IR, ^{1}H, and ^{13}C NMR spectra for (*R*)-2 and (*R*)-4. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*Tel.: +86 24 23986456. E-mail: jiaxian206@163.com.

*Tel./Fax: +86 24 23986436. E-mail: yousong206@aliyun.com.

Author Contributions

G.-Z.M and Z.-Q.X. contributed equally to this study.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T. Industrial Methods for the Production of Optically Active Intermediates. *Angew. Chem., Int. Ed.* **2004**, *43* (7), 788−824.

(2) Träff, A.; Lihammar, R.; Bäckvall, J.-E. A Chemoenzymatic Dynamic Kinetic Resolution Approach to Enantiomerically Pure (R)- and (S)-Duloxetine. *J. Org. Chem.* **2011**, *76* (10), 3917−3921.

(3) Truppo, M. D.; Hughes, G. Development of an Improved Immobilized CAL-B for the Enzymatic Resolution of a Key Intermediate to Odanacatib. *Org. Process Res. Dev.* **2011**, *15* (5), 1033−1035.
(4) Pesti, J. A.; Yin, J.; Zhang, L.-h.; Anzalone, L.; Waltermire, R. E.; Ma, P.; Gorko, E.; Confalone, P. N.; Fortunak, J.; Silverman, C.; Blackwell, J.; Chung, J. C.; Hrytsak, M. D.; Cooke, M.; Powell, L.; Ray, C. Efficient Preparation of a Key Intermediate in the Synthesis of Roxifiban by Enzymatic Dynamic Kinetic Resolution on Large Scale. *Org. Process Res. Dev.* **2003**, *8* (1), 22−27.
(5) Hu, L.; Schaufelberger, F.; Zhang, Y.; Ramstrom, O. Efficient asymmetric synthesis of lamivudine via enzymatic dynamic kinetic resolution. *Chem. Commun.* **2013**, *49* (88), 10376−10378.
(6) (a) Hoy, S.; Keating, G. Rasagiline. *Drugs* **2012**, *72* (5), 643−669. (b) Perez-Lloret, S.; Rascol, O. Safety of rasagiline for the treatment of Parkinson's disease. *Expert Opin. Drug Safety* **2011**, *10* (4), 633−643. (c) Weinreb, O.; Amit, T.; Riederer, P.; Youdim, M. B. H.; Mandel, S. A., Neuroprotective profile of the multitarget drug rasagiline in Parkinson's disease. In *International Review of Neurobiology*; Moussa, B. H. Y., Peter, D., Eds.; Academic Press: New York, 2011; Vol. *100*, pp 127−149.
(7) (a) Chen, T. T.; Yao, C. H. Method for producing compound for preparation of anti-parkinson's disease drug. US2011218361A1, 2011. (b) Thanedar, A. A.; Deshmukh, S. A.; Zope, S. S.; Kelkar, L. M.; Koilpillai, J. P.; Gajera, J. M. Processes for the preparation of propargylated aminoindans or a pharmaceutically acceptable salt thereof. WO2011048612A2, 2011. (c) Cherukupally, P.; Vajrala, V. R.; Adla, V. K.; Rangineni, S.; Kanniah, S. Preparation of rasagiline and salts thereof. WO 2010059913A2, 2010. (d) Allegrini, P.; Romano, B. G.; Attolino, E.; Artico, M.; Rossi, D. Crystalline Form of Rasagiline and Process for the Preparation Thereof. US2010029987A1, 2010. (e) Goel, O. P. Improved process for the resolution of 1-aminoindanes. EP0235590A2, 1987. (f) Berger-Paskin, T.; Finberg, J. P. M.; Lerner, D.; Levy, R.; Sterling, J.; Veinberg, A.; Yellin, H.; Youdim, M. B. H. R-enantiomer of n-propargyl-1-aminoindan, salts, compositions and uses thereof. WO9511016, 1995. (g) Youdim, M. B. H.; Finberg, J. P. M.; Levy, R.; Sterling, J.; Lerner, D.; Berger-Paskin, T.; Yellin, H. R-Enantiomer of N-propargyl-1-aminoindan, its preparation and pharmaceutical compositions containing it. EP0436492, 1994. (h) Feng, Q. Simple and novel process for preparing indenes derivatives. CN1990455A1, 2007. (i) Gutman, A. L.; Nisnevich, G.; Ponomarev, V.; Sotrihin, M.; Zaltzman, I. Process for the preparation of rasagiline and its salts. WO2002068376 A1, 2002.
(8) (a) Colyer, J. T.; Andersen, N. G.; Tedrow, J. S.; Soukup, T. S.; Faul, M. M. Reversal of Diastereofacial Selectivity in Hydride Reductions of N-tert-Butanesulfinyl Imines. *J. Org. Chem.* **2006**, *71* (18), 6859−6862. (b) Uiterweerd, P. G. H.; van der Sluis, M.; Kaptein, B.; de Lange, B.; Kellogg, R. M.; Broxterman, Q. B. (S)-1-Aminoindane: synthesis by chirality transfer using (R)-phenylglycine amide as chiral auxiliary. *Tetrahedron: Asymmetry* **2003**, *14* (22), 3479−3485. (c) Pakulski, M. M.; Mahato, S. K.; Bosiak, M. J.; Krzeminski, M. P.; Zaidlewicz, M. Enantioselective reduction of ketoxime ethers with borane−oxazaborolidines and synthesis of the key intermediate leading to (S)-rivastigmine. *Tetrahedron: Asymmetry* **2012**, *23* (9), 716−721.
(9) Kim, Y.; Park, J.; Kim, M.-J. Fast racemization and dynamic kinetic resolution of primary benzyl amines. *Tetrahedron Lett.* **2010**, *51* (42), 5581−5584.
(10) (a) Paetzold, J.; Bäckvall, J. E. Chemoenzymatic Dynamic Kinetic Resolution of Primary Amines. *J. Am. Chem. Soc.* **2005**, *127* (50), 17620−17621. (b) Reetz, M. T.; Schimossek, K. Lipase-Catalyzed Dynamic Kinetic Resolution of Chiral Amines: Use of Palladium as the Racemization Catalyst. *CHIMIA Int. J. Chem.* **1996**, *50* (12), 668−669.
(11) Qin, B.; Liang, P.; Jia, X.; Zhang, X.; Mu, M.; Wang, X.-Y.; Ma, G.-Z.; Jin, D.-N.; You, S. Directed evolution of Candida antarctica lipase B for kinetic resolution of Profen esters. *Catal. Commun.* **2013**, *38* (0), 1−5.
(12) Thalén, L. K.; Bäckvall, J.-E. Development of dynamic kinetic resolution on large scale for (±)-1-phenylethylamine. *Beilstein J. Org. Chem.* **2010**, *6*, 823−829.
(13) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. Chemoenzymatic Dynamic Kinetic Resolution of Alcohols and Amines. *Eur. J. Org. Chem.* **2010**, *2010* (6), 987−987.
(14) Duward F. Shriver, M. A. D. *The Manipulation of Air-Sensitive Compounds*, 2nd ed.; John Wiley & Sons, Inc.: New York, 1986.
(15) Sathe, D. G. Process for preparation of rasagiline and salts thereof. EP2364967A2, 2011.