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Kinetic resolution of iodophenylethanols by *Candida antarctica* lipase and their application for the synthesis of chiral biphenyl compounds

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ABSTRACT

The kinetic resolution of (±)-iodophenylethanols was carried out using lipase from *Candida antarctica* and in some cases the enantiomeric excesses were high (up to >98%). Enantiomerically enriched (*S*)-iodophenylethanols produced by the enzymatic resolution process were used in the synthesis of chiral biphenyl compounds by the Suzuki reaction with good yields (63–65%).

1. Introduction

The synthesis of enantiomerically pure drugs has been a great challenge in both academia and the pharmaceutical industry.[1] In this scenario, chiral alcohols have emerged as important building blocks for the synthesis of optically active compounds,[2] including biologically active compounds, due to the ease of access to their frameworks by a number of methods including, for example, the addition of the organometallics to aldehydes in the presence of chiral ligands,[3] the catalytic asymmetric hydrogenation of prochiral ketones,[4] and organocatalyzed direct asymmetric aldol reactions.[5] In addition to these methods to produce chiral secondary alcohols, biocatalyzed transformations have arisen as advantageous alternatives.[6,7] In this context, we mention the microbial reduction of prochiral ketones[5] and the enzymatic kinetic resolution of secondary alcohols as important means of obtaining enantiopure alcohols.[6] These methods are attractive because they employ simple and low cost procedures, which are environmentally friendly and produce a broad range of enantiomerically enriched alcohols.[6,7] All these advantages led us to become interested in this area in which we have reported kinetic resolutions of secondary alcohols by *Candida antarctica* lipase[8] and bioreductions of aromatic ketones using microbial cells.[9] Herein, we report the first kinetic resolution of (±)-iodophenylethanols using immobilized CALB lipase (Novozym 435®) and the application of the enantiomerically enriched (*S*)-alcohols obtained in the preparation of chiral biphenyl compounds by the Suzuki cross-coupling reaction. The chiral biphenyl compounds produced can be considered versatile intermediates in organic synthesis which may be employed in the preparation of biologically active substances.[10]

2. Results and discussion

Initially, we accomplished the reactions of (±)-iodophenylethanols **1–3** with vinyl acetate and *C. antarctica* lipase in hexane at 32 °C and 130 rpm to obtain enantiomerically enriched (*S*)-iodophenylethanols **1–3** and (*R*)-iodophenyl acetates **4–6** (Table 1).

The results depicted in Table 1 show that the use of hexane as the solvent produced the enzymatic resolution of (±)-iodophenylethanols **2–3** in short reaction times. In these cases, (*S*)-alcohols **2–3** and (*R*)-acetates **5–6** were produced with high enantiomeric excess (>98% ee) and in good isolated yields (41–46%). Consequently, these enzymatic resolutions presented high enantiomeric rate values (E >200). On the other hand, when the (±)-iodophenylethanol **1** was treated with vinyl acetate and immobilized CALB lipase, (*R*)-acetate **4** was obtained with >98% enantiomeric excess in only 25% of conversion after 24 h (Table 1). Presumably the *ortho*-iodo substituent bonded the (±)-iodophenylethanol **1** aromatic ring and hindered the transesterification reaction promoted by the lipase (Table 1).

Analyses using gas chromatography with a chiral stationary phase for the enzymatic resolution of (±)-iodophenylethanols **1–3** in the presence of vinyl acetate and *C. antarctica* lipase were performed. The enantiomers of (±)-iodophenylethanol **2** could not be separated by gas chromatography with chiral stationary phase. Thus, the enantiomeric excess of the (*S*)-alcohol **2** produced by kinetic resolution employing immobilized CALB lipase was determined by chiral separation of its corresponding acetate (>98% ee) obtained using acetic anhydride in pyridine.[13]

After determining the absolute configurations of the (*S*)-alcohols **1** and **3** by comparing their specific rotation values with values reported in the literature,[12,13] we could conclude that the immobilized *C. antarctica* lipase has stereochemical preference for (*R*)-alcohol esterification. The preparation of enantiomerically enriched (*S*)-iodophenylethanol **2** and (*R*)-iodophenyl acetates **5** and **6** is described

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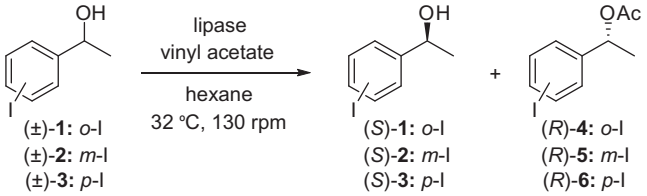
Table 1
Enzymatic resolution of (±)-iodophenylethanols **1–3** using vinyl acetate and immobilized CALB lipase in hexane[a]



(±)-**1:** *o*-I (*S*)-**1:** *o*-I (*R*)-**4:** *o*-I
(±)-**2:** *m*-I (*S*)-**2:** *m*-I (*R*)-**5:** *m*-I
(±)-**3:** *p*-I (*S*)-**3:** *p*-I (*R*)-**6:** *p*-I

Chiral alcohol	*t* (h)	*c* (%)	ee (%)	AC	Chiral acetate	*t* (h)	*c* (%)	ee (%)	AC
1	2	96	6	*S*	**4**	2	4	>98	*R*
	24	75	24	*S*		24	25	>98	*R*
2	2	50[b]	>98	*S*	**5**	2	50[c]	>98	*R*
	24	50	>98	*S*		24	50	>98	*R*
3	2	50[d]	>98	*S*	**6**	2	50[e]	>98	*R*
	4	50	>98	*S*		4	50	>98	*R*

[a] Reaction conditions: To a 50-mL erlenmeyer flask were added HPLC grade hexane (10 mL), vinyl acetate (1 mL), immobilized CALB lipase (100 mg), and the appropriate alcohol **1–3** (0.8 mmol, 200 mg). The Erlenmeyer flask was sealed using a rubber stopper, and the reaction mixture was stirred in an orbital shaker at 32 °C and 130 rpm.
[b] Isolated yield: 41%.
[c] Isolated yield: 43%.
[d] Isolated yield: 46%.
[e] Isolated yield: 45%. *t* (h): reaction time. *c* (%): conversion. ee (%): enantiomeric excess. AC: absolute configuration.

for the first time, and the absolute configurations of these compounds were proposed according to the Kazlauskas's rule.[18]

In order to demonstrate the great versatility of enantiomerically enriched (*S*)-alcohols **1–3** and also with the aim of producing interesting chiral building blocks, we subjected the (*S*)-alcohols **1–3** to the Suzuki reaction to give enantiopure biphenyl compounds **8** and **9** (Scheme 1).

As can be seen in Scheme 1, chiral biphenyl compounds **8** and **9** were obtained in good isolated yields (63–65%) using the Suzuki reaction conditions from (*S*)-iodophenylethanols **2** and **3**, respectively. However, (*S*)-iodophenylethanol **1** did not lead to the formation of the chiral biphenyl compound **7** under the same reaction conditions, probably because of the steric effect around the iodine substituent present and its aromatic ring (Scheme 1).

The structures of compounds **1–6**, **8**, and **9** were assigned on the basis of a variety of spectroscopic techniques, namely, in accordance with their ^{1}H and ^{13}C NMR and IR spectra. All new compounds **2**, **5**, and **8** provided high resolution mass spectra that agree with the proposed structures.

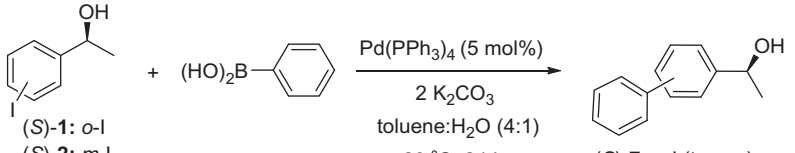
3. Conclusions

In summary, a simple and efficient two-step synthesis of chiral biphenyl compounds was developed by the versatile combination of bio- and metal-catalyzed processes. (±)-Iodophenylethanols were resolved by immobilized *C. antarctica* lipase, producing (*S*)-iodophenylethanols and (*R*)-iodophenyl acetates in high enantiomeric excesses. The enantiomerically enriched (*S*)-iodophenylethanols produced chiral biphenyl compounds by the Suzuki reaction in good yields. All enantiomerically enriched compounds synthesized in the course of this work are useful chiral building blocks and should find use in the construction of optically active molecules with important biological properties.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC-200 spectrometer (^{1}H at 200 MHz and ^{13}C at 50 MHz). The spectra were taken in chloroform-*d* ($CDCl_3$) and the chemical shifts were given in ppm using tetramethylsilane (TMS) as internal standard. Near-IR spectra were recorded on a Bomem MB-102 spectrometer. HRMS (high resolution mass spectra) were taken with a Micro TOF-MS Bruker Daltonics ESI. Enzymatic kinetic resolutions were carried out using a Tecnal TE-421 orbital shaker. Optical rotation values were measured with a Perkin–Elmer 241 polarimeter. The reported data were determined using the sodium D line (589 nm) and a 1 dm cuvette. The absolute configurations for the enantiomerically enriched compounds obtained were determined by comparing their specific optical rotation values with the corresponding values reported in the literature. Enzymatic reactions were analyzed using a Shimadzu GC 2010 gas chromatograph equipped with an AOC 20i auto injector, a flame ionization detector (FID), and a Varian chiral column CP-Chiralsil-DEX (β-cyclodextrin) (25 m × 0.25 mm × 0.39 μm). The conditions employed in the gas chromatography analyses were the following: carrier gas: nitrogen (60 kPa); injector temperature: 200 °C; injector split ratio: 1:20;



(*S*)-**1:** *o*-I
(*S*)-**2:** *m*-I
(*S*)-**3:** *p*-I

(*S*)-**7:** *o*-I (traces)
(*S*)-**8:** *m*-I (65% yield)
(*S*)-**9:** *p*-I (63% yield)

Scheme 1. Palladium-catalyzed Suzuki reaction between (*S*)-alcohols **1–3** and phenylboronic acid.

detector temperature: 200 °C; oven (initial temperature): 120 °C; oven (final temperature): 165 °C; heating rate: 2 °C min^{-1}, and time analysis: 32.5 min. The enantiomeric excesses (ee) of iodophenylethanols **1–3** and iodophenyl acetates **4–6** were determined by gas chromatography analyses with chiral stationary phase employing the retention times obtained for both enantiomers (*R*/*S*) of the compounds **1** to **6** which were the following: compound **1**: *R* = 16.0 min and *S* = 19.0 min; compound **2**: *R* = 16.5 min and *S* = 16.5 min; compound **3**: *S* = 19.8 min and *R* = 20.5 min; compound **4**: *R* = 10.5 min and *S* = 10.5 min; compound **5**: *S* = 11.2 min and *R* = 11.6 min, and compound **6**: *R* = 16.5 min and *S* = 17.5 min. Reagents and solvents were used as obtained commercially and when necessary were purified and/or dried using procedures described in the literature.[11] Column chromatography separations were carried out using Silica Gel 60 (400–230 mesh) and hexane/ethyl acetate mixtures as eluent. (±)-Iodophenylethanols **1–3** were obtained by reduction of their corresponding iodoacetophenones using $NaBH_4$ in ethanol.[12] (±)-Iodophenyl acetates **4–6** were obtained by acetylation of their corresponding (±)-iodophenylethanols **1–3** using acetic anhydride in pyridine.[13]

4.2. General procedures

4.2.1. Kinetic resolution of (±)-iodophenylethanols 1–3 by immobilized CALB lipase

To a 50-mL Erlenmeyer flask were added HPLC grade hexane (10 mL), vinyl acetate (1 mL), immobilized CALB lipase (100 mg), and the appropriate alcohol **1–3** (0.8 mmol, 200 mg). The Erlenmeyer flask was sealed using a rubber stopper, and the reaction mixture was stirred in an orbital shaker at 32 °C and 130 rpm. The reaction progress was monitored by collecting samples (0.1 mL) according to the time indicated in Table 1, which were analyzed by gas chromatography with chiral stationary phase. After the reaction was complete, the immobilized lipase was filtered off. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using 8:2 hexane/ethyl acetate as eluent, yielding the enantiomerically enriched alcohols **1–3** and acetates **4–6**.

4.2.2. Preparation of chiral biphenyl compounds 8–9 by the Suzuki cross-coupling reaction

To a vial (20 mL) were added the appropriate (*S*)-alcohol **1–3** (0.3 mmol, 74 mg), phenylboronic acid (0.3 mmol, 37 mg), K_2CO_3 (0.6 mmol, 83 mg), $Pd(PPh_3)_4$ (0.015 mmol, 17 mg), distilled water (1 mL), and toluene (4 mL). The vial was sealed using a cap, and the reaction mixture was stirred for 24 h at 80 °C. Afterwards, brine (20 mL) was added to the mixture, which was extracted with ethyl acetate (3 × 20 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using 7:3 hexane/ethyl acetate as eluent yielding the desired products **8–9**.

4.2.3. Assignment of the absolute configuration and characterization data for compounds 1–9

(*S*)-(−)-1-(2-Iodophenyl)ethanol **1**: experimental data: $[\alpha]_D^{25} = -13.8$ (*c* 0.07, $CHCl_3$; 24% ee); literature: $[\alpha]_D^{25} = -41.3$ (*c* 0.20, $CHCl_3$; 97% ee).[12] The spectroscopic data are in agreement with those reported in the literature.[12]

(*S*)-(−)-1-(3-Iodophenyl)ethanol **2**: experimental data: $[\alpha]_D^{25} = -20.7$ (*c* 0.10, $CHCl_3$; 98% ee). ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 7.67 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.84 (q, *J* = 6.4 Hz, 1H), 1.70 (s, 1H), 1.45 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 148.1, 136.4, 134.5, 130.2, 124.6, 94.4, 69.5, 25.1; IR (film) ν (cm^{-1}): 3348 (OH), 1086 (C–O); HRMS (ESI) *m*/*z*; calcd for C_8H_9IO $[M+Na]^+$: 247.9698, found: 247.9675.

(*S*)-(−)-1-(4-Iodophenyl)ethanol **3**: experimental data: $[\alpha]_D^{25} = -38.5$ (*c* 6.90, $CHCl_3$; 98% ee); literature: $[\alpha]_D^{25} = -32.7$ (*c* 5.99, $CHCl_3$; 96% ee).[13] The spectroscopic data are in agreement with those reported in the literature.[14]

(*R*)-(+)-1-(2-Iodophenyl)ethyl acetate **4**: experimental data: $[\alpha]_D^{25} = +7.9$ (*c* 0.12, $CHCl_3$; 98% ee); literature: $[\alpha]_D^{25} = -6.8$ (*c* 0.785, $CHCl_3$; 69% ee).[13] The spectroscopic data are in agreement with those reported in the literature.[13]

(*R*)-(+)-1-(3-Iodophenyl)ethyl acetate **5**: experimental data: $[\alpha]_D^{25} = +6.9$ (*c* 0.18, $CHCl_3$; 98% ee). ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 7.58–7.69 (m, 2H), 7.27–7.32 (m, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 5.78 (q, *J* = 6.7 Hz, 1H), 2.07 (s, 3H), 1.49 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 170.0, 144.0, 136.8, 135.0, 130.0, 125.3, 94.4, 71.3, 22.2, 21.2; IR (film) ν (cm^{-1}): 3059 (H-Ar), 1727 (C=O), 1238 (C–O); HRMS (ESI) *m*/*z*; calcd for $C_{10}H_{11}IO_2$ $[M+Na]^+$: 289.9804, found: 289.9797.

(*R*)-(+)-1-(4-Iodophenyl)ethyl acetate **6**: experimental data: $[\alpha]_D^{25} = +71.1$ (*c* 3.80, $CHCl_3$; 98% ee). The spectroscopic data are in agreement with those reported in the literature.[15]

(*S*)-(−)-1-(Biphenyl-3-yl)ethanol **8**: experimental data: $[\alpha]_D^{25} = -13.0$ (*c* 1.00, $CHCl_3$; 98% ee). ^1H NMR (200 MHz, $CDCl_3$), δ (ppm): 7.60 (m, 1H), 7.51 (m, 2H), 7.49 (m, 1H), 7.46 (m, 2H), 7.44 (m, 1H), 7.37 (m, 1H), 7.32 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 146.4, 141.5, 141.1, 129.6, 129.0, 128.8, 127.4, 127.2, 128.4, 124.4, 70.6, 25.3. IR (film) ν (cm^{-1}): 3373 (OH), 1076 (C–O). HRMS (ESI) *m*/*z*; calcd for $C_{14}H_{14}O$ $[M+Na]^+$: 221.0942, found: 221.0935.

(*S*)-(−)-1-(Biphenyl-4-yl)ethanol **9**: experimental data: $[\alpha]_D^{25} = -13.2$ (*c* 1.00, $CHCl_3$; 98% ee); literature: $[\alpha]_D^{25} = -29.5$ (*c* 1.0, $CHCl_3$, 77% ee).[16] The spectroscopic data are in agreement with those reported in the literature.[17]

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