

## Chemoenzymatic Resolution of $\beta$ -Azidophenylethanols by *Candida antarctica* and their Application for the Synthesis of Chiral Benzotriazoles

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As resoluções cinéticas de ( $\pm$ )- $\beta$ -azidofeniletanóis foram realizadas usando a lipase de *Candida antarctica* fornecendo os compostos enantiomericamente enriquecidos, (*R*)- $\beta$ -azidofeniletanóis e acetato de (*S*)- $\beta$ -azidofeniletila em bons excessos enantioméricos (até > 99%). Os (*R*)- $\beta$ -azidofeniletanóis enantiomericamente enriquecidos foram submetidos à reação de ciclização com o triflato de 2-(trimetilsilil)fenila e CsF resultando em 1,2,3-benzotriazóis em bons rendimentos (75-86%) pela reação de cicloadição [3 + 2], a qual envolve a formação *in situ* de benzino.

The kinetic resolutions of ( $\pm$ )- $\beta$ -azidophenylethanols were carried out using lipase from *Candida antarctica*, and enantiomerically enriched (*R*)- $\beta$ -azidophenylethanols and their corresponding (*S*)- $\beta$ -azidophenylethyl acetates were obtained in good enantiomeric excesses (up to > 99%). The enantiomerically enriched (*R*)- $\beta$ -azidophenylethanols were subjected to cyclization reaction with 2-(trimethylsilyl)phenyl triflate and CsF producing chiral 1,2,3-benzotriazole compounds in good yields (75-86%) by a [3 + 2] cycloaddition, which involves the benzyne formation.

**Keywords:** CALB, lipase, biocatalysis, click chemistry, [3 + 2] cycloaddition

### Introduction

The chemistry of azides has been reviewed several times, some of these overviews focus only on one subclass of azides.<sup>1</sup> The synthesis of  $\alpha$ -azidoketones can be commonly achieved by azide-halogen exchange reactions of  $\alpha$ -haloketones.<sup>2</sup> These compounds are precursors of  $\beta$ -azidoalcohols known as synthons of molecules such as agrochemicals, fragrances, drugs, among others.<sup>3,4</sup>

Lipases have been used for the optical resolution of several highly functionalized chiral molecules, such as  $\beta$ -azidoalcohols, amino acids and hydroxy acids.<sup>5-7</sup> The use of these enzymes is advantageous in several respects, particularly to simplify the separation of the product, and avoid undesired product formation. Chiral  $\beta$ -azidoalcohols are also immediate precursors of chiral aziridines and

amino alcohols.<sup>4</sup> There has been growing interest in chiral aziridines due to the increasing importance of functionalized aziridines in organic synthesis and their presence in bioactive molecules, e.g., radiation sensitizers and enzyme inhibitors.<sup>8</sup> Another example, chiral 1,2-aminoalcohols are very important substances, as illustrated by the biologically active natural product ephedrine and the pharmacologically active bronchodilators, such as salmeterol and albuterol.<sup>5</sup>

Chiral  $\beta$ -azidoalcohols have been reported for the synthesis of different triazoles.<sup>9</sup> With the advent of click chemistry, specifically the use of Cu(I)-catalyzed or benzyne precursor by a 1,3-dipolar cycloaddition reaction with derivative azides, yielding the 1,2,3-triazoles subunit that has become a significant component of various small molecules and macromolecular systems, ranging from therapeutics, self-assembling systems and polymers to proton exchange membranes.<sup>10,11</sup> In addition, triazole compounds constitute promising therapeutic agents for

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the treatment of fungal infections, for which there is not effective therapy. It has been reported that triazole derivatives exhibit higher antifungal and antibacterial properties.<sup>12</sup> Triazole compounds containing three nitrogen atoms in the five-membered aromatic azole ring are readily able to bind with a variety of enzymes and receptors in biological system via diverse non-covalent interactions, and thus display versatile biological activities.<sup>13</sup>

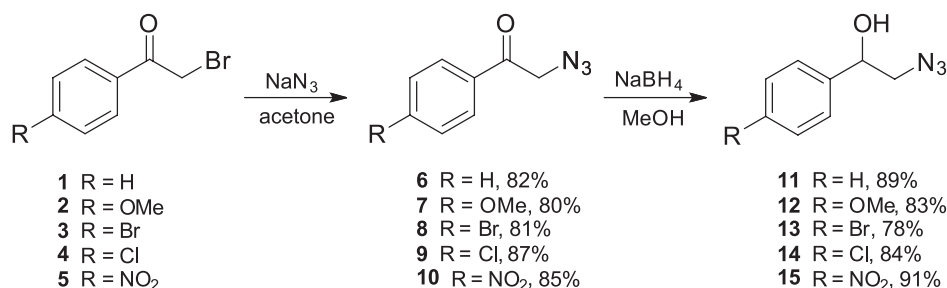
The chemoenzymatic kinetic resolution of a set of aromatic and aliphatic alcohols by immobilized *Candida antarctica* lipase (CALB) in organic media was recently investigated. These resolutions have shown the dependence between the structure of the substrate and the enantioselectivity of enzymatic transesterification according to the empirical Kazlauskas rule.<sup>14-17</sup>

In this work, we studied the kinetic resolutions of ( $\pm$ )- $\beta$ -azidophenylethanols to the production of enantiomerically enriched (*R*)- $\beta$ -azidophenylethanols, and their corresponding (*S*)- $\beta$ -azidophenylethyl acetates using lipase from CALB in organic medium. In addition, the enantiomerically enriched (*R*)- $\beta$ -azidophenylethanol products were subjected to the cyclization reaction with 2-(trimethylsilyl)phenyl triflate and cesium fluoride in order to produce chiral 1,2,3-benzotriazole compounds by a [3 + 2] cycloaddition via benzyne formation and organic azides.

## Results and Discussion

$\alpha$ -Haloacetophenones **1-5** were transformed into their  $\alpha$ -azidophenylketones **6-10** by treatment with  $\text{NaN}_3$  in acetone. In addition, the compounds **6-10** were reduced using sodium borohydride in methanol to yield ( $\pm$ )- $\beta$ -azidophenylethanols **11-15**. All carried out reactions led to the desired products in good yields (Scheme 1). Products **11-15** were characterized by spectroscopic data which are in agreement with those reported in the literature.<sup>6,7,18-20</sup>

The ( $\pm$ )- $\beta$ -azidophenylethanols **11-15** were previously acetylated using acetic anhydride and pyridine, yielding the ( $\pm$ )- $\beta$ -azidophenyl acetates **16-20**, which were used as standards by chromatographic analysis on chiral column.



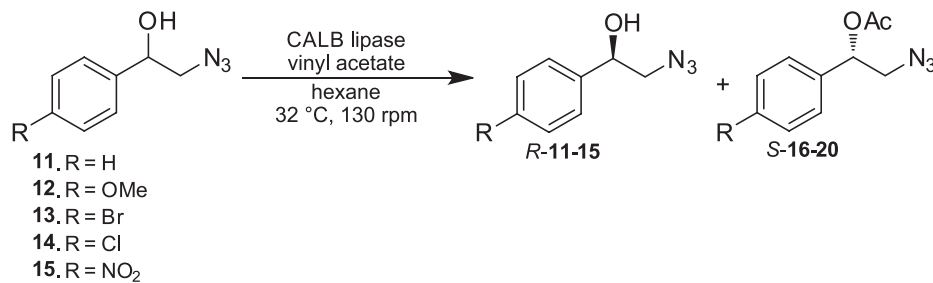
**Scheme 1.** Synthesis of ( $\pm$ )- $\beta$ -azidophenylethanols **11-15** from  $\alpha$ -bromoacetophenones **1-5**.

The enzymatic resolutions of the ( $\pm$ )- $\beta$ -azidophenylethanols **11-15** were performed using immobilized CALB, vinyl acetate as the acyl donor and hexane as solvent in an orbital shaker. The results are shown in Table 1. The development of the reactions was followed by TLC (thin layer chromatography) analysis and aliquots were collected between 5 and 10 days of incubation to conclusion of the reaction. Next, aliquots were analyzed by HPLC (high performance liquid chromatography) using chiral phase column to determine conversion of  $\beta$ -azidophenyl acetates and enantiomeric excess.

In these conditions, the *R*-alcohols **11-15** and *S*-acetates **16-20** were obtained with excellent selectivity ( $E > 200$ ). The  $\beta$ -azidoalcohols **11**, **12** and **14**, and their respective acetates **16**, **17** and **19**, were obtained in excellent yields and high enantiomeric excesses ( $> 99\%$  ee). While for the  $\beta$ -azidoalcohol **13** remaining in reaction for a period of 10 days, no complete resolution was observed (Table 1). No complete resolution was observed for the nitroazidoalcohol **15**, possibly owing to the nitro electron-withdrawing group hindering the interaction of the substrate with the active site of CALB.<sup>21</sup> The attribution of the absolute configuration of the alcohols **11-14** was assigned as *R* configuration by comparison with optical rotation value described in the literature.<sup>6,7,19</sup> Consequently, it was possible to suggest that the immobilized CALB has stereochemical preference for *S*-alcohol esterification. Kazlauskas rule predicts this esterification preference.<sup>22,23</sup>

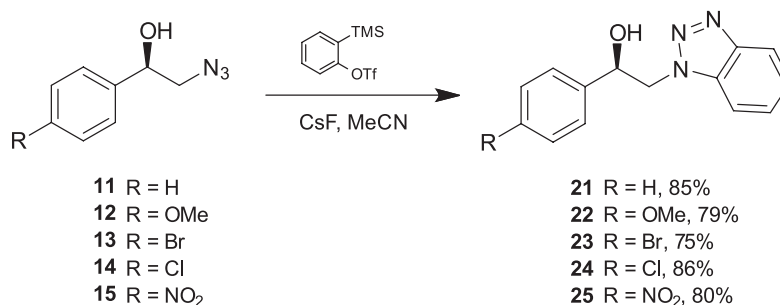
The (*R*)- $\beta$ -azidophenylethanols **11-15** were subjected to cyclization reaction with 2-(trimethylsilyl)phenyl triflate and  $\text{CsF}$  in acetonitrile at room temperature, producing chiral 1,2,3-benzotriazole **21-25** in good yields (75-86%) by a [3 + 2] cycloaddition, which involves the benzyne formation (Scheme 2).<sup>24-27</sup>

The [3 + 2] cycloaddition involving chiral azides and arynes, as shown in Scheme 2, may be considered a versatile extension of the click chemistry, providing rapid access to chiral benzotriazoles, which are known to possess important biological properties, such as: antimicrobial activity, anti-inflammatory activity, analgesic activity and anticancer activity.<sup>28</sup>

**Table 1.** Enzymatic resolution of ( $\pm$ )- $\beta$ -azidophenylethanols **11-15** by using vinyl acetate and immobilized CALB lipase in hexane<sup>a</sup>

Chiral $\beta$ -azidoalcohol	time / day	Concentration / %	Yield / %	Selectivity	ee / %	AC	Chiral $\beta$ -azidoacetates	time / day	Conversion / %	Yield / %	Selectivity	ee / %	AC
<b>11</b>	5	50	48	> 200	> 99	R	<b>16</b>	5	50	48	> 200	> 99	S
<b>12</b>	5	50	44	> 200	> 99	R	<b>17</b>	5	50	45	> 200	> 99	S
<b>13</b>	10	60	55	> 200	70	R	<b>18</b>	10	40	38	> 200	> 99	S
<b>14</b>	7	50	46	> 200	> 99	R	<b>19</b>	7	50	48	> 200	> 99	S
<b>15</b>	10	72	65	> 200	49	R	<b>20</b>	10	28	24	> 200	> 99	S

<sup>a</sup>Reaction conditions: HPLC grade hexane (10 mL), vinyl acetate (1 mL), immobilized CALB lipase (100 mg) and the appropriate  $\beta$ -azidoalcohol (**11-15**) (0.8 mmol, 200 mg) were added to a 50 mL Erlenmeyer flask. 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. ee: enantiomeric excess. AC: absolute configuration.

**Scheme 2.** Synthesis of benzotriazoles from (*R*)- $\beta$ -azidophenylethanols **11-15**.

## Conclusions

In summary, a simple and efficient synthesis of 1,2,3-triazoles **21-25**, known as benzotriazoles, was developed. Chiral  $\beta$ -azidoalcohols **11-15** were obtained by immobilized *Candida antarctica* lipase, producing *S*-azidoalcohols **11-15** and *R*-azido acetates **16-20** in high selectivities ( $E > 200$ ). The enantiomerically enriched *S*-azidoalcohols **11-15** yielded chiral benzotriazoles by [3 + 2] cycloaddition reaction in good yields (75-86%).

## Experimental

### General methods

Reagents (vinyl acetate,  $\alpha$ -halobenzophenones **1-5**, anhydride acetic, pyridine, cesium fluoride and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate) and solvents (ethyl acetate (EtOAc), hexane, methanol,

isopropanol and acetonitrile) were purchased from Sigma-Aldrich (USA) and Synth (Brazil), respectively. Acetonitrile was distilled from calcium hydride under a nitrogen atmosphere prior to use. Purification of the reaction products was carried out by column chromatography (CC) over silica gel (230-400 mesh) eluted with mixtures of *n*-hexane and EtOAc (9:1, 8:2, 7:3). The reactions were monitored by TLC using aluminum plates precoated with silica gel 60 F254, eluted with hexane and EtOAc, and visualized by spraying with phosphomolybdic acid or *p*-anisaldehyde staining solutions followed by heating. Novozyme 435<sup>®</sup>, immobilized lipase from *Candida antarctica*, was provided by NovoNordisk (Araucária, Paraná, Brazil). <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AC-200 III spectrometer (<sup>1</sup>H and <sup>13</sup>C at 200 and 50 MHz, respectively) and on a Bruker/AVANCE spectrometer (<sup>1</sup>H and <sup>13</sup>C at 400 and 100 MHz, respectively). The spectra were taken in deuterated chloroform (CDCl<sub>3</sub>) or dimethylsulfoxide (DMSO-*d*<sub>6</sub>) and the chemical shifts

were given in ppm using tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra were recorded on a Bomem MB-102 spectrometer. High resolution mass spectrometry (HRMS) analyses were carried out on a Bruker Daltonics MicroTOF focus mass spectrometer equipped with an electrospray ionization (ESI) source. External calibration was achieved with 0.1 mol L<sup>-1</sup> sodium formate solution. The samples were prepared in a 1:1 water/ethanol mixture and measured in the positive mode. 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 of the compounds were determined comparing their specific optical rotation values with the corresponding values reported in the literature.<sup>6,7,19</sup> Enzymatic reactions were analyzed using Shimadzu LC-10AD or a Shimadzu 20AT equipments with UV detector (190-254 nm) and a Chiralcel® OD-H chiral column (0.46 cm × 25 cm; 5  $\mu$ m); hexane/2-propanol (95:5), 0.5 mL min<sup>-1</sup> flow rate. The Shimadzu LC-10AD® model, equipped with detector photodiode array SPD-M10A, degasser DGU-14A, control center SCL-10A and injector manual Rheodyne® and Shimadzu LC-20AT® model, equipped with detector diode array SPD- M20A, degasser DGU-20A5, control center CBM-20A, automatic injector Sil-20A and oven CTO-20A. Acquisition and data analysis were performed using the application LCSolution/CLASS-VP software. The enantiomeric excesses of azidophenylethanols **11-15** and azidophenyl acetates **16-20** were determined by HPLC analysis employing chiral column with hexane/2-propanol mobile phase. Enantioseparations of azidophenylethanols **11-15** and azidophenyl acetates **16-20** obtained by HPLC analysis are as follow: (*R*-**11**, 35.0 min; *S*-**11**, 33.0 min), (*R*-**12**, 27.0 min; *S*-**12**, 23.0 min), (*R*-**13**, 24.0 min; *S*-**13**, 28.0 min), (*R*-**14**, 21.2 min; *S*-**14**, 23.1 min), (*R*-**15**, 46.0 min; *S*-**15**, 50.0), (*R*-**16**, 22.0 min; *S*-**16**, 27.0 min), (*R*-**17**, 19.0 min; *S*-**17**, 22.0 min), (*R*-**18**, 13.0 min; *S*-**18**, 16.0), (*R*-**19**, 12.0 min; *S*-**19**, 11.4 min) and (*R*-**20**, 37.0 min; *S*-**20**, 42.0 min).

#### General procedures

##### Preparation of ( $\pm$ )- $\beta$ -azidophenylethanols **11-15** and ( $\pm$ )- $\beta$ -azidophenyl acetates **16-20**

The azidoacetophenones **6-10** were obtained from the commercial  $\alpha$ -bromoacetophenones **1-5**, respectively, using NaN<sub>3</sub> in acetone.<sup>29</sup> These compounds were subsequently reduced with NaBH<sub>4</sub> providing the ( $\pm$ )-azidophenylethanols **11-15**.<sup>30</sup> The products were purified by CC over silica gel eluted with *n*-hexane/EtOAc (8:2) and obtained in good

yields (Scheme 1). The ( $\pm$ )- $\beta$ -azidophenylethyl acetates **16-20** were obtained by acetylation of their corresponding ( $\pm$ )- $\beta$ -azidophenylethanols **11-15** using acetic anhydride in pyridine.<sup>15</sup> Products **11-15** were characterized by spectroscopic data which are in agreement with those reported in the literature.<sup>6,7,18-20</sup>

##### Kinetic resolution of ( $\pm$ )-azidophenylethanols **11-15** by immobilized CALB

HPLC grade hexane (10 mL), vinyl acetate (1 mL), immobilized CALB (100 mg, 10,000 propyl laurate units *per* g) and the appropriate ( $\pm$ )-azidophenylethanols **11-15** (1.20, 1.0, 0.8, 1.0, 0.9 mmol, respectively) were added to 50 mL Erlenmeyer flasks. These flasks were sealed using a rubber stopper, and the reaction mixture was stirred in orbital shaker at 32 °C and 130 rpm. The reaction progress was monitored by collecting samples (1.0 mL) according to the time indicated in Table 1, which were analyzed by liquid chromatography with chiral stationary phase. After the reaction proceeds to completion, the immobilized lipase was filtered off. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane/EtOAc (8:2) as eluent yielding the alcohols **11-15** and acetates **16-20**. The attributions of the absolute configuration of the alcohols **11-14** and acetates **16-19** were assigned and compared with the literature values (Table 2).<sup>6,7,19</sup>

##### Preparation of chiral triazole compounds **21-25** by click chemistry reaction

The (*R*)- $\beta$ -azidophenylethanols **11-15** (1.0 mmol), 2-(trimethylsilyl)phenyl triflate (1.5 mmol, 0.45 g), acetonitrile (5 mL) and CsF (3.0 mmol, 0.46 g) were added to a vial (10 mL). The vial was sealed using a cap, and the reaction mixture was stirred for 18-24 h at room temperature. Afterward, a solution of 10% NaHCO<sub>3</sub> (5 mL) was added to the mixture, which was extracted with EtOAc (3 × 10 mL). The organic phase was dried over MgSO<sub>4</sub>. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by CC on silica gel, using a mixture of hexane/EtOAc (7:3) as eluent, yielding the desired products **21-25**. The structures of compounds **21-25** were assigned on the basis of a variety of spectroscopic techniques, namely, according to their IR, and <sup>1</sup>H and <sup>13</sup>C NMR spectra, one-bond (HSQC) and long-range (HMBC) <sup>1</sup>H-<sup>13</sup>C NMR correlation experiments. All compounds **21-25** provided HRMS data that agree with the proposed structures.

(-)-(*R*)-2-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-1-phenylethanol (**21**): [ $\alpha$ ]<sub>D</sub><sup>25</sup> -20.5 (*c* 1.20, CHCl<sub>3</sub>, > 99% ee); mp 130-131 °C; IR (KBr)  $\nu$ /cm<sup>-1</sup> 3217, 2950, 2902, 2849,

**Table 2.** Data of optical rotations for the azidoalcohols **11-14** and **16-19** azido acetates obtained by CALB

Chiral $\beta$ -azidoalcohol	Optical rotation experimental $[\alpha]_D^{25}$	Optical rotation literature <sup>6,1</sup> $[\alpha]_D^{25}$	Chiral $\beta$ -azidoacetate	Optical rotation experimental $[\alpha]_D^{25}$	Optical rotation literature <sup>6</sup> $[\alpha]_D^{25}$
( <i>R</i> )- <b>11</b>	-69.1 ( <i>c</i> 1.6, HCl <sub>3</sub> , > 99% ee)	-89.2 ( <i>c</i> 1.0, CHCl <sub>3</sub> , 98% ee) <sup>6</sup>	( <i>S</i> )- <b>16</b>	+93.1 ( <i>c</i> 1.9, CHCl <sub>3</sub> , > 99% ee)	+89.2 ( <i>c</i> 1.0, CHCl <sub>3</sub> ; 94% ee) <sup>6</sup>
( <i>R</i> )- <b>12</b>	-93.1 ( <i>c</i> 1.9; CHCl <sub>3</sub> , > 99% ee)	-116.9 ( <i>c</i> 1.2, CHCl <sub>3</sub> , 98% ee) <sup>7</sup>	( <i>S</i> )- <b>17</b>	+94.1 ( <i>c</i> 1.2, CHCl <sub>3</sub> , > 99% ee)	+123.7 ( <i>c</i> 1.0, CHCl <sub>3</sub> , 98% ee) <sup>7</sup>
( <i>R</i> )- <b>13</b>	-66.6 ( <i>c</i> 1.1, CHCl <sub>3</sub> , 70% ee)	-77.0 ( <i>c</i> 1.0, CHCl <sub>3</sub> , 90% ee) <sup>6</sup>	( <i>S</i> )- <b>18</b>	+62.4 ( <i>c</i> 1.2, CHCl <sub>3</sub> , > 99% ee)	+93.8 ( <i>c</i> 1.1, CHCl <sub>3</sub> , > 99% ee) <sup>6</sup>
( <i>R</i> )- <b>14</b>	-51.8 ( <i>c</i> 1.0, MeOH, > 99% ee)	-82.5 ( <i>c</i> 1.0, CHCl <sub>3</sub> , > 99% ee) <sup>19</sup>	( <i>S</i> )- <b>19</b>	+55.8 ( <i>c</i> 1.0, MeOH, > 99% ee)	+104.9 ( <i>c</i> 1.0, CHCl <sub>3</sub> , > 99% ee) <sup>6</sup>
( <i>R</i> )- <b>15</b>	49% ee	-	( <i>S</i> )- <b>20</b>	99% ee	-

*c*: concentration.

1594, 1492, 1451, 1426, 1275, 1233, 1189, 1158, 1124, 1071, 1029, 883, 749, 746, 699, 586, 525, 484; <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>)  $\delta$  4.73 (dd, *J* 12.0, 8.0, 1H, CH<sub>2</sub>), 4.82 (dd, *J* 12.0, 4.0, 1H, CH<sub>2</sub>), 5.36 (dd, *J* 8.0, 4.0, 1H, CHOH), 7.28-7.30 (m, 1H, Bt-H\*), 7.36-7.39 (m, 2H, Ph-H), 7.41-7.45 (m, 3H, 2Ar-H and 1H, Bt-H), 7.50 (dt, *J* 8.5, 0.9, 1H, Bt-H), 7.91 (dt, 1H, *J* 8.5, 0.9, 1H, Bt-H); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  55.3, 73.1, 109.8, 119.5, 123.8, 125.5, 126.0, 127.3, 128.4, 133.8, 140.5, 145.5; HRMS (FTMS + pESI) *m/z*, calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>3</sub>O [M]<sup>+</sup>: 240.1131, found: 240.1134; \*Bt-H: benzotriazole hydrogens.

(-)-(*R*)-2-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-1-(4-methoxyphenyl)ethanol (**22**):  $[\alpha]_D^{25}$  43.3 (*c* 1.50, CHCl<sub>3</sub>; > 99% ee); mp 136-137 °C; IR (KBr)  $\nu$ /cm<sup>-1</sup> 3281, 2926, 2839, 1610, 1581, 1510, 1446, 1311, 1263, 1190, 1132, 1003.932, 926, 708; <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>)  $\delta$  3.76 (s, 3H, OCH<sub>3</sub>), 4.68 (dd, *J* 14.3, 8.0, 1H, CH<sub>2</sub>), 4.73 (dd, *J* 14.3, 4.2, 1H, CH<sub>2</sub>), 5.27 (dd, *J* 8.0, 4.2, 1H, CHOH), 6.84 (d, *J* 8.5, 2H, Ar-H), 7.23 (d, *J* 8.4, 2H, Bt-H\*), 7.30 (d, *J* 8.5, 2H, Ar-H), 7.38 (d, *J* 8.4, 1H, Bt-H), 7.49 (d, *J* 8.4, 1H, Bt-H), 7.76 (d, *J* 8.4, 1H, Bt-H); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  55.2, 55.5, 72.7, 110.0, 114.0, 119.2, 123.9, 127.0, 127.2, 132.6, 133.6, 145.1, 159.4; HRMS (FTMS + pESI) *m/z*, calcd. for C<sub>15</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub> [M]<sup>+</sup>: 270.1237, found: 270.1243; \*Bt-H: benzotriazole hydrogens.

(-)-(*R*)-2-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-(4-bromophenyl)ethanol (**23**):  $[\alpha]_D^{25}$  -6.8 (*c* 0.90, CHCl<sub>3</sub>, 70% ee); mp 165-166 °C; IR (KBr)  $\nu$ /cm<sup>-1</sup> 3393, 3059, 2941, 2895, 1494, 1493, 1450, 1407, 1245, 1327, 1231, 1158, 1066, 1007, 875, 858, 820, 756, 735, 538, 510; <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>)  $\delta$  4.68 (dd, *J* 16.0, 8.0, 1H, CH<sub>2</sub>), 4.82 (dd, 1H, *J* 16.0, 4.0, 1H, CH<sub>2</sub>), 5.41 (dd, *J* 8.0, 4.0, 1H, CHOH), 7.24 (d, *J* 8.0, 2H, Ar-H), 7.28 (d, 1H, *J* 8.0, 1H, Bt-H); 7.43-7.50 (m, 4H, 2Ar-H and 2Bt-H\*), 7.87 (d, *J* 8.0, 1H, Bt-H); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  55.4,

72.8, 109.5, 119.5, 124.4, 127.6, 127.7, 131.9, 133.8, 134.5, 139.3, 145.0; HRMS (FTMS + pESI) *m/z*, calcd. for C<sub>14</sub>H<sub>13</sub>BrN<sub>3</sub>O [M]<sup>+</sup>: 318.0236, found: 318.0246; \*Bt-H: benzotriazole hydrogens.

(-)-(*R*)-2-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-1-(4-chlorophenyl)ethanol (**24**):  $[\alpha]_D^{25}$  -34.8 (*c* 1.00, CHCl<sub>3</sub>, > 99% ee); mp 157-158 °C; IR (KBr)  $\nu$ /cm<sup>-1</sup> 3394, 3058, 2948, 2923, 1492, 1454, 1421, 1307, 1222, 1143, 1062, 744, 541, 516; <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>)  $\delta$  4.68 (dd, *J* 16.0, 8.0, 1H, CH<sub>2</sub>), 4.82 (dd, *J* 16.0, 4.0, 1H, CH<sub>2</sub>), 5.41 (dd, *J* 8.0, 4.0, 1H, CHOH), 7.30 (td, *J* 8.3, 1.0, 1H, Bt-H\*), 7.36 (d, *J* 8.0, 2H, Ar-H), 7.41 (d, *J* 8.0, 2H, Ar-H), 7.47 (td, *J* 8.3, 1.0, 1H, Bt-H), 7.53 (dt, *J* 8.3, 1.0, 1H, Bt-H), 7.88 (dt, *J* 8.3, 1.0, 1H, Bt-H); <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  55.7, 72.7, 109.5, 119.5, 124.1, 127.2, 127.4, 129.2, 134.5, 138.7, 138.9, 145.5; HRMS (FTMS + pESI) *m/z*, calcd. for C<sub>14</sub>H<sub>13</sub>ClN<sub>3</sub>O [M]<sup>+</sup>: 274.0741, found: 274.0749; \*Bt-H: benzotriazole hydrogens.

(*R*)-2-(1*H*-benzo[d][1,2,3]triazol-1-yl)-1-(4-nitrophenyl)ethanol (**25**): mp 201-203; IR (KBr)  $\nu$ /cm<sup>-1</sup> 3388, 3107, 3062, 2960, 2921, 2850, 1932, 1801, 1606, 1529, 1344, 1261, 1224, 1159, 1114, 1105, 1068, 869, 802, 773, 740, 694, 538, 509, 439; <sup>1</sup>H NMR (200.1 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  4.92-4.98 (m, 2H, CH<sub>2</sub>), 5.28-5.34 (m, 1H, CH<sub>2</sub>), 7.37 (t, *J* 8.0, 1H, Bt-H\*), 7.51 (t, *J* 8.0, 1H, Bt-H), 7.67 (d, 2H, *J* 8.5, Ar-H), 7.86 (d, *J* 8.2, 1H, Bt-H), 8.00 (d, *J* 8.2, 1H, Bt-H),  $\delta$  8.19 (d, *J* 8.5, 2H, Ar-H); <sup>13</sup>C NMR (50.3 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  59.8, 70.9, 111.4, 118.9, 123.3, 123.8, 127.0, 127.6, 133.7, 138.5, 146.9, 149.8; HRMS (FTMS + pESI) *m/z*, calcd. for C<sub>14</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>3</sub> [M]<sup>+</sup>: 285.0982, found: 285.0987; \*Bt-H: benzotriazole hydrogens.

## Supplementary Information

Supplementary data are available free of charge at <http://jbcbs.sbgq.org.br> as a PDF file.



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