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Candida zeylanoides as whole-cell biocatalyst to perform asymmetric bioreduction of benzophenone derivatives

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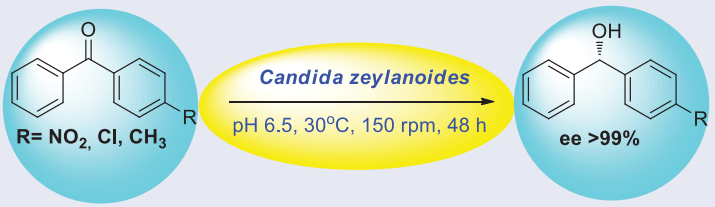
ABSTRACT

Candida zeylanoides P1 was investigated as whole cell biocatalyst for the bioreduction of biaryl prochiral ketones into chiral carbinols, which can be used as pharmaceutical intermediate. Bioreduction of different biaryl ketones was carried out to their corresponding chiral biaryl carbinols such as (*S*)-(4-chlorophenyl) (phenyl) methanol (**2a**), which can be used in the synthesis of L-cloperastine drug, with antitussive, antiepidemic activity and bronchial musculature relaxant characteristics, in gram scale, enantiopure form (>99%) and excellent yields. The selectivity of *C. zeylanoides* P1 in enantioselective reduction of biaryl ketones was not affected by the steric and electronic effects of substrates. The current method demonstrates an encouraging green chemistry approach for the production of biaryl secondary chiral alcohols of pharmaceutical importance in mild, inexpensive and environmentally friendly process. The present study has many benefits since this yeast biocatalyst were successfully applied bioreduction of structurally bulky prochiral substrates, which cannot be reducted by chemical catalysis.

GRAPHICAL ABSTRACT



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Chirality; *Candida zeylanoides*; chiral benzophenone carbinols; enantioselective reduction; (S)-(4-chlorophenyl) (phenyl) methanol

Introduction

The production of enantiomerically pure compounds is very important for the pharmaceutical, agricultural, food and perfume industries.[1] In racemic mixtures, each of enantiomers can have very different effects. The main reason for interest in optically active products is that the enantiomers exhibit different biological activities. While one of the enantiomers in the drug has the desired activity, the other enantiomer can show different and often harmful pharmacological properties, or exhibits serious side effects.

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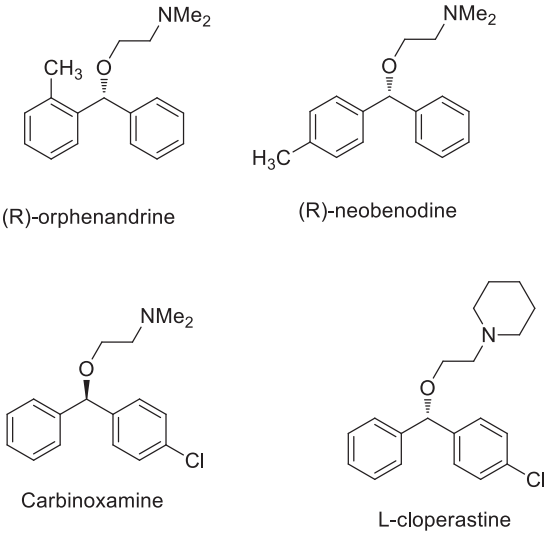


Figure 1. Diarylcarbinol-based drugs.

The two enantiomers may independently have a different therapeutic effect or the combination of both enantiomers may be advantageous for treatment. Diaryl carbinols can use as precursors of numerous biologically and pharmacologically important molecules, such as (*R*)-orphenadrine, (*R*)-neobenodine, (*S*)-cetirizine, carbinoxamine and L-cloperastine, which possesses antitussive and antiedemic activity, also relaxes the bronchial musculature (Figure 1).[2–4] Numerous articles have been published years using various methods to produce enantiopure diaryl carbinols in recent.[5,6] Various chemical approach are employed such as enantioselective reduction of ketones in the presence of chiral catalysts or by nucleophilic addition to the aldehydes, by means of aryl nucleophiles that are generally costly diphenylzinc or aryl zinc reagents obtained *in situ* from aryl boronic acids. However, the enantioselective reduction of biaryl ketones by chemical catalysts have own disadvantages such as limited substrate scope and harsh conditions.[7–9] These drawbacks restrict its application in industrial-scale production. Biocatalysts have many benefits compared to chemical catalysts. Compared with asymmetric chemical processes, biotransformation processes of chiral secondary alcohol production afford several advantages, such as milder reaction operation conditions (ambient pressure and temperature), no need to use toxic chemicals and expensive heavy metal catalysts.[10,11] Biocatalytic methods are typically employed in industrial scale using either the resolution of racemate or asymmetric reduction of prochiral ketones. In resolution of racemate, there is always 50% of the unwanted enantiomer unlike asymmetric reduction which preferably results in the generation of only one enantiomer in high enantiomeric purity and chemical yields.[12] Chiral secondary alcohols can be synthesized by isolated enzyme, but expensive reducing cofactors, such as NADPH, and purification of enzymes are disadvantage for this reaction. These disadvantages limit its use in industrial-scale synthesis.[13,14] When compared to isolated enzymes, whole cell biocatalysts are more advantageous as these biocatalysts are usually cheap and stable. Moreover, the use of whole cell biocatalysts avoids enzyme purification and cofactor addition.[15,16] Also, whole cell biocatalyst is well accepted to be a

safe, economical, and mild reaction conditions to synthesis chiral secondary carbinols.[17,18] Chiral biaryl secondary alcohols are very important intermediates in the synthesis of large number of biologically active molecules and can also be used in the synthesis of drugs.[19–21] At the same time, the alcohol functional group can be easily transformed into the desired functional groups without racemization.[22,23] Biocatalysts have been indicated to be extremely enantioselective in the bio-reduction of a broad range of ketones bearing some bulky groups, furnishing a supplementary way of enantioselective reduction of biaryl prochiral ketones that are difficult with other chemical catalysts.[24–27] Many diaryl ketones used in the scope of this study were reduced with good selectivity by selecting various biocatalysts.[28–30] Although good selectivity was obtained in these studies, it was observed that the conversions were below 30%. Diaryl ketones have been reported previously known as "hard to reduce" substances for the biocatalyst due to large steric hindrances and the like of two aromatic groups.[8,26,31,32] High conversion and selectivity were obtained by asymmetric reduction of diaryl ketones using *Sporobolomyces salmonicolor* and its mutant enzymes however, these results were obtained using expensive pure enzymes and cofactors.[33] In our previous study, it has been found that *C. zeylanoides* P1 isolated from pastirma a fermented Turkish meat product catalyzed the extremely enantioselective bioreduction of prochiral ketones that it was a good biocatalyst for the reduction of prochiral ketones.[34] We envisioned that the *C. zeylanoides* P1 could also reduce sterically bulky biaryl ketones as substrates. Importantly, as food isolates, this biocatalyst has major potential to use confidently for the industrial aims that rise their value as biocatalyst.

Herein, we reported that a variety of biaryl ketones were enantioselectively reduced by this biocatalyst in gram scale using optimized conditions of *C. zeylanoides* P1 as a yeast whole cell biocatalyst. Besides, we have shown that *C. zeylanoides* P1 can be used as a new biocatalyst for synthesis of chiral bulky secondary alcohols on gram scale. Also, (*S*)-(4-chlorophenyl) (phenyl) methanol (**2a**), which can be used in the synthesis of *L*-cloperastine drug, with antitussive, antiepidemic activity and bronchial musculature relaxant, was obtained in gram scale, enantiopure form (>99%) and excellent yields.

Results and discussion

The asymmetric reduction of prochiral biaryl ketones to the corresponding chiral biaryl secondary alcohols is one of the most widespread reactions in organic chemistry.[35] From synthetic bio-organic perspective, it is essential to optimize bioreduction conditions that improve the efficiency of the biocatalyst to perform enantiomerically pure alcohols.[36] We have successfully optimized these asymmetric reduction conditions using model substrate acetophenone (1 mmol) with *C. zeylanoides* P1 biocatalyst and in all reactions numbers of the *C. zeylanoides* P1 cells were similar determined by OD600 measurements and plating to YPD agar.[34] The optimum condition for the asymmetric bioreduction of acetophenone to (*S*)-1-phenyl ethanol was obtained at pH of 6.5, temperature of 30 °C, incubation period of 48 h, and agitation speed of 150 rpm.[34] Under these optimized conditions, the reduction activity of *C. zeylanoides* P1 for bioreduction of substrates were also studied using different concentrations of **1–3** (0.5, 1 and 1.5 g/L). The full conversion of substrates was obtained with 0.5 and 1 g/L, however the

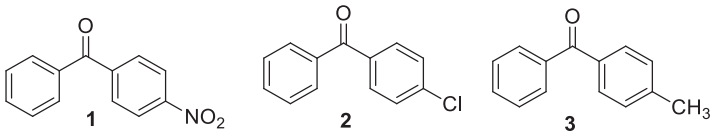
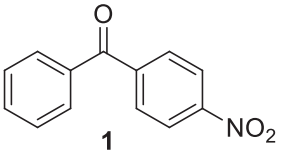
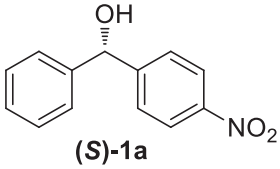
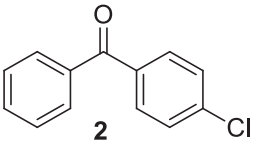
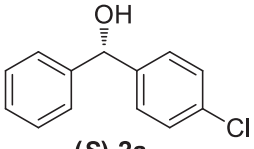
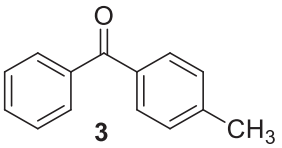
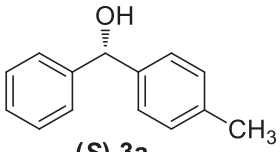


Figure 2. Biarly ketones used in this study.

conversions were obtained below 99% when 1.5 g/L of the substrates used. This may be due to the reduction in the enzyme catalytic activity, suggesting substrate toxicity as reported previously.[37] Hence 1 g/L substrate concentration was chosen for the bioreduction. Under these optimized conditions, asymmetric reductions of different biaryl prochiral bulky-bulky ketones (Figure 2) were carried out on gram scale (Table 1). In view of the significant results obtained previously study[34], we then investigated the efficiency and stereoselectivity of bioreduction of a series of benzophenone derivatives bearing different electron-withdrawing and electron-donating groups as substituents on the aromatic ring (Table 1). As seen in Table 1, bioreduction of substituted benzophenones **1–3** by suspension cell cultures of *C. zeylanoides* P1 gave the corresponding chiral alcohols **1a–3a** in excellent ee (>99%) with 100% conversion. In the literature, the (*S*)-(4-nitrophenyl)(phenyl)methanol compound was synthesized in high enantiomeric purity by the asymmetric reduction of the corresponding prochiral ketone using chemical catalyst and by the asymmetric addition of the corresponding groups to the aldehyde.[38–40] The asymmetric reduction of (4-nitrophenyl) (phenyl) methanone **1** with pure enzyme biocatalyst was carried out to corresponding chiral alcohols in 97% ee and small scale.[27] In our study, the bioreduction of substrate **1** using *C. zeylanoides* P1 as a whole cell biocatalyst was reduced to the (*S*)-carbinol **1a** in >99% ee and 89% yield in the reaction conditions of pH 6.5, 30 °C, 150 rpm and 48 h. Diaryl ketone 4-chloro benzophenone **2** and 4-methyl benzophenone **3** are important prochiral bulky-bulky ketones for the production of diaryl carbinols, which are important precursors for the production of pharmaceutically interesting compounds.[41] In the literature, in the presence of plant and microbial biocatalysts (*R*)-(4-chlorophenyl) (phenyl)methanol was obtained with a long reaction time in a greater than 99% selectivity, conversion and a small scale.[41] In the present study, the *C. zeylanoides* P1 mediated gram-scale bioreduction of substrate **2** furnished 91% **(*S*)-2a** carbinol with >99% enantiomeric purity in the optimized conditions. In the literature, it has been reported that the pure enzyme was used as biocatalyst, and the substrate **3** is reduced to (*R*)-phenyl (*p*-tolyl) methanol in 92% ee and small scale.[33] In this study, the bioreduction of substrate **3** using *C. zeylanoides* P1 was performed and furnished >99% enantiopure (*S*)-phenyl (*p*-tolyl)methanol, **(*S*)-3a** in 93% yield. These results show that different electron withdrawing groups (NO_2, Cl) and electron donating group (CH_3) did not exhibit any effects on the substrate conversions and product ee. The configurations of the obtained products have occurred according to the Prelog rule, the pro-*R* hydride of NADPH is given to the *Re* face of the prochiral ketone to produce on *S* alcohol.[42] This biocatalyst provides a sustainable alternative way for the production of these pharmaceutically important molecules. By using various of prochiral ketones at high concentration as substrates, the *C. zeylanoides* P1 is successfully employed for efficient synthesis of enantiomerically pure chiral alcohols with ee value more than 99%, indicating that the *C. zeylanoides* P1 is potential for further catalytic applications.

Table 1. Asymmetric bioreduction of ketones **1–3** using *C. zeylanoides* P1.

Substrate	Product[a]	ee [%][b]	Yield [%][c]
 **1**	 **(*S*)-1a**	99	89
 **2**	 **(*S*)-2a**	99	91
 **3**	 **(*S*)-3a**	99	93

[a]Configurations were assigned on the basis of the comparison of the rotation sign with literature data.
[b]Determined by chiral HPLC.
[c]Isolated yield.

Conclusion

There is striking attention in whole cells biocatalysts in the pharmaceutical, agrochemical and chemical industries for their ability to produce useful chiral biaryl carbinol. In this study, we have seen that *C. zeylanoides* P1 effectively catalyzed the enantioselective reduction of biaryl aromatic ketones with excellent enantiomeric purity and yield to give chiral carbinols. Compared with the previous reports, biarly substrate **1–3** was reduced to **1a–3a** in a perfect conversion, yield and ee.[27,33,41] The results approved the suitability of *C. zeylanoides* P1 as a precious whole cell biocatalyst for the production of chiral biaryl carbinols in the drug industry. Furthermore, this study demonstrates the effective synthesis of biaryl carbinols by the yeast biocatalyst and biaryl ketones **1–3** was the "easy-to-reduce" substrate for *C. zeylanoides* P1. Thus, in the framework of green chemistry, this study has indicated a hopeful application of yeast biocatalyst *C. zeylanoides* P1 in the production of optically pure biaryl carbinols in simple, inexpensive and environmentally friendly conditions.

Experimental section

General

The chemicals and solvents used in this study were purchased from Sigma-Aldrich (Sigma-Aldrich Corporate, St. Louis, MO USA) (purity of >99%). Thin-layer chromatography (TLC) was used for the monitoring of the reactions and performed by using TLC plates (aluminum, silica gel 60 F254 Merck, 0.25 mm). Purification of chiral secondary alcohols were performed by column chromatography filled with silica gel

(0.063–0.2 mm) and the product was eluted with a mixture of hexane: ethyl acetate (90:10, v/v). HPLC analysis was performed on an Agilent 1260 systems equipped with chiral column (Daicel Chemical Industries, Ltd, France), UV and chiral detector (Ibz Messtechnik Gmbh). The racemic **1b–3b** alcohols were obtained by reducing the **1–3** with $NaBH_4$ in methanol at room temperature. Optical rotation was measured with a Bellingham + Stanley, ADP220, 589 nm spectropolarimeter. ^1H and 13C NMR spectra were recorded on Bruker 400 MHz spectrometer in $CDCl_3$.

Yeast strain and culture conditions

Candida zeylanoides strain used in this study was isolated previously from pastirma a fermented Turkish meat product.[34,43] Yeast strain was stored their glycerol stock in −80 °C. YPD medium contains 1% yeast extract, 1% peptone from casein and 2% glucose. In all reactions, the number of yeast cells were determined before and after the reactions by OD600 measurements and plating to YPD agar.

General procedure for bioreduction of substrate 1–3

Yeast strain was propagated from their glycerol stocks by inoculation to 10 mL YPD medium followed by 48 h growth at 30 °C. From this cultures, exponentially grown yeast cell was inoculated to 50 mL sterilized fresh YPD culture medium as working volume in 250 mL Erlenmeyer flask at 10% concentration and adjusted with 1M HCI to 6.5 and shaken 2 h, then 100 mg substrate (**1–3**), which is dissolve in 2% ethanol, was directly added to the medium and incubated on a shaker (150 rpm) at 30 °C for 48 h. At the end of the incubation period, the cells were separated by centrifugation at 6000 × g for 5 min at 4 °C and the supernatant saturated with NaCl, then extracted with CH_2CI_2. Dichloromethane extracts were combined and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, NMR analysis was used for the identification of the crude product followed by purification by column chromatography on silica gel using hexane: ethyl acetate as eluents (90:10). The absolute configuration was determined by the sign of specific rotation. The conversion was determined by chromatography on a chiral HPLC after filtering the crude products with a column containing small silica gel and comparing the alcohol peaks with the ketone peak. The HPLC analysis conditions of the ketones were the same as those of the corresponding alcohols. Enantiomeric excess of the products was determined by HPLC analysis using chiral column and the yields were determined after purification of the crude product by column chromatography (supporting information).

Gram scale asymmetric reduction of 1a–3a

The gram scale asymmetric reduction of substrate **1–3** was performed as follows. Yeast strain was propagated from their glycerol stocks by inoculation to 10 mL YPD medium (1% yeast extract, 1% peptone from casein, 2% glucose) followed by 48 h growth at 30 °C. From this cultures, exponentially grown yeast cell was inoculated to 500 mL sterilized fresh YPD culture medium as working volume in 2.5 L Erlenmeyer flask at 10%

concentration and pH was adjusted with 1M HCl to 6.5 and shaken 2 h, followed by the addition of substrate **1–3** (1 g), which is dissolve in 2% ethanol, to the medium and incubated on a shaker at 30 °C, 150 rpm for 48 h. 2% concentration of ethanol did not inactivate the yeast activity. The supernatant of the medium obtained and saturated with NaCl, then extracted with CH_2Cl_2. The dichloromethane extract washed with water and dried over saturated Na_2SO_4. After removal of the solvent under reduced pressure, the secondary chiral alcohols were isolated, purified and characterized as described above. The configuration of the product was determined by the sign of the specific rotation and comparison with the literature data. Conversion of all substrates were found to be 100%.

Acknowledgements

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Data availability

The data that support the findings of this study are openly available in https://doi.org/10.1002/cbdv.201700121, reference number.[34]

Spectroscopic datas, copies of ^{1}H, ^{13}C NMR spectra, substrate, chiral, and racemic HPLC chromatograms of **1a–3a** related to this article can be found at supplementary data.

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