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ORIGINAL PAPER

Asymmetric reduction of aromatic heterocyclic ketones with bio-based catalyst *Lactobacillus kefiri* P2

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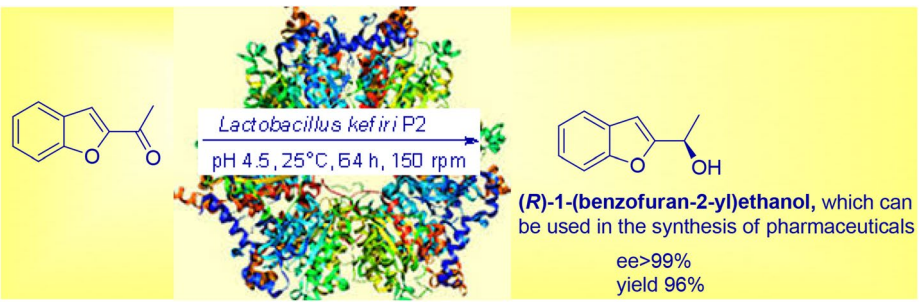
Abstract

Chiral heterocyclic secondary alcohols have received much attention due to their widespread use in pharmaceutical intermediates. In this study, *Lactobacillus kefiri* P2 biocatalysts isolated from traditional dairy products, were used to catalyze the asymmetric reduction of prochiral ketones to chiral secondary alcohols. Secondary chiral carbinols were obtained by asymmetric bioreduction of different prochiral substrates with results up to > 99% enantiomeric excess (ee). (*R*)-1-(benzofuran-2-yl)ethanol **5a**, which can be used in the synthesis of pharmaceuticals such as bufuralols potent nonselective β-blockers antagonists, Amiodarone (cardiac anti-arrhythmic), and Benziodarone (coronary vasodilator), was produced in gram-scale, high yield and enantiomerically pure form using *L. kefiri* P2 biocatalysts. The gram-scale production was carried out, and 9.70 g of ***(R)*-5a** in enantiomerically pure form was obtained in 96% yield. Also, production of ***(R)*-5a** in terms of yield and gram scale through catalytic asymmetric reduction using the biocatalyst was the highest report so far. This is a cost-effective, clean and eco-friendly process for the preparation of chiral secondary alcohols compared to chemical processes. From an environmental and economic perspective, this biocatalytic method has great application potential, making it a green and sustainable way of synthesis.

Graphical Abstract



Keywords Asymmetric reduction · *Lactobacillus kefiri* · Chiral alcohol · Biocatalytic transformation · (*R*)-1-(benzofuran-2-yl)ethanol

Introduction

Chirality has become important in various industries such as, pharmaceutical, agrochemical and fine chemical. Chiral aromatic and hetero aromatic alcohols are widely used for synthetic procedures in the pharmaceutical and fine-chemical industries, owing to their stable structure (Quaglia et al. 2013). The functional groups of chiral secondary alcohols can be easily transformed into other functional

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groups without racemation (Şahin and Dertli 2019). Enantiopure 1-phenylethanol and its derivatives are useful chiral building blocks or intermediates for synthesis of various complex molecules used in a spectrum of industries. For instance, (*S*)-1-phenyl ethanol, 2-naphthyl ethanol and (*S*)-1-(3-methoxyphenyl) ethanol are used as chiral auxiliaries in chemical and pharmaceutical industries (Lou et al. 2009; Mangas-Sánchez et al. 2009). On the other hand, important examples of heteroarylmethanols are (*R*)-neobenodine, (*R*)-orphenadrine, (*S*)-cetrazine, (*S*)-carbinoxamine, (*S*)-duloxetine, (1*R*,2*S*)-mefloquine, HIV reverse-transcriptase inhibitor furo[2,3-c]pyridine thiopyrimidine ether, *β*-blocker 2-(2-tert-butylamino-1-hydroxyethyl)benzofuran and analgetic (*S*)-phenyl(pyridin-2-yl)methanol (Şahin et al. 2019a, b). Enantiopure N-heteroaryl methanols, such as (*R*)-1-(pyridin-2-yl)ethanol **(1a)**, are widely used in synthetic organic and medicinal chemistry as key intermediates for the synthesis of various pharmaceutical products (Nian et al. 2019). The (*R*)-1-(furan-2-yl)ethanol **(2a)** is valuable structural motif, widely used in the total synthesis of numerous pharmaceutical and natural product such as Landomycins A, E (Zhou and O'Doherty 2008), (−)-Angiopterlactone B (Thomson et al. 2017), and (+)- and (−)-*cis*-Osmundalactone (Blume et al. 2016). Enantioenriched chiral aryl heteroaryl alcohols (*R*)-phenyl(thiophen-2-yl)methanol **(3a)** and (*S*)-phenyl(pyridin-2-yl)methanol **(4a)** are significant precursors in the synthesis of numerous pharmaceuticals, and agrochemicals, such as bepotastine besilate (Ohnmacht et al. 1971), carbinoxamine (Salvi et al. 2009), and (*R,S*)-mefloquine (Corey and Helal 1996; Nian et al. 2019). Benzofuran-based structures, such as (*R*)-1-(benzofuran-2-yl)ethanol **(5a)**, are significant synthetic building blocks in the manufacturing of pharmaceuticals such as bufuralols potent nonselective β-blockers antagonists, Amiodarone (cardiac anti-arrhythmic), and Benziodarone (coronary vasodilator) (Goudarshivannanavar et al. 2009). Antifungal and antibacterial properties of various benzofuran carbinol derivatives were investigated. At the same time, such compounds have found wide application area in the cosmetic industry and chemical pesticides (Ryu et al. 2010). Molecules contained piperonyl ring, such as (*S*)-1-(benzo[d][1,3]dioxol-5-yl)ethanol **(6a)**, are found in the skeleton of natural products such as podophylltoxin and diphyllin, which have been reported to exhibit biological activity such as anticancer (Oliveira et al. 2010), anticonvulsant (Prasanthi et al. 2013; Aboul-Enein et al. 2012), antiamoebic (Wani et al. 2012), antiproliferactive (Alizadeh et al. 2010), antiviral (Yeo et al. 2005), antitumor properties (Feng et al. 2009).

Different chemical processes are used to prepare secondary alcohols such as enantioselective crystallization, electrode reduction, chromatography separation and asymmetric reduction of prochiral ketone using different chiral specific catalysts that are derived from transition metals such as Rh-complexes with different nitrogen containing compounds, metal–ligand complexes, chiral Lewis acid and oxazaborolidine (Yadav and Devendran 2012a, b; Touchard et al. 1999; Mikhailine and Morris 2010; He et al. 2014). However, there are several drawbacks associated with chemical processes such as requirement of expensive chiral ligands and hazardous metals, harsh conditions, low conversion and low enantioselectivity, and formation of by-products (Şahin and Dertli 2017; Shrivas and Pratap 2019). Various biocatalytic approaches for synthesis of enantioselective chiral secondary alcohols have been introduced as alternatives to chemical approaches (Matsunami et al. 2018). Biocatalytic processes can offer highly selective, environmentally benign and energy effective solution for production of optically active compounds. They have advantages such as mild reaction conditions, no need of tedious protection/de-protection steps, less or absence of by-product formation and they can exhibit high chemo-, regio- and stereo-selectivity (Ni and Xu 2012; Muñoz Solano et al. 2012; Şahin 2020). These biocatalysts have two procedures, such as direct asymmetric reduction of ketones or resolution of racemic alcohols. However, enzymatic resolution was limited by 50% theoretical yield. Therefore, a suitable biocatalyst that can be used to production of chiral alcohol is more advantageous. Enantioselective bioreduction can be carried out using either isolated enzymes or whole cells. Whole-cell biocatalysts are advantageous as they are generally inexpensive and more stable. They contain multiple dehydrogenases that are able to accept a broad range of unnatural substrates. All enzymes and co-factors are well protected within their natural cellular environment. Moreover, the use of whole-cell biocatalysts avoids enzyme purification and cofactor addition (Yu et al. 2018). Chemical chiral reductants are used limited in the commercial production because of low chiral selectivity and costly (Yılmaz et al. 2017). Therefore, different biocatalytic approaches for production of enantioselective chiral secondary alcohols have been introduced as alternatives to chemical approaches like whole-cell or purified enzymes (Yadav and Devendran 2012a, b; Wu et al. 2007; Schmidt et al. 2017; Şahin et al. 2019a, b). Biocatalytic reduction seems to be the most potential and competitive industrialization process, which is reflected in the application of some important products. It has been reported that the chiral compounds produced by biocatalytic reduction accounted for 20% of the total chiral alcoholic intermediates in industrial products (Honda et al. 2017). Asymmetric bioreduction of prochiral ketones via biocatalysts is one of the most encouraging and simple routes to production of enantiomerically pure secondary alcohols. Although there are many studies in the literature involving asymmetric reduction of heteroaromatic substrates with chemical catalysts, there are limited studies on the reduction of these substrates with biocatalysts. Therefore, it is very important to develop new biocatalysts

that can be reduced heteroaromatic substrates as an asymmetric. In the literature, pure alcohol dehydrogenase enzyme (ADH) isolated from *L. kefiri* was used catalysts for asymmetric reduction of aromatic ketones and different prochiral ketones to corresponding chiral secondary alcohols with high ee and conversion (Weckbecker and Hummel 2006). Ethyl (*S*)-4-chloro-3-hydroxybutanoate was obtained with high ee and yield using *L. kefiri* (Amidjojo and Weuster-Botz 2005). (2,5)-hexanedione was reduced to (5R)-hydroxyhexane-2-one with > 99% ee using with whole-cell immobilized *L. kefiri* (Tan et al 2006). These studies show that *L. kefiri* is an important biocatalyst. However, to our knowledge, the use of *L. kefiri* for asymmetric reduction in the hetero aromatic ketones has not been investigated yet.

The aim of this study is to investigate the catalytic activity of *L. kefiri* P2 in asymmetric reduction of hetero aromatic ketones. In our previous work, *L. kefiri* P2 was demonstrated effective biocatalysts for the asymmetric reduction of aromatic ketones (Baydaş et al. 2020). Herein, we report on the application of *L. kefiri* P2 for the synthesis of heterocyclic aromatic secondary alcohols. Moreover, to the best of our knowledge, it is the first report that ***(R)*-5a** was synthesized as enantiopure form using biocatalyst in the highest yield and highest gram. The present study provides a practical approach for producing ***(R)*-5a**, which can meet the demand for industrial green production of this heterocyclic chiral alcohol. The effect of the steric properties of the hetero aromatic ketones on the bioreaction catalyzed by *L. kefiri* P2 is also discussed.

Experimental

Materials

Chemicals

MRS, which is growth medium of bacteria, solvents and substrate were purchased from Fluka and Aldrich. Purification of **1a–6a** were carried out by column chromatography and the alcohols were obtained using ethyl acetate/hexane: (10:90, v/v) solvent mixture. TLC was used for checked the progress of reaction, using ethyl acetate/hexane (10:90, v/v) as a mobile phase. Racemic alcohols **1a–6a** as a reference sample was obtained by reducing the substrate with $NaBH_4$ in the CH_3OH at room temperature. Agilent 1260 HPLC system, which have UV and chiral detector, was used for the HPLC analysis of substrate and product. The product characterization was determined by Bruker NMR spectrometer (Bruker Ltd., Germany). Bellingham + Stanley (ADP220, 589 nm) spectropolarimeter was used for the optical rotation of the product. The conversion rate was calculated by comparison of the ketone peak with the alcohol peak after HPLC analysis of the crude product.

Culture medium and bacterial strain

Lactobacillus kefiri P2 strain used in this study was previously isolated from kefir and stored at − 80 °C in glycerol and this strain was grown in MRS broth as described previously (Baydaş et al. 2020).

General procedure for asymmetric bioreduction

Lactobacillus kefiri P2 was added from its glycerol stock by inoculation to 10 mL MRS mixture ($MgSO_4 \cdot 7H_2O$ 11.5% (w/v), K_2HPO_4 2 g/L, pepton [Oxoid] 10 g/L, yeast extract 2% glucose, [Difco] 5 g/L, $C_2H_3NaO_2 \cdot 3H_2O$ 5 g/L, salt solution [$MgSO_4 \cdot 7H_2O$ 11.5% (w/v), triamonium citrate 2 g/L], Tween 80 1 mL/L) followed by 48 h growth at 37 °C. From this mixture, 1 mL bacterial cell was inoculated to 100 mL sterilized MRS mixture in 250 mL Erlenmeyer flask and then pH was adjusted to 4.5 by 1 M HCl (approximately 1 mL). Following the 2 h of incubation, 1 mmol of **1–6** were added directly to the reaction medium and the reaction was stirred at 25 °C for 64 h under agitation at 150 rpm. After the catalytic reaction was complete, the supernatant was separated with centrifuged. The aqueous phase was saturated with solid NaCl and extracted with dichloromethane (2 × 100 mL). The organic phase back-extracted with brine (50 mL). After the organic phase was combined, they were dried over anhydrous Na_2SO_4 and filtered to remove the salt. The organic solvent was removed in a vacuum and the crude product was characterized by NMR analysis. The crude product was purified using column chromatography with mixture of hexane: ethyl acetate (90:10, v/v) solvent.

Gram scale production of *(R)*-5a

The gram scale asymmetric bioreduction of ketone **5** was performed as follows. *L. kefiri* P2 was added from its glycerol stock by inoculation to 10 mL MRS mixture followed by 48 h growth at 37 °C. Then this 10 mL starting culture was inoculated to 1 L sterilized MRS mixture in 5 L Erlenmeyer flask and incubation for 2 h under optimization conditions. Then the pH of the mixture was adjusted to 4.5 by 1 M HCl (approximately 2 mL). Following the 2 h of incubation, substrate **5** (10 g) was added directly as the solid to the mixture and incubated on an orbital shaker at 25 °C, 150 rpm for 64 h. At the end of the incubation period, the cell was separated by centrifugation at 6000×*g* for 5 min at 4 °C. The aqueous phase was saturated with solid NaCl and extracted with dichloromethane (2 × 600 mL). The organic phase back-extracted with brine (100 mL). After the organic phases were combined, they were dried over anhydrous

Na_2SO_4 and filtered to remove the salt. The organic solvent was removed in a vacuum and the crude product was characterized by NMR analysis. After removal of the solvent under reduced pressure, the crude product was purified on a 40 cm column containing 50 g silica gel and eluted using hexane: ethyl acetate (90:10, v/v) to afford the product. As a result of purification, 9.7 g of ***(R)*-5a** was obtained in 96% yield.

(*R*)-1-(pyridin-2-yl)ethanol (1a) (Wu et al. 2016) Colorless oil, ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 8.49$ (d, $J = 4.8$ Hz, 1H), 7.67 (t, $J = 7.6$ Hz, 1H), 7.27 (d, $J = 7.9$ Hz, 1H), 7.17–7.14 (m, 1H), 1.86 (q, $J = 6.5$, 6.4 Hz, 1H), 1.47 (d, $J = 6.5$ Hz, 3H);^{13}C-NMR (100 MHz, $CDCl_3$) $\delta = 163.2$, 148.1, 136.8, 122.2, 119.8, 68.9, 24.2; $[\alpha]_D^{25} = 19.5$ (c 0.52, CH_2Cl_2), 93% ee; Lit.$[\alpha]_D^{25} = 20.8$ (c 0.52, CH_2Cl_2, 99% ee for *R* enantiomer) (Wu et al. 2016); HPLC condition of product, Chiralcel OD-H column, 230 nm, flow rate: 0.6 mL/min, *i*-PrOH/*n*-hexane 3:97, t_R (*R*) 20.8, (*S*) 24.2 min. HPLC analysis condition of ketone **1** is the same as alcohol ***(R)*-1a** and retention time of substrate was determined as 9.4 min.

(*R*)-1-(furan-2-yl)ethanol (2a) (Kang and Shin 2017) Pale yellow oil, ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.36$ (dd, $J = 1.8$, 0.7 Hz 1H), 6.31 (dd, $J = 3.2$, 1.8 Hz 1H), 6.21 (d, $J = 3.2$ Hz 1H), 4.86 (q, $J = 6.4$ Hz 1H), 1.20 (s, 1H, (OH)), 1.52 (d, $J = 6.6$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) $\delta = 157.6$, 141.9, 110.1, 105.1, 63.6, 21.2; $[\alpha]_D^{25} = 7.69$ (c 0.9, CH_2Cl_2), 95% ee; Lit.$[\alpha]_D^{25} = 7.86$ (c 0.9, $CHCl_3$, % 97 ee for *R* enantiomer) (Kang and Shin 2017); HPLC condition of product, Chiralcel AS-H column, 220 nm, flow rate: 1.0 mL/min, *i*-PrOH/*n*-hexane 1:99, t_R (*R*) 46.4, (*S*) 40.6 min. HPLC analysis condition of ketone **2** is the same as alcohol ***(R)*-2a** and retention time of substrate was determined as 18.1 min.

Phenyl(thiophen-2-yl)methanol (3a) (Wang et al. 2017) White solid, M.p: 51–53 °C ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.47$–7.26 (m, 6H), 6.96–6.88 (m, 2H), 6.06 (d, $J = 3.9$ Hz, 1H), 2.42 (d, $J = 3.9$ Hz, 1H (OH)); ^{13}C-NMR (100 MHz, $CDCl_3$) $\delta = 148.1$, 143.1, 128.5, 128.0, 126.4, 126.3, 125.4, 124.9, 72.4; $[\alpha]_D^{25} = 0$ (c 1.0, $CHCl_3$), 0% ee; HPLC condition of product, Chiralcel OD-H column, 220 nm, flow rate: 0.8 mL/min, *i*-PrOH/*n*-hexane 8:92, t_R (*R*) 18.1, (*S*) 16.6 min. HPLC analysis condition of ketone **3** is the same as alcohol **3a** and retention time of substrate was determined as 9.6 min.

(*S*)-phenyl(pyridin-2-yl)methanol (4a) (Maerten and Agbossou-Niedercorn 2008) White solid, M.p: 72–74 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 8.56$–8.54 (m, 1H), 7.63–7.59 (m, 1H), 7.40–7.27 (m, 5H), 7.20–7.15 (m, 1H), 5.76 (s, 1H), 5.38 (bs, 1H (OH)); ^{13}C-NMR (100 MHz, $CDCl_3$) $\delta = 160.9$, 147.8, 143.2, 136.8, 128.6, 127.8, 127.1, 122.4, 121.3, 75.0; $[\alpha]_D^{25} = 21.5$ (c 1.0, $CHCl_3$), 43% ee; Lit.$[\alpha]_D^{25} = 35.0$ (c 1.0, $CHCl_3$, %70 ee for *S* enantiomer) (Maerten and Agbossou-Niedercorn 2008); HPLC condition of product, Chiralcel AD column, 254 nm, flow rate: 0.8 mL/min, *i*-PrOH/*n*-hexane 10:90, t_R (*R*) 15.9, (*S*) 19.8 min. HPLC analysis condition of ketone **4** is the same as alcohol ***(S)*-4a** and retention time of substrate was determined as 9.3 min.

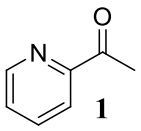
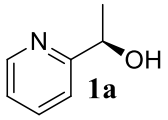
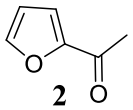
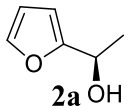
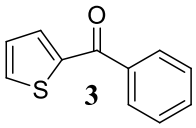
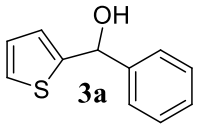
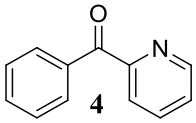
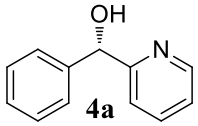
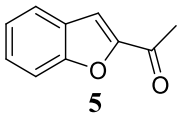
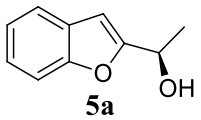
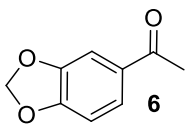
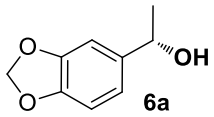
(*R*)-1-(benzofuran-2-yl)ethanol (5a) (Sokeirik et al. 2007) Light yellow oil, ^{1}H-NMR (400 MHz, $CDCl_3$)) $\delta = 7.55$–7.52 (m, 1H), 7.48–7.44 (m, 1H), 7.29–7.19 (m, 1H), 7.24–7.20 (m, 1H), 6.61 (s, 1H), 5.02 (q, $J = 6.5$, Hz, 1H), 2.19 (bs, 1H (OH)), 1.64 (d, $J = 6.5$, Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) $\delta = 160.2$, 154.7, 128.1, 124.2, 122.8, 121.1, 111.2, 101.8, 64.2, 21.4; $[\alpha]_D^{25} = 23.5$ (c 0.53, $CHCl_3$), > 99% ee; Lit.$[\alpha]_D^{25} = 19.8$ (c 0.53, $CHCl_3$, %84 ee for *R* enantiomer) (Sokeirik et al. 2007); HPLC condition of product, Chiralcel OD-H column, 254 nm, flow rate: 0.5 mL/min, *i*-PrOH/*n*-hexane 1:99, t_R (*R*) 72.8, (*S*) 68.8 min. HPLC analysis condition of ketone **5** is the same as alcohol ***(R)*-5a** and retention time of substrate was determined as 19.4 min.

(*S*)-1-(benzo[d][1,3]dioxol-5-yl)ethanol (6a) (Şahin 2018) Colorless oil, ^{1}H-NMR (400 MHz, $CDCl_3$ $\delta = 6.89$–6.75 (m, 3H), 5.94 (s, 2H), 4.81 (q, $J = 6.4$, Hz, 1H), 1.82 (bs, 1H, (OH)), 1.45 (d, $J = 6.4$ Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) $\delta = 148.0$, 147,1, 140.2, 118.9, 108.3, 106.3, 101.1, 70.5, 25.4; $[\alpha]_D^{20} = -33.9$ (c 1.0, $CHCl_3$), 73% ee; Lit.$[\alpha]_D^{20} = 46.5$ (c 1.0, $CHCl_3$) for 99% ee for *R* enantiomer) (Şahin 2018), HPLC condition of product, Chiralcel OD column, 210 nm, flow rate: 1.0 mL/min, *i*-PrOH/*n*-hexane 5:95, t_R (*R*) 18.7, (*S*) 16.8 min. HPLC analysis condition of ketone **6** is the same as alcohol ***(S)*-6a** and retention time of substrate was determined as 10.0 min.

Results and discussion

In this study, the biocatalytic reactions were carried out using 1 mmol substrates (**1–6**) under optimized conditions which is obtained in the previous study (Table 1). In our previous study, asymmetric reduction reaction conditions were optimized using the model substrate acetophenone with *L. kefiri* P2 and optimization conditions were obtained as pH 4.5, time 64 h, temperature 25 °C, agitation speed 150 rpm (Baydaş et al.2020). The catalytic activity of *L. kefiri* P2 on heteroaromatic ketones (1–6) was investigated and compared to the literature (Table 1). *L. kefiri* P2 effectively catalyzed the reduction of **1** to ***(R)*-1a** with 93% ee and satisfactory conversion (56%) (Table 1, entry 1). In the literature, (*S*)-**1a** was reported to be synthesized in small scale in high enantiomeric purity by asymmetric reduction of 2-acetylpyridine **1** using expensive pure enzyme and cofactor (Yanga et al. 2008; Ni et al. 2011). However, to our

Table 1 Asymmetric reduction of prochiral ketones (**1–6**) with novel *L. kefiri* P2 biocatalyst

Entry	Substrate	Product	ee (%)[a,b]	Conversion(%)[c]	Yield (%)[d]
1	 **1**	 **1a**	93 (*R*)	56	52
2	 **2**	 **2a**	95 (*R*)	99	95
3	 **3**	 **3a**	Racemic	27	24
4	 **4**	 **4a**	43 (*S*)	8	6
5	 **5**	 **5a**	> 99 (*R*)	> 99	96
6	 **6**	 **6a**	73 (*S*)	98	95

[a]Determined by HPLC using a chiral column

[b]Determination of absolute configuration was carried out by comparison of the sign of optical rotation relative to the values in the literature

[c]The conversions were determined by chiral HPLC

[d]Isolated yield

knowledge, the synthesis of ***(R)*-1a** with biocatalyst has not been known yet. The asymmetric reduction of the **1** with seed *adzuki bean* was carried out to corresponding chiral seconder alcohol ***(S)*-1a** in > 81% ee with 44% conversion and small scale (Xie et al. 2009). In the literature, synthesis of ***(R)*-1a** at high ee was carried out using chemical catalyst (Utepova et al. 2018; Zhou et al. 2012). High conversion (99%) and ee (95%) were obtained in asymmetric reduction of **2** with whole-cell *L. kefiri* P2 (Table 1, entry 2). The enantioselective reduction of **2** with alcohol dehydrogenase enzyme was carried out to (***S***)-**2a** in 99% ee with 85% yield (Blume et al. 2016). Asymmetric reduction of aryl heteroaryl ketones are generally carried out using toxic metals, such as Ru, Rh, Ir, and Pd, as efficient catalysts (Ling et al. 2019). The *L. kefiri* P2 mediated bioreduction of substrate **3** was reduced to racemic **3a** with 27% conversion and 24% yield (Table 1, entry 3). The asymmetric reduction of **3** to the (***S***)-**3a** with *L. paracasei* BD101 as biocatalyst had been previously reported for the first time by Sahin and co-workers in the enantiopurepure form, high yield, and gram-scale (Şahin and Dertli 2019). Substrate **4** was reduced to (***S***)-**4a** with *L. kefiri* P2 in 43% ee and 8% conversion (Table 1, entry 4). In the literature, in the presence of biocatalysts such as, carbonyl reductase enzyme, isolated fungal strains, *Camellia sinensis* cell culture, and cell cultures of *Nicotiana tabacum*, **4a** was obtained with 99%, 91%, 86%, 48% ee respectively, in good yields and small scale (Li et al. 2009; Pal et al. 2012; Takemoto and Tanaka 2001; Takemoto et al. 1995). Additionally, substrate **4** was reduced to (***R***)-**4a** with 19% ee and 92% yield using *Catharanthus Roseus* (Takemoto and Achiwa 1995). Compared with the literature, low conversion and ee was achieved in the asymmetric reduction of substrates **3** and **4** in the presence of *L. kefiri* P2 biocatalyst (Table 1, entries 3, 4). The reason for the low conversion of substrates **3** and **4** may be due to the low solubility of these substrates in water. Therefore, it was observed that

there were no changes in the conversion and ee using organic solvents such as 5% ethyl alcohol, isopropyl alcohol and DMSO in the reaction medium. The low ee and conversion for substrates **3** and **4** could be explained by the bulky groups on both sides of the carbonyl group in this substrates. Since it is difficult for substrates to interact with the active site of the enzyme due to the bulky groups, conversion and ee may be reduced. This indicated that the bulky groups on the both side of carbonyl group adversely affected the conversion rate of the enzymatic reaction. Similarly, ketone **1** was converted faster than **4** with *L. kefiri* P2. Clearly, for ketone **3** and **4**, the steric effect is influence the conversion. In this study, excellent enentiomeric excess (> 99%) and conversion (> 99%) was achieved in the asymmetric bioreduction of substrate **5** to ***(R)*-5a** using *L. kefiri* P2 (Table 1, entry 5). Baker's yeast reduction of **5** gave ***(S)*-5a** with moderate enantiomeric purity (55%) and in moderate yield (60%) (Toşa et al. 2008). *Rhizopus arrhizus* mediated bioreduction of **5** furnished ***(S)*-5a** in 99% yield with 92% enantiomeric purity (Salvi and Chattopadhyay 2016). The enzymatic reduction of prochiral heterocyclic ketone **5** by carrot root (*Daucus carota*) in water afforded the corresponding ***(S)*-5a** with 47% yield and 95% ee (Aldabalde et al. 2007). In our previous study, we reported that ***(S)*-5a** had reached 92% yield with ee of higher than 99% using *L. paracasei* BD87E6 (Şahin 2019). Under the optimized conditions, piperonyl methyl ketone **6** was reduced to the corresponding chiral alcohol ***(S)*-6a** by *L. kefiri* P2 with good ee (73%) and high conversion (98%) (Table 1, entry 6). The (***R***)-**6a** has been obtained in the high enantioselectivity by reducing piperonyl methyl ketone **6** with the expensive chiral reagent and toxic chemical catalysts (Ling et al. 2018; Chen and Lu 2016). The limited study is available on obtaining this chiral secondary alcohol **6a** with biocatalysts. In one of these studies, production of ***(R)*-6a** was performed in 89% yield and 99% enantiomeric purity *L. paracasei* BD101 (Şahin 2018).

Substrates **5** and **6**, which are similar in sterically, are reduced to the corresponding alcohol with almost the same conversion ratio. However, ***(R)*-5a** was obtained with higher ee. Thus, benzofuran structure of substrate **5** might be better stabilized in the enzyme active site in such a way to increase the ee of the product. This shows that the heteroatoms in the substrate structure are very important in selectivity.

The configurations of obtained alcohols in this study varied according to the structure of substrates. The probable reason for this can be explained by the fact that different configurations might occur due to the different interaction of substrates with the active center of the enzyme. Based on these results, it can be concluded that this biocatalyst might work as substrate selective as previously stated in the literature (Baydaş et al. 2020). When the bioreduction reactions were performed in the absence of the *L. kefiri* P2 in the medium, practically no conversion occurred, which indicated that the cause of the conversion in the reactions was the *L. kefiri* P2.

The last aim of the study was to attempt gram scale synthesis of ***(R)*-5a** using the determined optimum bioreduction conditions, since highly gram scale synthesis of enantiopure chiral alcohol using green method is extremely significant for industrial applications. The asymmetric reduction of **5** for the high gram scale synthesis of ***(R)*-5a** with *L. kefiri* P2 is seen in Fig. 1.

It has been shown that a change in substrate concentration has an effect on ee of product and the conversion of substrate, higher concentrations decrease the biotransformation, which has been reported to cell toxicity and product/substrate inhibition (Roy et al. 2003). In line by this information, the concentration of substrate from 5 to 15 g was gradually varied and examined. Higher than concentrations of 10 g decreased the ee and yield of product. The best ee (> 99%) of product and complete conversion were achieved with 10 g/2L concentration of substrate **5**. Under optimized conditions, substrate **5** (62.4 mmol) was converted to ***(R)*-5a** in 96% yield with > 99% ee and conversion with the *L. kefiri* P2. There is only one study in the literature involving the biocatalytic gram-scale synthesis of ***(R)*-5a** (Şahin 2019). Şahin (2019) reported the gram scale production of ***(R)*-5a** (6.26 g, ee > 99%, 99% conversion, 92% yield) from 6.73 g **5** whole cells of *L. paracasei* BD87E6. This study in the literature gave relatively lower yield and low substrate tolerance. The present study gave advantages of higher substrate tolerance (10 g/2L) and yield (96%). This is the first report on production of ***(R)*-5a** with *L. kefiri* P2 as a whole-cell biocatalyst in highest gram and yield. These results indicate that *L. kefiri* P2 can be used on a gram scale in the production of substantial drug precursors. In light of this information, these results may reveal useful information for further investigation of purified enzyme systems from these bacteria.

Conclusions

In conclusion, *L. kefiri* P2 was proved an effective biocatalyst for asymmetric bioreduction of prochiral hetero aromatic ketones with high conversion (8–99%) and ee (0–99%). ***(R)*-5a**, which can be used in the synthesis of pharmaceuticals such as bufuralols potent nonselective β-blockers antagonists, Amiodarone (cardiac anti-arrhythmic), and

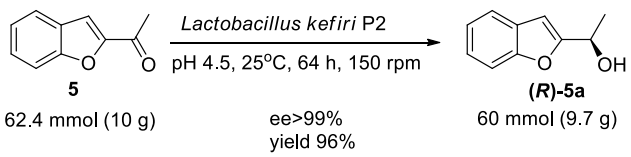


Fig. 1 Gram scale synthesis of (*R*)-1-(benzofuran-2-yl)ethanol **(5a)**

Benziodarone (coronary vasodilator), was synthesized in gram scale, high yield and enantiomerically pure form using *L. kefiri* P2. Compared with the past report, which used biocatalyst, **5** was bioreduced to ***(R)*-5a** in higher yield and gram scale. To the best of our knowledge, we are the first to successfully synthesis highest amount of enantiopure ***(R)*-5a** from **5** using a whole-cell biocatalytic reduction method. These results showed that current process has significant potential for the green synthesis of ***(R)*-5a** at an industrial scale. The biocatalytic reduction should have great importance for the synthesis of optically pure chiral alcohols owing to the alluring biocatalysts and environmentally friendly reaction condition. *L. kefiri* P2 catalyzed asymmetric bioreduction of prochiral hetero aromatic ketones is a cost-effective, environmentally benign and easily scalable processes compared to chemical processes. To expand the catalytic reduction activity of this biocatalyst, studies are continuing on new substrates, in particular, which could be drug precursors.

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References

Aboul-Enein MN, El-Azzouny AA, Attia MI, Maklad YA, Amin KM, Abdel-Rehim M, El-Behairy MF (2012) Design and synthesis of novel stiripentol analogues as potential anticonvulsants. Eur J Med Chem 47:360–369. https://doi.org/10.1016/j.ejmech.2011.11.004

Aldabalde V, Arcia P, Gonzalez A, Gonzalez D (2007) Enzymatic synthesis of chiral heteroaryl alcohols using plant fragments as the only biocatalyst and reducing agent. Green Chem Lett Rev 1:25–30. https://doi.org/10.1080/17518250701756983

Alizadeh BH, Foroumadi A, Emami S, Khoobi M, Panah F, Ardestani SK, Shafiee A (2010) Isochaihulactone analogues: synthesis and anti-proliferative activity of novel dibenzylbutyrolactones. Eur J Med Chem 45:5979–5984. https://doi.org/10.1016/j.ejmech.2010.09.064

Amidjojo M, Weuster-Botz D (2005) Asymmetric Synthesis of the Chiral Synthon Ethyl (*S*)-4-Chloro-3-Hydroxybutanoate Using *Lactobacillus Kefiri*. Tetrahedron:Asymmetry16: 899–901. https://doi.org/10.1016/j.tetasy.2005.01.013

Baydaş Y, Dertli E, Şahin E (2020) Green synthesis of chiral aromatic alcohols with *Lactobacillus kefiri* P2 as a novel biocatalyst. Synth Commun 50:1035–1045. https://doi.org/10.1080/00397911.2020.1729809

Blume F, Liu YC, Thiel D, Deska J (2016) Chemoenzymatic total synthesis of (+)- & (−)-*cis*-osmundalactone. J Mol Catal B Enzym 134:280–284. https://doi.org/10.1016/j.molcatb.2016.11.010

Chen X, Lu Z (2016) Iminophenyl oxazolinylphenylamine for enantioselective cobalt-catalyzed hydrosilylation of aryl ketones. Org Lett 18:4658–4661. https://doi.org/10.1021/acs.orglett.6b02260

Corey EJ, Helal CJ (1996) Asymmetric synthesis of (*S*)-carbinoxamine. New aspects of oxazaborolidine-catalyzed enantioselective carbonyl reduction. Tetrahedron Lett 37:5675–5678. https://doi.org/10.1016/0040-4039(96)01198-7

Feng W, Satyanarayana M, Tsai YC, Liu AA, Liu LF, LaVoie EJ (2009) Novel topoisomerase I-targeting antitumor agents synthesized from the *N*,*N*,*N*-trimethylammonium derivative of ARC-111,5H–2,3-dimethoxy-8,9-methylenedioxy-5-[(2-*N*, *N*, *N*-trimethylammonium)-ethyl]di-benzo[c, h][1,6]naphthyridin-6-one iodide. Eur J Med Chem 44:3433–3438. https://doi.org/10.1016/j.ejmech.2009.02.004

Goudarshivannanavar BC, Jayadevappa H, Mahadevan KM (2009) A convenient synthesis of 2(2-benzo[b]furo)indoles and benzofuropyrazoles. Indian J Chem 48:1419–1423

He P, Zheng H, Liu X, Lian X, Lin L, Feng X (2014) Asymmetric reduction of amino ketones with a KBH_4 solution catalyzed by chiral lewis acids. Chem A Eur J 20:13482–13486. https://doi.org/10.1002/chem.201404732

Honda K, Inoue M, Ono T, Okano K, Dekishima Y, Kawabata H (2017) Improvement of operational stability of *Ogataea minuta* carbonyl reductase for chiral alcohol production. J Biosci Bioeng 123:673–678. https://doi.org/10.1016/j.jbiosc.2017.01.016

Kang BC, Shin SH (2017) Highly enantioselective hydrosilylation of ketones catalyzed by a chiral oxazaborolidinium ion. Org Lett 19:6316–6319. https://doi.org/10.1021/acs.orglett.7b03076

Li H, Zhu D, Hua L, Biehl ER (2009) Carbonyl reductase from *Sporobolomyces salmonicolor* and its mutant enzymes. Adv Synth Catal 351:583–588. https://doi.org/10.1002/adsc.200900045

Ling F, Nian S, Chen J, Luo W, Whang Z, Lv Y, Zhong W (2018) Development of ferrocene-based diamine-phosphine-sulfonamide ligands for iridium-catalyzed asymmetric hydrogenation of ketones. J Org Chem 83:10749–10761. https://doi.org/10.1021/acs.joc.8b01276

Ling F, Hou H, Chen J, Nian S, Yi X, Wang Z, Song D, Zhong W (2019) Highly enantioselective synthesis of chiral benzhydrols via manganese catalyzed asymmetric hydrogenation of unsymmetrical benzophenones using an imidazole-based chiral PNN tridentate ligand. Org Lett 21:3937–3941. https://doi.org/10.1021/acs.orglett.9b01056

Lou WY, Wang W, Smith TJ, Zong MH (2009) Biocatalytic antiprelog stereoselective reduction of 4′-methoxyacetophenone to (*R*)-1-(4-methoxyphenyl)ethanol with immobilized *Trigonopsis Variabilis* AS2.1611 cells using an ionic liquid-containing medium. Green Chem 11:1377–1384. https://doi.org/10.1039/B823502C

Maerten E, Agbossou-Niedercorn F (2008) Preparation of pyridinyl aryl methanol derivatives by enantioselective hydrogenation of ketones using chiral Ru (diphosphine)(diamine) complexes. Attribution of their absolute configuration by ^{1}H NMR spectroscopy using Mosher's reagent. Tetrahedron 64:8700–8708. https://doi.org/10.1016/j.tet.2008.06.104

Mangas-Sánchez J, Rodríguez-Mata M, Busto E, Gotor-Fernández V, Gotor V (2009) Chemoenzymatic synthesis of rivastigmine based on lipase-catalyzed processes. J Org Chem 74:5304–5310. https://doi.org/10.1021/jo900784g

Matsunami A, Ikeda M, Nakamura H, Yoshida M, Kuwata S, Kayaki Y (2018) Accessible Bifunctional oxy-tethered ruthenium (II) catalysts for asymmetric transfer hydrogenation. Org Lett 20:5213–5218. https://doi.org/10.1021/acs.orglett.8b02157

Mikhailine AA, Morris RH (2010) Effect of the structure of the diamine backbone of P−N−N−P ligands in iron (II) complexes on catalytic activity in the transfer hydrogenation of acetophenone. Inorg Chem 49:11039–11044. https://doi.org/10.1021/ic101548j

Muñoz Solano D, Hoyos P, Hernáiz MJ, Alcántara AR, Sánchez-Montero JM (2012) Industrial biotransformations in the synthesis of building blocks leading to enantiopure drugs. Bioresour Technol 115:196–207. https://doi.org/10.1016/j.biortech.2011.11.131

Ni Y, Li CX, Ma HM, Zhang J, Xu JH (2011) Biocatalytic properties of a recombinant aldo-keto reductase with broad substrate spectrum and excellent stereoselectivity. Appl Microbiol Biotechnol 89:1111–1118. https://doi.org/10.1007/s00253-010-2941-4

Ni Y, Xu JH (2012) Biocatalytic ketone reduction: a green and efficient access to enantiopure alcohols. Biotechnol Adv 30:1279–1288. https://doi.org/10.1016/j.biotechadv.2011.10.007

Nian S, Ling F, Chen J, Wang Z, Shen H, Yi X, Yang YF, She Y, Zhong W (2019) Highly enantioselective hydrogenation of non-ortho-substituted 2-pyridyl aryl ketones via iridium-f-diaphos catalysis. Org Lett 21:5392–5396. https://doi.org/10.1021/acs.orglett.9b01415

Ohnmacht CJ, Patel AR, Lutz RE (1971) Antimalarials. 7. Bis (trifluoromethyl)-. alpha.-(2-piperidyl)-4-quinolinemethanols. J Med Chem 14:926–928. https://doi.org/10.1021/jm00292a008

Oliveira AN, Bocca CC, Carvalho JE, Ruiz ALG, Silva TP, Rittner R, Hoehr NF (2010) New substituted 4-arylaminoquinazolines as potent inhibitors of breast tumor cell lines: in vitro and docking experiments. Eur J Med Chem 45:4339–4342. https://doi.org/10.1016/j.ejmech.2010.04.034

Pal M, Srivastava G, Moon LS, Jolly RS (2012) Bioreduction of methyl heteroaryl and aryl heteroaryl ketones in high enantiomeric excess with newly isolated fungal strains. Bioresour Technol 118:306–314. https://doi.org/10.1016/j.biortech.2012.05.031

Prasanthi G, Prasad KVSRG, Bharathi K (2013) Design, synthesis and evaluation of dialkyl 4-(benzo[d][1,3]dioxol-6-yl)-1,4-dihydro-2,6-dimethyl-1substituted pyridine-3,5-di carboxylates as potential anticonvulsants and their molecular properties prediction. Eur J Med Chem 66:516–525. https://doi.org/10.1016/j.ejmech.2013.06.006

Roy A, Bhattacharyya MS, Ravi Kumar L, Chawla HPS, Banerjee UC (2003) Microbial reduction of 1-acetonapthone: a highly efficient process for multigram synthesis of S(−)-1-(1′-napthyl) ethanol. Enzym Microb Technol 33:576–580. https://doi.org/10.1016/S0141-0229(03)00178-9

Quaglia D, Pori M, Galletti P, Emer E, Paradisi F, Giacomini D (2013) His-tagged horse liver alcohol dehydrogenase: immobilization and application in the bio-based enantioselective synthesis of (*S*)-arylpropanols. Process Biochem 48:810–818. https://doi.org/10.1016/j.procbio.2013.03.016

Paizs C, Toşa M, Majdik C, Moldovan P, Novak L, Kolonits P, Marcovici A, Irimie FD, Poppe L (2003) Optically active 1-(benzofuran-2-yl)ethanols and ethane-1,2-diolsby enantiotopic selective bioreductions. Tetrahedron Asymmetry 14:1495–1501. https://doi.org/10.1016/S0957-4166(03)00222-2

Ryu KC, Song LA, Lee YJ, Hong AJ, Yoon HJ, Kim A (2010) Synthesis and antifungal activity of benzofuran-5-ols. Bioorg Med Chem Lett 20:6777–6780. https://doi.org/10.1016/j.bmcl.2010.08.129

Şahin E (2020) *Candida zeylanoides* as whole-cell biocatalyst to perform asymmetric bioreduction of benzophenone derivatives. Synth Commun 50:612–619. https://doi.org/10.1080/00397911.2019.1710213

Şahin E (2019) Green synthesis of enantiopure (*S*)-1-(benzofuran-2-yl) ethanol by whole-cell biocatalyst. Chirality 31:892–897. https://doi.org/10.1002/chir.23123

Şahin E (2018) Production of (*R*)-1-(1, 3-benzodioxol-5-yl) ethanol in high enantiomeric purity by *Lactobacillus paracasei* BD 101. Chirality 30:189–194. https://doi.org/10.1002/chir.22782

Şahin E, Dertli E (2019) Biocatalyzed enantiomerically pure production of (*S*)-phenyl (thiophen-2-yl) methanol. J Heterocycl Chem 56:2884–2888. https://doi.org/10.1002/jhet.3681

Şahin E, Dertli E (2017) Highly enantioselective production of chiral secondary alcohols with *Candida zeylanoides* as a new whole cell biocatalyst. Chem Biodivers 14:e1700121. https://doi.org/10.1002/cbdv.201700121

Şahin E, Serencam H, Dertli E (2019a) Production of enantiomerically pure (*S*)-phenyl (pyridin-2-yl) methanol with *Lactobacillus paracasei* BD101. Biocatal Biotransform 37:448–454. https://doi.org/10.1080/10242422.2019.1602611

Şahin E, Serencam H, Dertli E (2019b) Whole cell application of *Lactobacillus paracasei* BD101 to produce enantiomerically pure (*S*)-cyclohexyl (phenyl) methanol. Chirality 31:211–218. https://doi.org/10.1002/chir.23048

Salvi L, Kim JG, Walsh PJ (2009) Practical catalytic asymmetric synthesis of diaryl-, aryl heteroaryl-, and diheteroarylmethanols. J Am Chem Soc 131:12483–12493. https://doi.org/10.1021/ja9046747

Salvi NA, Chattopadhyay S (2016) Laboratory scale-up synthesis of chiral carbinols using *Rhizopus arrhizus*. Tetrahedron Asymmetry 27:188–192. https://doi.org/10.1016/j.tetasy.2016.01.008

Schmidt S, Pedroso de Almeida T, Rother D, Hollmann F (2017) Towards environmentally acceptable synthesis of chiral α-hydroxy ketones via oxidase-lyase cascades. Green Chem 19:1226–1229. https://doi.org/10.1039/C7GC00020K

Shrivas P, Pratap U (2019) Biocatalytic one-pot three-component synthesis of 4*H*-chromene derivatives in non-aqueous medium. Chem Pap 73:1301–1307. https://doi.org/10.1007/s11696-018-00679-5

Sokeirik YS, Mori H, Omote M, Sato K, Tarui A (2007) Synthesis of a fluorous ligand and its application for asymmetric addition of dimethylzinc to aldehydes. Org Lett 9:1927–1929. https://doi.org/10.1021/ol070466n

Takemoto M, Achiwa K (1995) The synthesis of optically active pyridyl alcohols from the corresponding racemates by *Catharanthus roseus* cell cultures. Tetrahedron Asymmetry 6:2925–2928. https://doi.org/10.1016/0957-4166(95)00388-6

Takemoto M, Moriyasu Y, Achiwa K (1995) Synthesis of optically active α-phenyl pyridyl methanols with cell cultures of *Nicotiana tabacum*. Chem Pharm Bull 43:1458–1461. https://doi.org/10.1248/cpb.43.1458

Takemoto M, Tanaka K (2001) Synthesis of optically active α-phenylpyridylmethanols by *Camellia sinensis* cell culture. J Mol Catal B Enzym 15:173–176. https://doi.org/10.1016/S1381-1177(01)00021-2

Tan AWI, Fischbach M, Huebner H, Buchholz R, Hummel W, Daussmann T, Wandrey C, Liese A (2006) Synthesis of enantiopure (*5R*)-hydroxyhexane-2-one with immobilised whole cells of *Lactobacillus Kefiri*. Appl Microbiol Biotechnol 71:289–293. https://doi.org/10.1007/s00253-005-0168-6

Thomson MI, Nichol GS, Lawrence AL (2017) Total synthesis of (−)-angiopterlactone B. Org Lett 19:2199–2201. https://doi.org/10.1021/acs.orglett.7b00929

Touchard F, Bernard M, Fache F, Lemaire M (1999) Ureas and Thioureas as Rh-ligands for the enantioselective hydride transfer reduction of acetophenone. J Mol Catal A Chem 140:1–11. https://doi.org/10.1016/S1381-1169(98)00212-X

Toşa MI, Podea PV, Paizs C, Florin Dan Irimie, FD (2008) Chemoenzymatic synthesis of (R)-and (S)-1-heteroarylethanols. Tetrahedron:Asymmetry. 19:2068–2071. https://doi.org/10.1016/j.tetasy.2008.08.023

Utepova IA, Serebrennikova PO, Streltsova MS, Musikhina AA, Fedorchenko TG, Chupakhin ON, Antonchick AP (2018) Enantiomerically enriched 1, 2-P, *N*-bidentate ferrocenyl ligands for 1, 3-dipolar cycloaddition and transfer hydrogenation reactions. Molecules 23:1311. https://doi.org/10.3390/molecules23061311

Wang Y, Zong H, Huang H, Song L (2017) Chiral thiophosphoramide catalyzed asymmetric aryl transfer reactions for the synthesis of functional diarylmethanols. Tetrahedron Asymmetry 28:90–97. https://doi.org/10.1016/j.tetasy.2016.11.011

Wani MY, Bhat AR, Azam A, Choi I, Athar F (2012) Probing the antiamoebic and cytotoxicity potency of novel tetrazole and triazine derivatives. Eur J Med Chem 48:313–320. https://doi.org/10.1016/j.ejmech.2011.12.033

Weckbecker A, Hummel W (2006) Cloning, expression, and characterization of an (R)-specific alcohol dehydrogenase from

Lactobacillus Kefiri. Biocatal Biotransform 24:380–389. https://doi.org/10.1080/10242420600893827

Wu S, Shen J, Zhou X, Chen J (2007) A novel enantioselective epoxide hydrolase for (*R*)-phenyl glycidyl ether to generate (*R*)-3-phenoxy-1,2-propanediol. Appl Microbiol Biotechnol 76:1281–1287. https://doi.org/10.1007/s00253-007-1098-2

Wu W, Liu S, Duan M, Tan X, Chen C, Xie Y, Lan Y (2016) Iridium catalysts with f-amphox ligands: asymmetric hydrogenation of simple ketones. Org Lett 18:2938–2941. https://doi.org/10.1021/acs.orglett.6b01290

Xie Y, Xu JH, Lu WY, Lin GQ (2009) Adzuki bean: a new resource of biocatalyst for asymmetric reduction of aromatic ketones with high stereoselectivity and substrate tolerance. Bioresour Tech 100:2463–2468. https://doi.org/10.1016/j.biortech.2008.11.054

Yadav GD, Devendran S (2012a) Lipase catalyzed kinetic resolution of (±)-1-(1-naphthyl) ethanol under microwave irradiation. J Mol Catal B Enzym 81:58–65. https://doi.org/10.1016/j.molcatb.2012.05.007

Yadav GD, Devendran S (2012b) Lipase catalyzed synthesis of cinnamyl acetate via transesterification in non-aqueous medium. Process Biochem 47:496–502. https://doi.org/10.1016/j.procbio.2011.12.008

Yanga W, Xua JH, Pana J, Xua Y, Wang ZL (2008) Efficient reduction of aromatic ketones with NADPH regeneration by using crude enzyme from *Rhodotorula cells* and mannitol as cosubstrate. Biochem Eng J 42:1–5. https://doi.org/10.1016/j.bej.2008.04.014

Yeo H, Li Y, Fu L, Zhu JL, Gullen EA, Dutschman GE, Lee Y, Chung R, Huang ES, Austin DJ, Cheng YC (2005) Synthesis and antiviral activity of helioxanthin analogues. J Med Chem 48:534–546. https://doi.org/10.1021/jm034265a

Yılmaz D, Şahin E, Dertli E (2017) Highly enantioselective production of chiral secondary alcohols using *Lactobacillus paracasei* BD 101 as a new whole cell biocatalyst and evaluation of their antimicrobial effects. Chem Biodivers 14:e1700269. https://doi.org/10.1002/cbdv.201700269

Yu S, Li H, Lu Y, Zheng G (2018) A catalyst from burkholderia cenocepacia for efficient anti-prelog's bioreduction of 3,5-bis(trifluoromethyl) acetophenone. Appl Biochem Biotechnol 184:1319–1331. https://doi.org/10.1007/s12010-017-2628-8

Zhou M, O'Doherty GA (2008) De novo synthesis of the trisaccharide subunit of landomycins A and E. Org Lett 10:2283–2286. https://doi.org/10.1021/ol800697k

Zhou X, Wu X, Yang B, Xiao J (2012) Varying the ratio of formic acid to triethylamine impacts on asymmetric transfer hydrogenation of ketones. J Mol Catal A Chem 357:133–140. https://doi.org/10.1016/j.molcata.2012.02.002

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