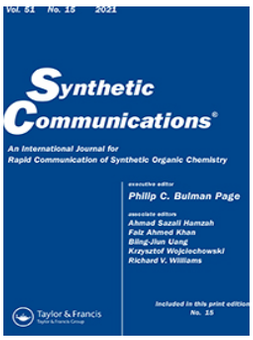

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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Nida Sezin Çolak, Erbay Kalay & Engin Şahin (2021) Asymmetric reduction of prochiral aromatic and hetero aromatic ketones using whole-cell of *Lactobacillus senmaizukei* biocatalyst, Synthetic Communications, 51:15, 2305-2315, DOI: 10.1080/00397911.2021.1931337

To link to this article: https://doi.org/10.1080/00397911.2021.1931337

Published online: 26 May 2021.

SYNTHETIC COMMUNICATIONS®
2021, VOL. 51, NO. 15, 2305–2315
https://doi.org/10.1080/00397911.2021.1931337

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Asymmetric reduction of prochiral aromatic and hetero aromatic ketones using whole-cell of *Lactobacillus senmaizukei* biocatalyst

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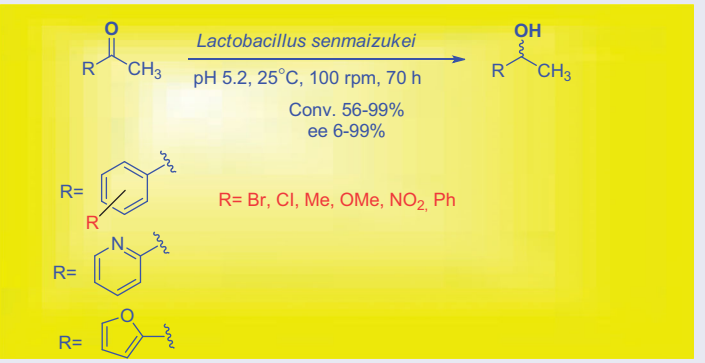
ABSTRACT

Asymmetric bioreduction of aromatic and heteroaromatic ketones is an important process in the production of precursors of biologically active molecules. In this study, the bioreduction of aromatic and hetero aromatic prochiral ketones into optically active alcohols was investigated using *Lactobacillus senmaizukei* as a whole-cell catalyst, since whole-cells are less expensive than pure enzymes. The study indicates enantioselective bioreduction of various substituted aromatic ketones (**1–16**) to the corresponding (*R*)-and (*S*)-chiral secondary alcohols (**1a–16a**) in low to excellent enantioselectivity (6–94%) with good yields (58–95%). In addition, heteroaromatic prochiral ketones 1-(pyridin-2-yl)ethanone (**17**) and 1-(furan-2-yl)ethanone (**18**) were reduced to **(*R*)-17a** and **(*R*)-18a** in enantiopure form with excellent conversion (>99%) and yields. These findings show that *L. senmaizukei* is a very important biocatalyst for asymmetric reduction of both 6-membered and 5-member heteroaromatic methyl ketones. This method promising a green synthesis for the synthesis of biologically important secondary chiral alcohols in an environmentally friendly and inexpensive process.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 19 March 2021

KEYWORDS
Aromatic ketones; asymmetric synthesis; bioreduction; hetero aromatic carbinol; *Lactobacillus senmaizukei*

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Introduction

The chemical industry plays an important role in production because it produces a vast variety of high-value-added goods and is one of the world's largest economic sectors. The advantages of biocatalytic processes for organic synthesis have led to an increase in biocatalytic applications. Organic chemistry relies heavily on biocatalytic reactions for the manufacture of pharmaceuticals and the investigation of chirality as a means of improving biological reactivity.[1] Chiral alcohol, amines, and amino acids are essential intermediates in the synthesis of a wide range of agrochemicals and pharmaceuticals. These compounds, especially chiral alcohols, are very important due to their stable structure and they can be converted into various functional groups without racemization.[2] Asymmetric reductions can be used to synthesize these compounds. One of the most important reactions in organic chemistry is the stereoselective reduction of prochiral ketones to chiral alcohols. Chiral alcohols are useful building blocks in industrial chemistry. These compounds, for example, are important intermediates in the manufacture of fine chemicals, natural products, and pharmaceuticals.[3–7] Some examples of pharmaceuticals that use chiral alcohols as building blocks are anticholesterol,[8] antiarrhythmic agents,[9] antihypertensive drugs,[10] and antiviral drugs.[11] Phenyl ethanol and its derivatives are other important examples of these compounds, which are useful starting materials for the synthesis of drug precursors.[12] One of the main nutrients, carbohydrates, which constitute the basic energy source of the human body, is the most important nutrient used to obtain energy in our body. Carbohydrates contain a chiral secondary alcohol functional group in their structure. Carbohydrates are also used in enzymatic synthesis reactions.[13,14] In the chemical and pharmaceutical industry, chiral auxiliaries such as (*S*)-1-phenyl ethanol,2-naphthyl ethanol, and (*S*)-1-(3-methoxyphenyl) ethanol are used.[15,16] On the other hand, chiral heteroaromatic alcohols are used as drug precursors.[17] N-heteroaromatic carbinols such as enantiomerically pure (*R*)-1-(pyridin-2-yl) ethanol (**17a**) are used as starting materials for the synthesis of various biologically active molecules.[18] The molecular motif (*R*)-1-(furan-2-yl)ethanol (**18a**) is extensively used in the total production of many pharmaceutical and natural products, including Landomycins A, E, (−)-Angiopterlactone B, and (+)- & (−)-cis-Osmundalactone.[19–21] Chemical and biocatalytic processes can be used to produce chiral alcohols. Chemical synthesis has a number of disadvantages, including the use of organic solvents and the need for harsh reaction conditions such as high or low temperature, high pressure, or the use of an inert atmosphere. In addition, the enantiomeric excesses (ee) obtained with chemical catalysts are not satisfactory. High enantiomeric excesses are required for the manufacture of natural products and especially in drug production. Biocatalytic approaches can be used to accomplish these aims. Biocatalytic processes are particularly appealing for the organic synthesis of industrial products since (a) biocatalysts are natural catalysts produced by fermentation; (b) biocatalysts are generally nontoxic catalysts and prevent substantial metal consumption (unlike many metal and organometallic catalysts); (c) reaction conditions are moderate and more environmentally friendly than chemical catalysts; (d) biocatalytic reactions are generally more selective and byproduct formation is low; (e) biocatalytic reactions usually take place in an aqueous medium and prevent large amounts of organic solvent consumption. Enzymatic resolution and reduction of ketones with pure enzyme or

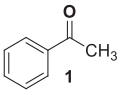
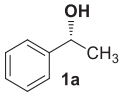
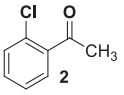
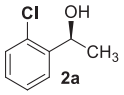
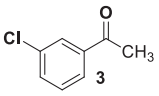
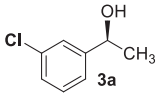
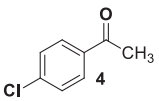
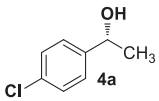
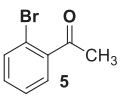
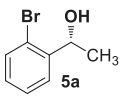
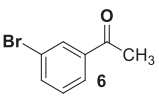
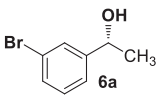
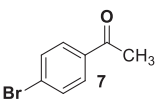
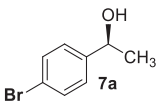
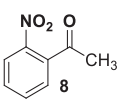
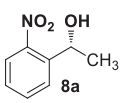
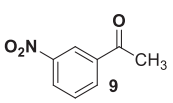
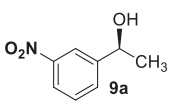
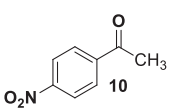
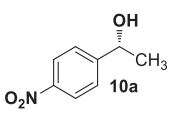
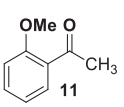
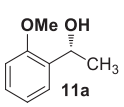
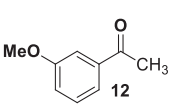
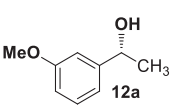
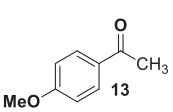
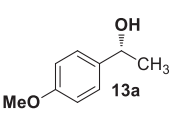
whole-cell biocatalysts are biocatalytic methods for producing optically pure alcohols.[22] Enzymatic resolutions, however, were restricted by a theoretical yield of 50%.[23] In asymmetric bioreduction reactions, whole-cell biocatalysis is superior to using an isolated enzyme, with the benefit of eliminating the expensive enzyme purification process. One of the most simple and encouraging routes to the production of enantiomerically pure secondary alcohols is asymmetric bioreduction of prochiral ketones using biocatalysts. There are many reports in the literature involving asymmetric reduction of acetophenone derivatives with biocatalysts.[24–26] While there are numerous studies in the literature concerning the asymmetric reduction of heteroaromatic substrates with chemical catalysts, there are few studies involving biocatalysts. It has been reported that 20% of chiral secondary alcohols used in industrial production were obtained by biocatalytic asymmetric reduction.[27] Therefore, it is very important to develop new biocatalysts that can be used for asymmetric reduction of both aromatic and heteroaromatic prochiral ketones.

In this research, whole-cell of *Lactobacillus senmaizukei* was investigated the reduction activity in asymmetric reduction of aromatic and hetero aromatic ketones. In our previous study, it was shown that *L. senmaizukei* can be used in the asymmetric reduction of acetophenone and the optimum reduction conditions of acetophenone were determined using the response surface methodology (RSM) optimization strategy.[28] Herein, asymmetric reductions of acetophenone derivatives and hetero aromatic ketones were carried out under previously optimized conditions using the whole-cell of *L. senmaizukei*. *Lactobacillus senmaizukei* biocatalyst was used for the first time in asymmetric reduction of acetophenone derivatives and hetero aromatic substrates, and the effects of substrates on ee and conversion have been extensively evaluated. The hetero aromatic carbinols (*R*)-1-(pyridin-2-yl) ethanol (**17a**) and (*R*)-1-(furan-2-yl) ethanol (**18a**) were obtained enantiomerically pure form with >99% conversion, high yield, and a gram scale.

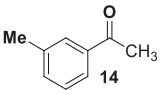
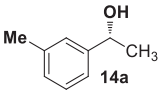
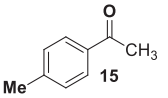
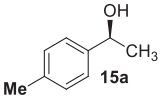
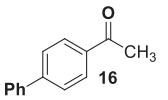
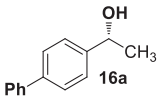
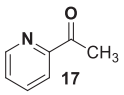
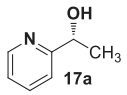
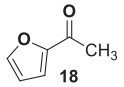
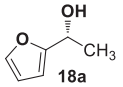
Results and discussion

In our previous study, the asymmetric reduction conditions (pH 5.25, 25 °C, 100 rpm and 70 h) were determined using the model substrate acetophenone **1** using the RSM optimization strategy.[28] Under these optimized conditions, asymmetric reductions of acetophenones (**2–16**), which have *ortho*-, *metha* and *para* electron-withdrawing, and electron-donating groups, and hetero aromatic substrates (**17, 18**) were reduced and the effects of substrates on selectivity and conversion were evaluated. Table 1 shows the results obtained depending on the location, electronic and steric effects of the groups. Under these optimized conditions, **1a** was obtained by asymmetric reduction of acetophenone **1** in 90% ee, 94% conversion, and 90% yield (Table 1, entry 1). A similar reactivity to acetophenone was observed in chloroacetophenones, and the corresponding chiral alcohols were obtained by conversion ranging from 87 to 97% (Table 1, entries 2–4). However, decreasing enantioselectivity was obtained by moving from the 2nd position of the chlorine atom in the benzene ring to the 4th position (69, 62, and 49 ee%, respectively). These results show that the steric effect is important in selectivity. In addition, chlorophenyl ethanols are very important compounds as they are found in drug

Table 1. Asymmetric bioreduction of aromatic and heteroaromatic ketons with *L. senmaizukei*.

Entry	Substrate	Product	ee (%)[a,b]	Conv. (%)[c]	Yield (%)[d]
1			80 (*R*)	94	90
2			69 (*S*)	92	87
3			62 (*S*)	87	82
4			49 (*R*)	97	91
5			76 (*R*)	56	51
6			52 (*R*)	75	68
7			12 (*S*)	95	90
8			6 (*R*)	67	58
9			88 (*S*)	99	95
10			28 (*R*)	95	89
11			49 (*R*)	79	69
12			14 (*R*)	97	91
13			30 (*R*)	91	83

(*continued*)

14			94 (*R*)	99	92
15			72 (*S*)	97	89
16			88 (*R*)	95	88
17			>99 (*R*)	>99	95
18			>99 (*R*)	99	92

Reaction conditions: substrate 0.5 mmol, pH 5.2, 25° C, 70 h, 100 rpm.
[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.

structures such as solabegron and chlorprenaline.[29] For 2-, 3- and 4-bromoacetophenones, as the bromine atom moves away from the carbonyl group, the conversion increases while the selectivity decreases (Table 1, entries 5–7). Compared to substrates with bromine atoms, substrates with chlorine atoms, the decrease in selectivity and the increase in the conversion rate are slightly more. This can be explained by the fact that the bromine atom is sterically bulkier than the chlorine atom. The best result for the reduction of nitroacetophenone derivatives was obtained from the reduction of the *meta*-nitroacetophenone derivative (88% ee and 99% conversion) (Table 1, entry 9). While a moderate conversion (67%) and low ee (6%) were obtained in the reduction of 2-nitroacetophenone, high conversion (95%) and low ee (28%) were obtained in the reduction of 4-nitroacetophenone (Table 1, entry and 10). The very low selectivity in 2-nitroacetophenone can be explained by a steric effect due to the proximity of the nitro group to the carbonyl group (Table 1, entry 8). It has been previously reported that a similar effect was observed in the reduction of 2-nitroacetophenone with a biocatalyst.[30] There are reports in the literature that both the carbonyl group and the nitro group are reduced in asymmetric reductions with nitro acetophenone derivatives using biocatalysts.[31] In this study, it was observed that the biocatalyst reduces the carbonyl group without reducing the nitro group. Enantiomeric excess decreased significantly when 2-methoxy, 3-methoxy- and 4-methoxyacetophenone were used as the substrates, compared to the reaction performed with acetophenone (Table 1, entries 11–13). However, while the conversion rate of 2-methoxyacetophenone is reduced compared to acetophenone, the conversion values obtained for 3-, and 4-methoxyacetophenone are very close to that obtained from acetophenone. 3-methylacetophenone was reduced corresponding chiral alcohol with excellent conversion (99%) and good ee (94%) compared to the acetophenone (Table 1, entry 14). Similarly, 4-methylacetophenone has been

converted to the corresponding secondary alcohol with an excellent conversion (97%) and good ee (72%) (Table 1, entry 15). 4-phenylacetophenone was reduced to corresponding chiral alcohol in high ee (88%) and conversion (95%) (Table 1, entry 16). The configurations of the obtained chiral secondary alcohols vary as *R* or *S*, depending on the steric and electronic properties of the attached group in the benzene ring as previously reported.[32] This can be explained by the different interactions of the groups with the active site of the enzyme. An excellent enantioselectivity (>99%), conversion (>99%), and yield (95%) in the reduction of 1-(pyridin-2-yl)ethanone (**17**) were obtained with whole-cell of *L. senmaizukei* (Table 1, entry 17). By asymmetric reduction of 2-acetylpyridine **17** with costly pure enzyme and cofactor, **(*S*)-17a** was obtained in high enantiomeric purity in the literature.[33,34] In literature, the chiral seconder alcohol **(*S*)-17a** was obtained by asymmetric reduction of the **17** with *seed adzuki* bean in >81% ee and 44% conversion.[35] Also, the synthesis of **(*R*)-17a** was reported to be synthesized using Lactobacillus *kefiri* P2 biocatalyst with 93% ee and 56% conversion,[36] and using a chemical catalyst **(*R*)-17a** was synthesized with high selectivity.[37,38] Compared to the studies in the literature, in this study **(*R*)-17a** was obtained in cheap, higher conversion, higher yield, and in enantiomerically pure form. Enantiomerically pure form (>99%) and excellent conversion (>%99) were obtained in bioreduction of **18** with whole-cell of *L. senmaizukei* (Table 1, entry 18). In the literature, it was reported that **(*S*)-18a** was obtained with 99% ee and 85% yield as a result of the use of expensive pure enzyme as a biocatalyst.[19] Also, the synthesis of **(*R*)-18a** was reported to be synthesized using whole-cell of *L. kefiri* P2 biocatalyst with 95% ee and 99% conversion.[36] However, in this study, **(*R*)-18a** was obtained in high yield, conversion and enantiomerically pure form by using whole-cell biocatalyst, which is a very cheap method compared to the pure enzyme.

The last target of this study was to perform the high gram scale manufacture of **(*R*)-17a** and **(*R*)-18a** using the optimum conditions, since, in the industrial production of chiral alcohols, high product concentration and high ee are important. In addition, substrate tolerance is one of the important indicators of biocatalyst potential for industrial applications.[39,40] We investigated the effect of the substrate concentration range of 5 to 25 mmol on the biocatalytic reduction under optimized conditions. When the substrate **17** and **18** concentrations were 15 mmol, the maximum (99%) ee and conversion (99%) were obtained (Figure 1). When the substrate concentrations passed the 15 mmol, the ee and conversion of the reactions had an important drop. This reduction can be explained by the decrease in the enzyme activity of the substrate's toxicity as previously reported.[41] In the present study, as a result of biocatalytic reduction of 1.81 g of substrate **17** and 1.65 g of substrate **18**, **(*R*)-17a** and **(*R*)-18a** were obtained as enantiopure form with 99% conversion and 95%, 92% yield, respectively. In the light of this information, these results show that this biocatalyst has the potential to be used in the asymmetric reduction of hetero aromatic substrates.

Conclusion

In conclusion, we identified a method for producing chiral carbinols using whole-cell of *L. senmaizukei* as the biocatalyst, which was very successful in reducing ketones to their

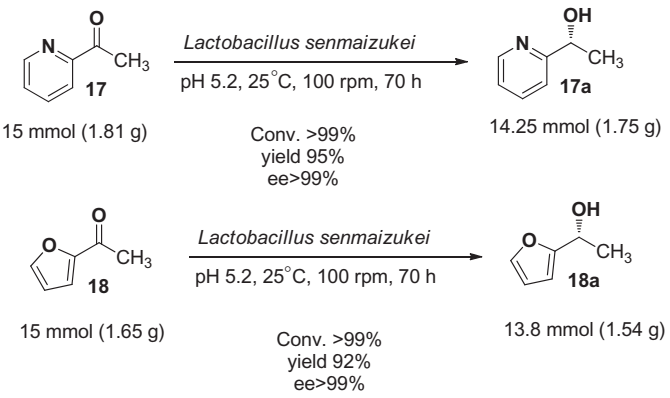


Figure 1. Gram scale synthesis of **17a** and **18a**.

chiral alcohols, some of which are important key intermediates in the synthesis of commercial drugs. **(*R*)-17a** and **(*R*)-18a**, which can be used as a biologically active compound, was produced in excellent yield, enantiomerically pure form, and gram-scale, using *L. senmaizukei*. Compared with past whole-cell biocatalytic methods, **(*R*)-17a** and **(*R*)-18a** were obtained in high conversion, yield, gram scale, and enantiopure form. This study is the first report in which the highest amount of **(*R*)-17a** and **(*R*)-18a** was obtained enantiomerically pure form by biocatalytic reduction of **17** and **18** with whole-cell of *L. senmaizukei*. The findings obtained here using *L. senmaizukei* whole-cell as the biocatalyst could promising method for the reduction of selected prochiral aromatic and heteroaromatic ketones. Moreover, this process as a green method preventing the use of expensive metal reducing agents and organic solvents that are widely used in inorganic synthesis.

Experimental section

General

All solvents, chemicals and culture medium (MRS) were obtained from commercial suppliers in high purity. The progress of the reactions was monitored by TLC using hexane: ethyl acetate (90:10) as mobile phase. Chiral alcohols (**1a–18a**) were purified by column chromatography charged with silica gel using hexane: ethyl acetate (90:10) solvent mixture. Enantiomeric excess was determined from a chiral HPLC analysis on an Agilent 1260 system equipped with UV and chiral detector. Specific optical rotation was measured by Bellingham + Stanley, ADP 220, polarimetry. A reference sample of the racemic alcohol was synthesized by reducing the ketone **1–18** with $NaBH_4$ in MeOH. The NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ using TMS as an internal standard (supporting information).

Culture condition and bacterial strain

This study used the *L. senmaizukei* strain, which was obtained from rye sourdough, previously.[42]

General asymmetric bioreduction process

Lactobacillus senmaizukei was inoculated to 10 mL MRS broth and incubated 2 days at 37 °C followed by the inoculation of grown cells at 10% concentration to 50 mL MRS broth in 100 mL Erlenmeyer. The pH of the reaction medium was adjusted to 5.2 using 0.1 M HCl and mixed in a shaker incubator at 25 °C and 100 rpm for 2 h. Then substrates (**1–18**) were added to the mixture and the mixture was stirred under the same conditions for 70 h. Then, the bacterial cell was separated by centrifugation at 6000 × *g* for 5 min at 4 °C and the supernatant was saturated with sodium chloride. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The extracts were dried over Na_2SO_4 and then evaporated in a vacuum. The crude product was purified by column chromatography using hexane: ethyl acetate (90:10) solvent mixture and characterized by NMR analysis. The absolute configuration of the product was determined by a comparison of their optical rotational values with literature data. Conversion of the substrate was determined by filtering a small amount of crude product through a small column containing silica gel and the obtained product was analyzed on a chiral column and comparing the ketone peak with the alcohol peaks. Enantiomeric excess was calculated by HPLC analysis using a chiral column. No product or transformation was obtained in the experiments conducted without using biocatalysts.

Gram-scale synthesis of (R)-17 and (R)-18

In gram-scale biotransformation reaction, 1 L Erlenmeyer flask, containing 500 mL of MRS broth, was inoculated with 10% concentration *L. senmaizukei*, and incubated for 2 h at 25 °C at 100 rpm in a shaker incubator. The pH of the reaction media was adjusted at 5.2 by adding 0.1 M HCI and the mixture was stirred for 2 h under the same conditions. Then, 15 mmol **17** and **18** were added to the reaction mixture and stirred at 100 rpm, 25 °C for 70 h. After completion of the reaction, characterization and analysis processes of the product were made as stated above.

Copies of ^{1}H, ^{13}C-NMR spectra, spectroscopic data, racemic and chiral HPLC chromatograms of **1a–18a** related to this article can be found in the supplementary data.

Acknowledgment

We would like to thank Dr. Enes Dertli (Yildiz Technical University) for providing the biocatalyst used in this study.

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