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One-pot synthesis of enantiomerically pure 1, 2-diols: asymmetric reduction of aromatic α-oxoaldehydes catalysed by *Candida parapsilosis* ATCC 7330

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ABSTRACT

A facile and simple one-pot method was developed to produce a series of optically active (*S*)-1-phenyl-1,2-ethanediols with good yields (up to 70%) and high enantiomeric excess (>99%) *via* asymmetric reduction of various substituted aromatic α-oxoaldehydes using *Candida parapsilosis* ATCC 7330.

1. Introduction

Enantiomerically pure forms of vicinal diols are valuable chiral building blocks for the synthesis of pharmaceuticals and agrochemicals.[1] In particular, enantiomerically pure substituted 1-phenyl-1,2-ethanediols are the precursors of Fluoxetine, an anti-depressant, together with Tembamide and Aegeline, which show hypoglycemic activity.[2] These diols can also be readily transformed into chiral epoxides,[3] aziridines and amino alcohols.[4] Enantiomerically pure (*S*)-1-phenyl-1,2-ethanediol has been used in stereoselective polymerizations to produce chiral biphosphones and also as a chiral initiator.[5]

Numerous chemical methods have been reported for the synthesis of enantiomerically pure 1,2-diols.[6] The reduction of α-oxoaldehydes is one of the methods used to prepare these diols and the only chemical method, which uses α-and β-oxoaldehydes as starting materials for the synthesis of 1,2-diols using $TiCl_3$ (4 equiv)/NH_3 as the catalyst for the reduction to give racemic phenyl-1,2-ethanediol in an 80% yield.[7]

Enantiomerically pure 1,2-diols can also be prepared by several biocatalytic methods. The biocatalytic hydrolysis of epoxides using enantioselective and enantioconvergent epoxide hydrolases is one of the most commonly used methods for the synthesis of enantiopure diols.[8] The enantioselective hydrolysis of racemic epoxides using a variety of epoxide hydrolases from different microbes has been reported with a maximum yield of 50% and moderate to good enantiomeric excess (ee).[9] A major drawback of these enantioselective epoxide hydrolases is the low theoretical yield of 50%. The enantioconvergent hydrolysis of racemic epoxides using epoxide hydrolases from *Solanum tuberosum* gave the corresponding (*R*)-diol with 97% ee and an 88% yield,[10] whereas a combination of bacterial and marine fish epoxide hydrolases gave the enantiopure (*R*)-phenyl-1,2-ethane diol with 90% ee and an 94% yield.[11] Other biocatalytic methods include microbial stereoinversion,[12] the kinetic resolution of vicinal diols by using lipases[13] [which requires an additional hydrolysis step to obtain the enantiopure (*S*)-diol], asymmetric dihydroxylation of styrene using dioxygenases[14] and microbial reduction of α-hydroxy and α-acetoxy ketones to give enantiomerically pure 1,2-diols.[24d] The asymmetric reduction of α-hydroxy ketones was reported by Tsujigami et al. using the microorganism *Yamadazyma farinosa* IFO 10896 in an anti-Prelog manner to give (*S*)-1-phenyl-1,2-ethane diol in high yield and with >99% ee, but the reaction time of the asymmetric reduction was quite long (24 h).[15] Recently, Xu et al. reported an anti-Prelog reduction of 2-hydroxyacetophenone to the (*S*)-1-phenyl-1,2-ethanediol using an alcohol dehydrogenase from *Candida parapsilosis* CCTCC M203011 with an enantiomeric purity of >99%.[16] They also explored the coenzyme specificity and enantioselectivity of the enzyme using site directed mutagenesis to produce (*R*)-1-phenyl-1,2-ethanediol with an enantiomeric purity of 51.8% and yield of 37.9%.[17]

Biocatalytic methods, which use α-oxoaldehydes as starting materials for the asymmetric reduction, report the use of a methylglyoxal reductase from *Saccharomyces cerevisiae*, which catalyses the selective reduction of methylglyoxal to lactaldehyde although the stereochemistry of the product was not mentioned.[18] More recently, two different enzymes, the aldoketo reductase from *Escherichia coli* and the alcohol dehydrogenase from *Lactobacillus brevis*, were used for the asymmetric reduction of phenylglyoxal to (*S*)-1-phenyl-1,2-ethanediol[19] but the total reaction time for the two-step process was 22 h, in addition to the fact that expensive cofactors were used.

Hence, a one pot reduction of α-oxoaldehydes to prepare a series of enantiomerically pure 1,2-diols without the need for the addition of cofactors is highly desirable. Whole cells of *Candida parapsilosis* ATCC 7330 are effective for the deracemization of α- and β-hydroxy esters,[20a–c] propargylic esters,[20d] allylic alcohols[20e] and the resolution of amino acids.[20f] This biocatalyst is also very

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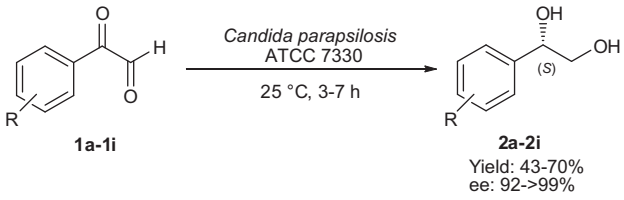
useful for the asymmetric reduction of alkyl-2-oxo-4-arylbutanoates, alkyl-2-oxo-4-arylbut-3-enoates[21a] and aryl imines[21b] to yield an array of chiral synthons. Extending the scope of the substrate for the biocatalyst *C. parapsilosis* ATCC 7330, allowed the synthesis of a series of enantiomerically pure (*S*)-1-phenyl-1,2-ethanediols in good yields and with high enantiomeric excess using various substituted aromatic α-oxoaldehydes as starting materials is reported herein. These aromatic α-oxoaldehydes contain both aldehyde and keto functionalities, and are therefore interesting molecules to study the selectivity and specificity of the biocatalyst *Candida parapsilosis* ATCC 7330 towards asymmetric reductions.

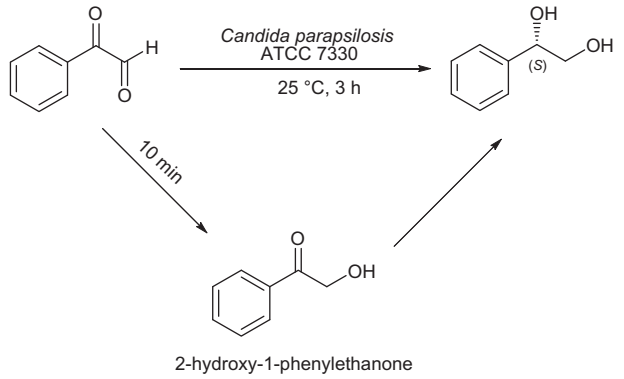
2. Results and discussion

A series of substituted aromatic α-oxoaldehydes **1a**–**1k** were synthesised according to the reported methods,[22] and 2-oxo-2-phenylacetaldehyde (phenylglyoxal) **1a** was used as a standard substrate for the optimisation of the biocatalytic asymmetric reduction reaction. Phenylglyoxal, when incubated with the whole cells of *C. parapsilosis* ATCC 7330 resulted in complete conversion to enantiomerically pure (*S*)-1-phenyl-1,2-ethanediol with a yield of 70% and ee of 99% in 3 h at 25 °C (Scheme 1). The time course of the reaction was monitored by HPLC using a reverse phase column and revealed an intermediate at 10 min which was identified as 2-hydroxy-1-phenylethanone.[23] This indicates that the biocatalyst *C. parapsilosis* ATCC 7330 first selectively reduces the aldehyde group of phenylglyoxal followed by the reduction of the keto group. The bioreduction of phenylglyoxal to enantiomerically pure (*S*)-1-phenyl-1,2-ethanediol using whole cells of *C. parapsilosis* ATCC 7330 involves a one-pot, two-step process *via* the formation of 2-hydroxy-1-phenylethanone (Scheme 2) as an intermediate. It is noteworthy that in the present study, the reduction of phenylglyoxal was completed in 3 h as compared to the multienzymatic preparation of (*S*)-1-phenyl-1,2-ethanediol reported by Gennaro et al., which requires 22 h for completion of the reaction.[19] As can be seen in Table 1, various α-oxoaldehydes were reduced by whole cells of *C. parapsilosis* ATCC 7330 to give enantiomerically



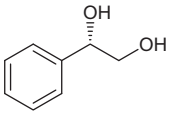
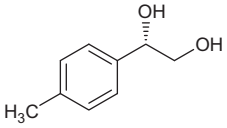
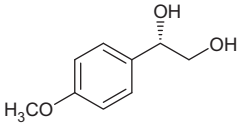
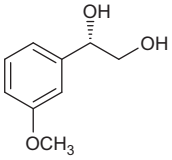
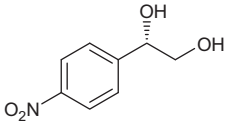
R = H, *p*-CH_3, *p*-OCH_3, *p*-NO_2, *p*-F, *p*-Cl, *p*-Br, *m*-NO_2, *m*-OCH_3, **o*-Cl, *o*-CH_3
*(*R*)-enantiomer was obtained as the major enantiomer

Scheme 1. Asymmetric reduction of aromatic α-oxoaldehydes **1a**–**1i** using the whole cells of *Candida parapsilosis* ATCC 7330.



Scheme 2. Intermediate in the asymmetric reduction of aromatic α-oxoaldehydes.

Table 1
Asymmetric reduction of various substituted phenylglyoxals using whole cells of *Candida parapsilosis* ATCC 7330

Entry	Product	ee[a] (%)	Yield[b] (%)	Reaction time (h)	$[\alpha]_D^{30}$ Values	Abs config[c]
2a		99	70	3	+66.9 (*c* 1.0, $CHCl_3$)	(*S*)
2b		>99	68	3	+68.5 (*c* 1.12, $CHCl_3$)	(*S*)
2c		>99	56	3	+60.3 (*c* 0.50, $CHCl_3$)	(*S*)
2d		90	63	5	+46.0 (*c* 1.0, $CHCl_3$)	(*S*)
2e		92	43	3	+16.5 (*c* 1.0, MeOH)	(*S*)

(*continued on next page*)