

Recent Advances in the Biocatalytic Asymmetric Reduction of Acetophenones and α,β -Unsaturated Carbonyl Compounds

J. Augusto R. Rodrigues^{1*}, Paulo J. S. Moran^{1*}, Gelson J. A. Conceição²
and Lucídio C. Fardelone³

¹Institute of Chemistry, State University of Campinas, CP 6154,
13084-971, Campinas, SP, Brazil

²Faculty of Zootechny and Food Engineering, University of São Paulo,
13635-000, Pirassununga, SP, Brazil

³Cristália Chemical and Pharmaceutical Products, 13970-970, Itapira, SP, Brazil

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Summary

Whole cells of living organisms, mainly of yeasts, have been used as reliable biocatalysts by synthetic organic chemists to perform redox reactions of various functional groups. This review focuses on the potential of these whole cells to reduce acetophenones and α,β -unsaturated carbonyl compounds (aldehydes and ketones) furnishing relevant chiral building blocks for fine chemicals and the pharmaceutical industries.

Key words: biocatalysis, oxidoreductase, acetophenones, chiral building blocks

Introduction

In 1987, the US Food and Drug Administration issued a set of initial guidelines on the submission of new drug applications, where the question of stereochemistry in the manufacture of drug substances was approached directly (1). The guidelines that were finally released in 1992 stipulated that the action of each enantiomer of a pharmaceutical product must be individually characterized. This regulation became a driving force for researchers and pharmaceutical companies to look for chemical or biochemical processes that result in enantiomerically pure compounds. The chemical industry is now turning more and more to enzymatic and fermentation processes in order to obtain enantiomerically pure aminoacids, aminoalcohols, amines, alcohols and epoxides as intermediates for the pharmaceutical industry and agrochemistry, where both a high degree of purity and large quantities of compounds are required (2).

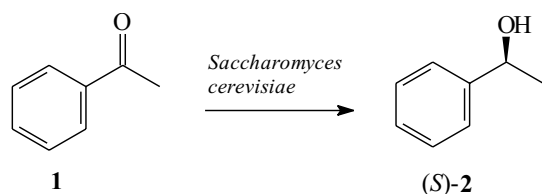
The major advantage of whole living cells over isolated NAD(P)H-dependent carbonyl reductases for use in reduction processes is that the cells regenerate their own cofactors. Further, they are easy to produce and handle, and are of relatively low cost. This review focuses on the potential of whole cells of living organisms, mainly yeast cells, to reduce acetophenones and α,β -unsaturated carbonyl compounds (aldehydes and ketones) furnishing relevant chiral building blocks for fine chemicals and the pharmaceutical industries.

Reduction of Acetophenone Derivatives

Acetophenone derivatives are probably the most studied substrates used for enantioselective bioreduction to the corresponding alcohols. This reduction is mediated by whole cells of a variety of microorganisms. The group of Mosher *et al.* (3) was one of the first to re-

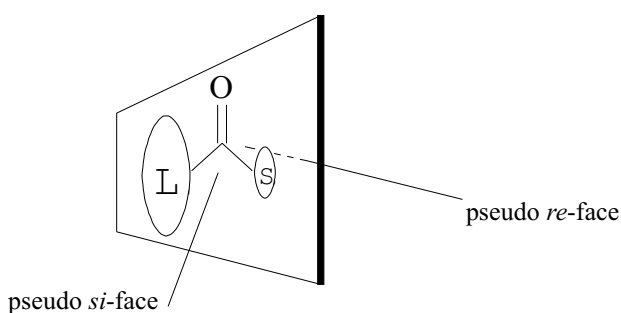
* Corresponding authors; E-mail: jaugusto@iqm.unicamp.br; moran@iqm.unicamp.br

duce acetophenone using *Saccharomyces cerevisiae* to obtain 1-phenyl-1-ethanol in reasonable yield and enantiomeric excess (e.e.) (Scheme 1). Over the past few years, many authors have used the products of enantioselective bioreductions of acetophenone derivatives as starting materials for the synthesis of a wide type of optically active compounds.



Scheme 1

In general, the reductions of acetophenone derivatives follow Prelog's rule (4) (the hydrogen transfer by pseudo *re*-face), taking into account that the aryl group is larger than the methyl group (Fig. 1). However, as pointed out in the next section, some microorganisms give products that have the opposite stereochemistry to that predicted by Prelog's rule.

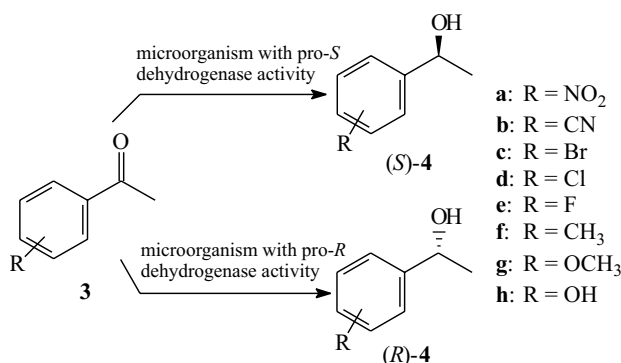
Fig. 1. Pseudo *si*-face and *re*-face of a ketone

Reduction of Acetophenones with Substituents on the Benzene Ring

Various researchers have used a variety of microorganisms to reduce acetophenones that have substituent groups attached to the *meta*, *ortho* or *para* positions of the benzene ring, obtaining the correspondent alcohols in high e.e. (5–21). The velocity of this reaction is enhanced when electron withdrawing groups (EWG) are attached to the *para* position of the aromatic ring and slowed when electron donating groups (EDG) are attached in this position (22,23). This observation agrees with proposal that the hydride transfer from NADH or NADPH to the ketone carbonyl carbon is mediated by a dehydrogenase rather than by a radical mechanism (24–29).

The enhancement and slowing effects may be observed in Table 1, which shows data collected from recent published works about the reduction of acetophenones by various microorganisms. The electronic effect can be observed when the substituents are in *meta* or

ortho positions, but some other types of effect, such as the bulk of the substituent group and polar interactions with the active site of the dehydrogenase, may become predominant. It is interesting to note that some microorganisms contain a predominance of pro-*R* dehydrogenases while others contain a predominance of pro-*S* dehydrogenases (Scheme 2). This complementary enantioselectivity is very convenient, allowing synthetic organic chemists to choose the best microorganisms for use in their synthesis projects. In fact, the information about the stereospecificity of each microorganism is so important that fast-screening methodologies have been developed in order to allow chemists to select the best biocatalyst for a specific biotransformation.



Scheme 2

Several workers have used these fast-screening methodologies. Homann *et al.* (23) selected 14 microorganisms in a screening involving 300 microorganisms for the reduction of 4-substituted-acetophenone. Goswami *et al.* screened about 100 microorganisms covering many species of *Candida*, *Pichia*, *Hansenula*, *Geotrichum*, *Rhodococcus* and *Aureobasidium*, for the stereospecific reduction of α -chloroketone (30). Chartrain *et al.* (31) screened more than 300 microorganisms for the reduction of 12 pharmaceutically relevant prochiral ketones, based on the constructions and accessibility of a microbial library.

Patel *et al.* (18) found 19 microorganisms in a screening for the enantioselective reduction of 2-bromo-4-fluoroacetophenone, giving the corresponding (*S*)-alcohol in excellent yield and e.e. In a screening of 416 microorganisms for reductase activity, Carballeira *et al.* isolated a new microorganism, *Diplogelasinospora grovesii* IMI 171018 that showed very high activity for reduction of a cyclic ketone (21).

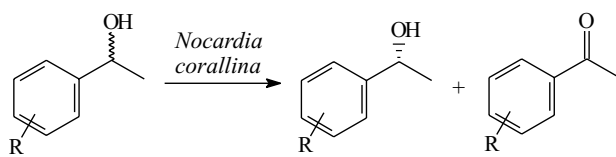
One of the disadvantages of ketone reductions involving whole cells is that pro-*S* and pro-*R* dehydrogenases may be competing for the substrate and if the two dehydrogenases have similar values of k_{cat}/K_M then the alcohol produced will have low values of e.e. (34). A number of strategies has been used to circumvent this disadvantage, such as reduction of substrate concentration, which favors the enzyme with the highest value of k_{cat}/K_M (35,36), the use of additives (37–40) and heat treatment (41) to deactivate one of those enzymes. Molecular biology offers an alternative approach to eliminating the catalytic activities of competing dehydroge-

Table 1. Bioreduction of acetophenones with substituents in the benzene ring mediated by various microorganisms

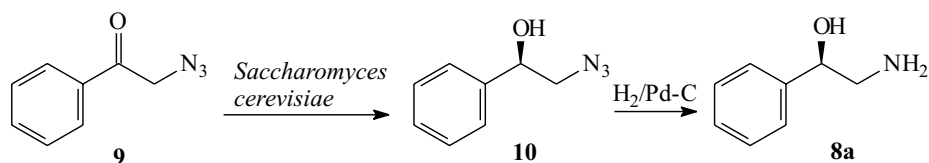
Entry	Ketone	Microorganism	Alcohol	Yield/%	e.e./%	Ref.
1	<i>p</i> -Cl	<i>Rhodotorula glutinis</i> 16740	(S)	80	>99	23
2	<i>p</i> -F	"	(S)	62	>99	"
3	<i>p</i> -Cl	<i>R. mucilaginosa</i> 64684	(S)	75	>99	"
4	<i>p</i> -F	"	(S)	68	95	"
5	<i>p</i> -OCH ₃	"	(S)	23	>99	"
6	<i>p</i> -Cl	<i>Yarrowia lipolytica</i> 8661	(R)	86	>99	"
7	<i>p</i> -F	"	(R)	87	85	"
8	<i>p</i> -Me	"	(R)	77	73	"
9	<i>p</i> -OCH ₃	"	(R)	61	>99	"
10	<i>o</i> -Cl	<i>Synechococcus</i> sp. PCC 7942	(S)	24	96	32
11	<i>m</i> -Cl	"	(S)	37	100	"
12	<i>p</i> -Cl	"	(S)	34	96	"
13	<i>o</i> -F	"	(S)	28	100	"
14	<i>m</i> -F	"	(S)	14	100	"
15	<i>p</i> -F	"	(S)	2	100	"
16	<i>o</i> -Me	<i>Synechococcus</i> sp. PCC 7942	(S)	8	100	"
17	<i>m</i> -Me	"	(S)	31	99	"
18	<i>p</i> -Me	"	(S)	6	100	"
19	<i>o</i> -OMe	"	(S)	10	100	"
20	<i>m</i> -OMe	"	(S)	19	100	"
21	<i>p</i> -OMe	"	(S)	4	100	"
22	<i>p</i> -OH	<i>Trichothecium</i> sp.	-	-	-	17
23	<i>p</i> -Cl	"	(R)	72	98	"
24	<i>p</i> -CH ₃	"	(R)	45	90	"
25	<i>p</i> -OCH ₃	"	-	-	-	"
26	<i>o</i> -Cl	<i>Geotrichum candidum</i>	(S)	99	3	33
27	<i>m</i> -Cl	"	(R)	90	16	"
28	<i>p</i> -Cl	"	(R)	97	89	"
29	<i>p</i> -F	"	-	-	-	"
30	<i>o</i> -CH ₃	"	(R)	99	2	"
31	<i>m</i> -CH ₃	"	(R)	89	21	"
32	<i>p</i> -CH ₃	"	(R)	95	79	"
33	<i>p</i> -OCH ₃	"	(R)	77	97	"
34	<i>p</i> -F	<i>Rhizopus arrhizus</i>	(S)	51	68	8
35	<i>p</i> -Cl	"	(S)	72	91	"
36	<i>p</i> -Br	"	(S)	62	94	"
37	<i>p</i> -I	"	(S)	59	96	"
38	<i>p</i> -OCH ₃	"	(S)	58	10	"
39	<i>p</i> -CN	"	(S)	55	46	"
40	<i>p</i> -CH ₃	"	(S)	72	72	"

nases. For example, a specific dehydrogenase can be expressed in *E. coli* and whole cells of the engineered strain can be used to reduce ketones (42,43). Expression of the gene encoding NAD(P)H-dependent carbonyl reductase in *E. coli* cells, together with the gene for glucose dehydrogenase, which acts as cofactor regenerator, allows the production of many chiral alcohols, as reported by Shimizu and Ogawa (44).

Microbial resolution of racemic secondary alcohols provides enantiomerically pure chiral alcohols, via oxidation of only one enantiomer to the ketone. 1-Arylethanol derivatives have been resolved by direct microbial de-racemization with either *Geotrichum candidum* (45) or *Nocardia corallina* (46) and by a combined microbial oxidation/reduction with *Bacillus stearothermophilus* and *Yarrowia lipolytica* (47). *Nocardia corallina* mediated the enantioselective oxidation of (3- or 4-substituted benzene)-1-ethanol in reasonable yield and excellent e.e. (Scheme 3). Substituents at position-2 gave poor yield and e.e.



Scheme 3



Scheme 5

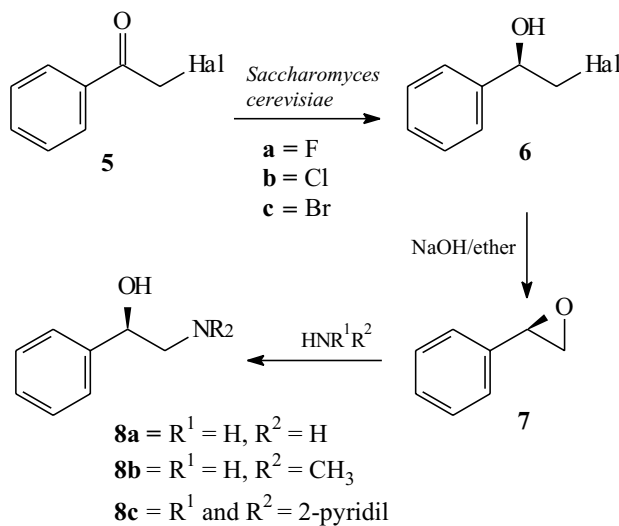
Reduction of Acetophenones with Substituents at the α -Carbon

The enantioselective reduction of acetophenones that have a suitable group attached to the α -carbon furnishes valuable intermediates that can be used as chiral building blocks in organic synthesis. Bioreduction of α -haloacetophenones **5a–c**, mediated by *Saccharomyces cerevisiae*, furnished halohydrins (R)-**6a–c** in 10–74 % yield and 82–97 % e.e. (48) and the halohydrin (R)-**6b** was used to prepare (R)-1-phenylethanolamines **8a–c** via chiral styrene oxide (Scheme 4) (49). The (R)-1-phenylethanolamine **8a** was also synthesized by reduction of α -azidoacetophenone **9**, mediated by *Saccharomyces cerevisiae* immobilized on montmorillonite K10, giving the corresponding azido alcohol **10** in 45 % yield and 97 % e.e. This was reduced by $H_2/Pd-C$ to (R)-2-amino-1-phenylethanol in 96 % yield and 97 % e.e. (Scheme 5) (50).

When α -iodoacetophenone **5d** was treated with *Saccharomyces cerevisiae*, dehalogenated products were obtained (48). Haloacetophenones were used as mechanistic probes to show that the reduction of acetophenones to give dehalogenated products by *Saccharomyces cerevisiae* occurs via hydride transfer from NADH or NADPH, mediated by a dehydrogenase present in the cells, to the

carbonyl carbon of acetophenones rather than by electron transfer (Scheme 6) (24–29) or glutathione-dependent (51) mechanisms.

In recent years, various microorganisms have been used to reduce α -haloacetophenones to the corresponding alcohols in good yield and e.e. (Table 2). The pro-

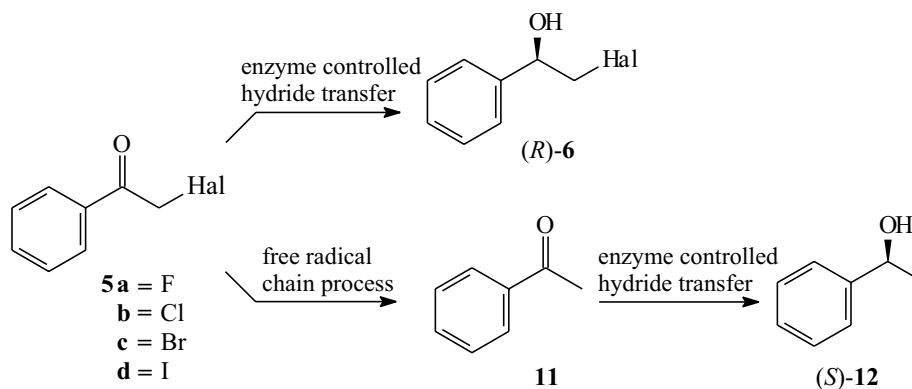


Scheme 4

tentality of the application of enantioselective microbial reduction of α -haloacetophenones is high due to the access to chiral epoxides (Scheme 4). The company Kaneka uses dehydrogenases in form of whole cells for production of (R)- and (S)-styrene oxides on a pilot plant scale (52).

Goswami *et al.* (30) found *Pichia pinus* SC 13864 and *Candida sonorensis* SC 16117 in a screening involving about 100 microorganisms. These microorganisms reduce ketone **13** to give (R)-**14** and (S)-**14**, respectively, thereby representing one approach for the construction of the chiral centers of the corresponding epoxides (Scheme 7).

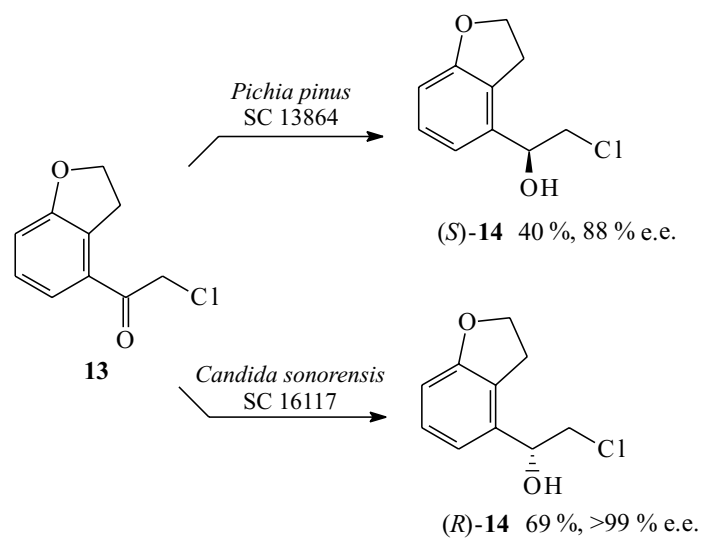
Chartrain *et al.* (31) selected *Hansenula subpelliculosa* MY 1552, *Pichia delftensis* MY 1568, *Kluyveromyces marxianus* MY 1516, *S. bayanus* MY 1930, *R. pilimanae* ATCC 32762 and *P. carsoni* MY 1622 from twenty strains that gave positive results for enantioselective bioreduction of α -haloacetophenone **15** to (S)-**16** ($X = Cl$) (Scheme 8). The alcohol that is obtained may be used as an intermediate in the synthesis of an endothelin receptor antagonist (57). Recently, we found that *Rhodotorula glutinis* CCT 2182 reduces **15** ($X = Cl, Br$ and N_3) to the corresponding alcohol (R)-**16** in excellent yield and e.e. (58). The alcohols (R)-**16** are also intermediates in the synthesis of (R)-epinephrine, (R)-norepinephrine and (R)-isoproterenol.



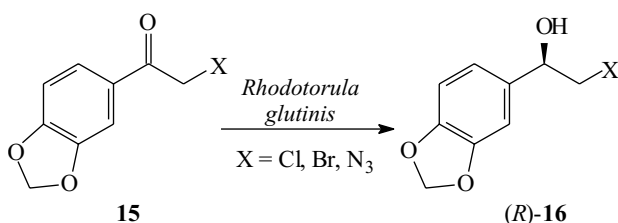
Scheme 6

Table 2. Bioreduction of α -haloacetophenones **5a–d** mediated by microorganisms

Entry	Ketone	Microorganism	Alcohol	Yield/%	e.e./%	Ref.
1	5a	<i>Sacharomyces cerevisiae</i>	(R)-6a	67	97	48,49
2	5b	"	(R)-6b	37	90	"
3	5c	"	(R)-6c	74	82	"
4	5d	"	(S)-12	32	73	35,36
5	5a	<i>Geotrichum</i> sp.	(S)-6a	65	75	53
6	5b	"	(S)-6b	86	87	"
7	5c	"	(S)-6c	15	94	"
8	5c	<i>Rhodotorula</i> sp. AS2.2241	(R)-6c	20	>99	12
9	5a	<i>R. mucilaginosa</i> CBS 2378	(R)-6a	88	>99	54
10	5b	<i>Cryptococcus macerans</i>	(R)-6b	80	100	55
11	5c	"	(R)-6c	95	93	"
12	5b	<i>Geotrichum candidum</i> CCT 1805	(S)-6b	89	>99	56
13	5c	"	(S)-6c	99	90	"
14	5d	"	(S)-6d	96	>99	"
15	5b	<i>Rhodotorula glutinis</i> CCT 2182	(R)-6a	98	92	"
16	5c	"	(R)-6c	97	>99	"
17	5d	"	(R)-6d	98	94	"

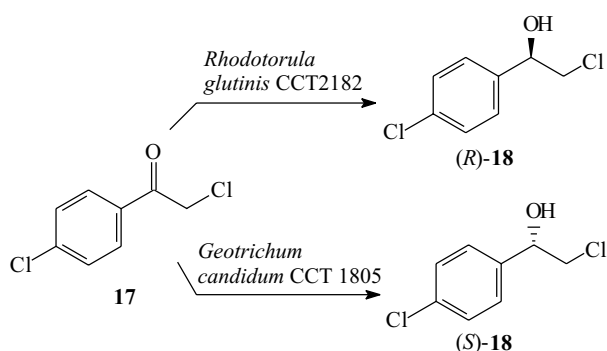


Scheme 7



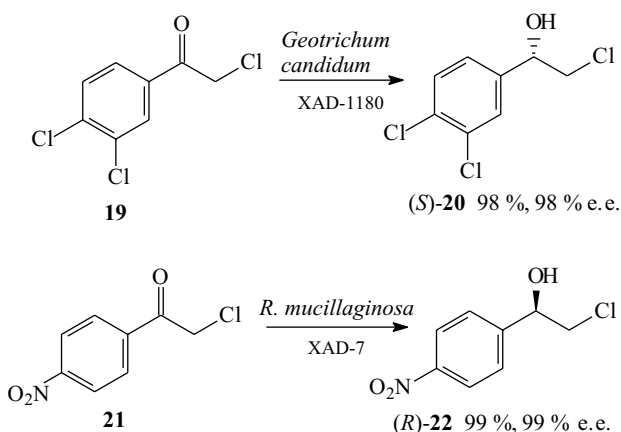
Scheme 8

The alcohol (*R*)-**18** is an important intermediate in the synthesis of Eliprodil® and may be obtained in excellent yield and e.e. by bioreduction of α -chloro ketone **17**, mediated either by engineered cells (**44**) or by *Rhodotorula glutinis* (Scheme 9) (59). The alcohol (*S*)-**18** is obtained when *Geotrichum candidum* is used.



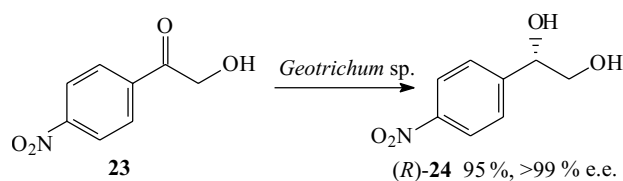
Scheme 9

Fantoni *et al.* (54,60) identified several microorganisms from their collection that reduced α -haloacetophenones **5**, **19** and **21** in the presence of polymeric absorbing resins, giving the corresponding alcohols in high yield and e.e. The alcohols obtained, **20** and **22**, may be used as chiral building blocks for the preparation of α - and β -adrenergic drugs such as Sertraline, Nifenalol and Sotalol, via their epoxides (Scheme 10).



Scheme 10

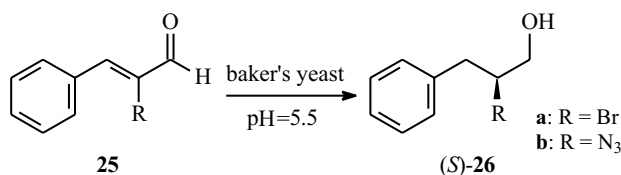
The drug Sotalol may also be prepared from (*S*)-1-(4-nitrophenylethanol) **24** obtained in excellent yield and e.e. by reduction of ketone **23** by *Geotrichum* sp. (Scheme 11) (61).



Scheme 11

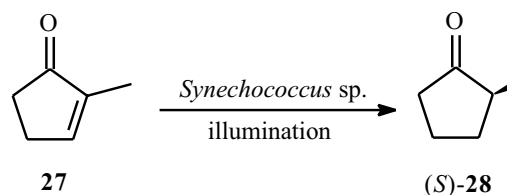
Reduction of α,β -Unsaturated Aldehydes and Ketones

It is well established that α,β -unsaturated aldehydes and ketones may be reduced with certain regio- and stereoselectivity using whole cells, with the selectivity depending mainly on (i) the biocatalyst, (ii) the substitution pattern of the C=C bond, (iii) the reaction conditions and (iv) the time of incubation. As such, the choice of appropriate conditions can allow the selective reduction of either the C=O or the C=C bond alone or the reduction of both groups. In terms of whole cells, baker's yeast is still the most popular reducing microorganism, mainly because of its availability and cheapness. As depicted in Scheme 12, Fardelone *et al.* (62) exploited the versatility of baker's yeast to prepare α -substituted-3-phenyl-1-propanols (**26**) through the asymmetric reduction of α -substituted-cinnamaldehydes (**25**) in excellent yields (up to 99%) and enantiomeric excesses (>99%). The control of the pH of the reaction mixture at 5.5 by adding CaCO₃ was crucial to ensure good yields of the products (Scheme 12). The chiral building blocks were used in alternative synthesis routes for the production of both L- and D-phenylalaninol.



Scheme 12

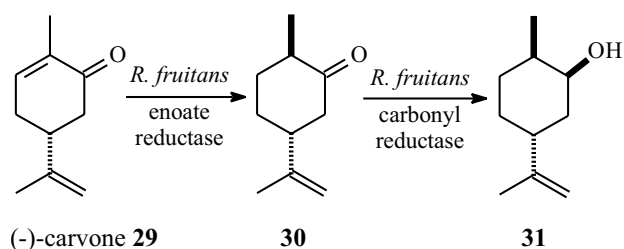
Reduction of cyclic enones by whole cells has been explored further. Shimoda *et al.* (63) found that *Synechococcus* sp. PCC 7942, a cyanobacterium, reduces both the endocyclic C=C bond of *s-trans* enones and the exocyclic C=C bond of *s-cis* enones to the corresponding (*S*)-ketones, under illumination (Scheme 13). It is worth mentioning that *Synechococcus* sp. PCC 7942 cells have the ability of catalyzing enantioselective reduction of *s-trans* enones to (*S*)-ketones. They specifically act on *s-trans*



Scheme 13

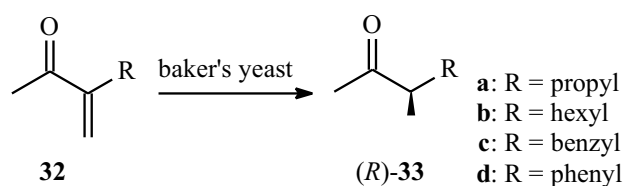
enones that lack substituents at the β -position in relation to the carbonyl group and only if the α -substituent is a relatively small group, like a methyl group.

Plant cells other than those of higher plants are also suitable for enone reduction. For instance, cell cultures of *Riccia fruitans*, a bryophyte, were able to biotransform the sterically hindered terpenoid (-)-(5*R*)-carvone, in a stereoselective fashion (Scheme 14) (64). The enoate reductase step of the reduction of (-)-(5*R*)-carvone (29) to (+)-*n*-dihydrocarvone (30) and the ensuing alcohol dehydrogenase step yielding *neo*-dihydrocarveol (31) both occurred with high diastereoselectivity.



Scheme 14

The work of Siqueira-Filho *et al.* represents significant progress in the field of stereoselective biotransformation of α -methylene ketones (65,66). Again, baker's yeast was the biocatalyst of choice in a systematic study of the effect on the reaction profile of the substituents attached to the enone group. As expected, the reduction of C=C bond by enoate reductase enzymes was much faster than the reduction of the C=O bond by carbonyl reductase enzymes. Ultimately, only the substrate **32** bearing a small methyl group attached to the carbonyl was satisfactorily reduced to the corresponding saturated (*R*)-ketone **33** in good yields and e.e.'s (up to >99 %) (Scheme 15).

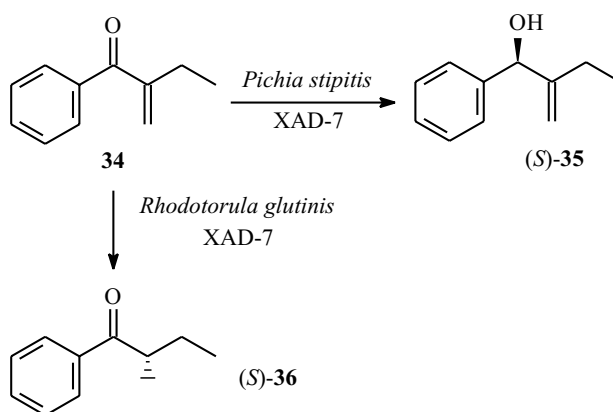


Scheme 15

A bottleneck in biotransformations with whole cells is the presence of multiple competing enzymes, which reduces or suppresses both the formation of the desired product and the stereoselectivity of the reaction. In the past years, the hydrophobic polymer method has presented itself as a good tool to harness the potential of multiple enzymes acting on the same substrate. For instance, Conceição *et al.* (67) circumvented the cumbersome reduction of α -methylene ketone **34** by the yeast *Pichia stipitis* CCT 2617 using Amberlite XAD-7 as adsorbing resin (Scheme 16). The formation of by-products and the pronounced toxic effect of the substrate on the biocatalyst were suppressed through the slow release of the substrate, which was adsorbed on the beads of

XAD-7, into the aqueous reaction medium. Low concentration of the substrate in the aqueous phase favored the action of the most active enzyme, a carbonyl reductase that delivered (*S*)-allylic alcohol **35** in high yield and e.e. (>99 %).

Amberlite XAD-7 was also exploited in the reduction of the same α -methylene ketone **34** by the yeast *Rhodotorula glutinis* CCT 2182 (Scheme 16) (68). The low yield and moderate enantiomeric excess of the product were dramatically changed when XAD-7 was used to control the concentration of the enone in the aqueous phase. As a result, the corresponding (*S*)- α -methylketone **36** was isolated in high yield and e.e. (99 %).



Scheme 16

Conclusion

The past few years have witnessed significant developments in the field of biocatalytic reduction of acetophenones and α,β -unsaturated carbonyl compounds. High efficiency of these processes makes them attractive alternatives to existing methods in asymmetric catalysis for obtaining highly functionalized chiral alcohols and ketones in enantiomerically pure form.

Acknowledgements

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References

1. S. Ahuja: *Chiral Separations by Chromatography*, Oxford University Press, Oxford (2000) p. 33.
2. M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßler, R. Sturmer, T. Zelinski, *Angew. Chem.-Int. Edit.* 43 (2004) 788–824.
3. R. MacLeod, H. Prosser, L. Fikentscher, J. Lanyi, H. S. Mosher, *Biochemistry*, 3 (1964) 838–846.
4. V. Prelog, *Pur. Appl. Chem.* 9 (1964) 119–130.
5. N. A. Salvi, P. N. Patil, S. R. Udupa, A. Banerjee, *Tetrahedron: Asymmetry*, 6 (1995) 2287–2290.
6. K. Nakamura, T. Matsuda, A. Ohno, *Tetrahedron: Asymmetry*, 7 (1996) 3021–3024.
7. K. Nakamura, *J. Mol. Catal. B-Enzym.* 5 (1998) 129–132.
8. N. A. Salvi, S. Chattopadhyay, *Tetrahedron*, 57 (2001) 2833–2839.

9. N. Itoh, N. Mizuguchi, M. Mabuchi, *J. Mol. Catal. B-Enzym.* 6 (1999) 41–50.
10. T. Matsuda, Y. Nakajima, T. Harada, K. Nakamura, *Tetrahedron: Asymmetry*, 13 (2002) 971–974.
11. W. Stampfer, B. Kosjek, C. Moitzi, W. Kroutil, K. Faber, *Angew. Chem.-Int. Edit.* 41 (2002) 1014–1017.
12. Y. Ni, J. H. Xu, *J. Mol. Catal. B-Enzym.* 18 (2002) 233–241.
13. W. Stampfer, B. Kosjek, K. Faber, W. Kroutil, *J. Org. Chem.* 68 (2003) 402–406.
14. J. V. Comasseto, A. T. Omri, L. H. Andrade, A. L. M. Porto, *Tetrahedron: Asymmetry*, 14 (2003) 711–715.
15. T. R. Gervais, G. Carta, J. L. Gainer, *Biotechnol. Progr.* 19 (2003) 389–395.
16. C. Paizs, M. Tosa, C. Majdik, P. Moldovan, L. Novák, P. Kolonits, A. Marcovici, F. D. Irimie, L. Poppe, *Tetrahedron: Asymmetry*, 14 (2003) 1495–1501.
17. D. Mandal, A. Ahmad, M. I. Khan, R. Kumar, *J. Mol. Catal. B-Enzym.* 27 (2004) 61–63.
18. R. N. Patel, A. Goswami, L. Chu, M. J. Donovan, V. Nanduri, S. Goldberg, R. Johnston, P. J. Siva, B. Nielsen, J. Fan, W. X. He, Z. Shi, K. Y. Wang, R. Eiring, D. Cazzulino, A. Singh, R. Mueller, *Tetrahedron: Asymmetry*, 15 (2004) 1247–1258.
19. L. H. Andrade, A. T. Omori, A. L. M. Porto, J. V. Comasseto, *J. Mol. Catal. B-Enzym.* 29 (2004) 47–54.
20. J. V. Comasseto, L. H. Andrade, A. T. Omori, L. F. Assis, A. L. M. Porto, *J. Mol. Catal. B-Enzym.* 29 (2004) 55–61.
21. J. D. Carballeira, E. Álvarez, M. Campillo, L. Pardo, J. V. Sinisterra, *Tetrahedron: Asymmetry*, 15 (2004) 951–962.
22. G. Eichberger, K. Faber, H. Griengl, *Mon. Chem.* 116 (1985) 1233–1236.
23. M. J. Homann, R. B. Vail, E. Previte, M. Tamarez, B. Morgan, D. R. Dodds, A. Zaks, *Tetrahedron*, 60 (2004) 789–797.
24. D. D. Tanner, H. K. Singh, *J. Org. Chem.* 51 (1986) 5182–5186.
25. D. D. Tanner, H. K. Singh, A. Kharrat, A. R. Stein, *J. Org. Chem.* 52 (1987) 2142–2146.
26. D. D. Tanner, A. R. Stein, *J. Org. Chem.* 53 (1988) 1642–1646.
27. D. D. Tanner, A. Kharrat, *Org. Chem.* 53 (1988) 1646–1650.
28. W. Adam, M. Heil, R. Hutterer, *J. Org. Chem.* 57 (1992) 4491–4495.
29. L. M. Aleixo, M. Carvalho, P. J. S. Moran, J. A. R. Rodrigues, *Bioorg. Med. Chem. Lett.* 3 (1993) 1637–1642.
30. A. Goswami, K. D. Mirfakhrae, M. J. Tottleben, S. Swaminathan, R. N. Patel, *J. Ind. Microbiol. Biotechnol.* 26 (2001) 259–262.
31. M. Chartrain, R. Greasham, J. Moore, P. Reider, D. Robinson, B. Buckland, *J. Mol. Catal. B-Enzym.* 11 (2001) 503–512.
32. K. Nakamura, Y. Inoue, Matsuda T., A. Ohno, *Tetrahedron Lett.* 35 (1995) 6263–6266.
33. K. Nakamura, R. Yamanaka, K. Tohi, H. Hamada, *Tetrahedron Lett.* 41 (2000) 6799–6802.
34. C. J. Sih, C. S. Chen, *Ang. Chem.-Int. Edit.* 23 (1984) 574–578.
35. P. D'Arrigo, C. Fuganti, G. P. Fantoni, S. Servi, *Tetrahedron*, 54 (1998) 15017–15026.
36. P. D'Arrigo, M. Lattanzio, G. P. Fantoni, S. Servi, *Tetrahedron: Asymmetry*, 9 (1998) 4021–4026.
37. K. Nakamura, K. Inoue, K. Ushio, S. Oka, A. Ohno, *Chem. Lett.* 16 (1987) 679.
38. K. Nakamura, Y. Kawai, N. Nakajima, A. Ohno, *J. Org. Chem.* 56 (1991) 4778.
39. D. H. Dao, M. Okamura, T. Akasaka, Y. Kawai, K. Hida, A. Ohno, *Tetrahedron: Asymmetry*, 9 (1998) 2725–2737.
40. R. Hayakwa, K. Nozawa, M. Shimizu, T. Fujisawa, *Tetrahedron Lett.* 39 (1998) 67–70.
41. K. Nakamura, S. Kondo, Y. Kawai, K. Hida, K. Kitano, A. Ohno, *Tetrahedron: Asymmetry*, 7 (1996) 409–412.
42. S. Rodriguez, K. T. Schroeder, M. M. Kayser, J. D. Stewart, *J. Org. Chem.* 65 (2000) 2586–2587.
43. J. D. Stewart, *Curr. Opin. Biotechnol.* 11 (2000) 363–368.
44. J. Ogawa, S. Shimizu, *Curr. Opin. Biotechnol.* 13 (2002) 367–375.
45. K. Nakamura, M. Fjii, Y. Ida, *Tetrahedron: Asymmetry*, 12 (2001) 3147–3153.
46. H. I. Pérez, H. Luna, N. Manjarrez, A. Solís, *Tetrahedron: Asymmetry*, 12 (2001) 1709–1712.
47. G. Fantin, M. Fogagnolo, P. P. Giovannini, A. Medici, P. Pedrini, *Tetrahedron: Asymmetry*, 6 (1995) 3047–3053.
48. M. Carvalho, M. T. Okamoto, P. J. S. Moran, J. A. R. Rodrigues, *Tetrahedron*, 47 (1991) 2073–2080.
49. E. C. S. Brenelli, M. Carvalho, M. T. Okubo, M. Marques, P. J. S. Moran, J. A. R. Rodrigues, A. E. P. M. Sorrilha, *Indian J. Chem.* 31B (1992) 821–823.
50. A. E. P. M. Sorrilha, M. Marques, I. Joekes, P. J. S. Moran, J. A. R. Rodrigues, *Biorg. Med. Chem. Lett.* 2 (1992) 191–196.
51. G. Jorg, M. Bertau, *Chembiochem*, 4 (2004) 87–92.
52. M. Breuer, K. Ditrach, T. Habicher, B. Hauer, M. Keßeler, R. Sturmer, T. Zelinski, *Angew. Chem.-Int. Edit.* 43 (2004) 788–824.
53. Z.-L. Wei, Z.-Y. Li, G.-Q. Lin, *Tetrahedron*, 54 (1998) 13059–13072.
54. C. Barbieri, E. Caruso, P. D'Arrigo, G. P. Fantoni, S. Servi, *Tetrahedron: Asymmetry*, 10 (1999) 3931–3937.
55. M. Imuta, K. Kawai, H. Ziffer, *J. Org. Chem.* 45 (1980) 3352–3355.
56. L. C. Fardelone, J. A. R. Rodrigues, P. J. S. Moran, *Arquivoc (Part 10)* (2003) 404–410.
57. B. Krulwicz, D. Tschaen, P. Devine, C. Roberge, S. Lee, R. Greasham, M. Chartrain, *Biocatal. Biotransform.* 19 (2000) 267–279.
58. H. Antunes, L. C. Fardelone, J. A. R. Rodrigues, P. J. S. Moran, *Tetrahedron: Asymmetry*, 15 (2004) 2615–2620.
59. P. J. S. Moran, L. C. Fardelone, J. A. R. Rodrigues, *BR Patent PI 0303790-8* (2003).
60. C. Barbieri, L. Bossi, P. D'Arrigo, G. P. Fantoni, S. Servi, *J. Mol. Catal. B-Enzym.* 11 (2001) 415–421.
61. Z.-L. Wei, G.-Q. Lin, Z.-Y. Li, *Bioorg. Med. Chem.* 8 (2000) 1129–1137.
62. L. C. Fardelone, J. A. R. Rodrigues, P. J. S. Moran, *J. Mol. Catal. B-Enzym.* 29 (2004) 41–45.
63. K. Shimoda, N. Kubota, H. Hamada, M. Kaji, T. Hirata, *Tetrahedron: Asymmetry*, 15 (2004) 1677–1679.
64. A. Speicher, R. Roeser, R. Heisel, *J. Mol. Catal. B-Enzym.* 22 (2003) 71–77.
65. E. P. Siqueira-Filho, J. A. R. Rodrigues, P. J. S. Moran, *J. Mol. Catal. B-Enzym.* 15 (2001) 23–28.
66. E. P. Siqueira-Filho, J. A. R. Rodrigues, P. J. S. Moran, *Tetrahedron: Asymmetry*, 12 (2001) 847–852.
67. G. J. A. Conceição, P. J. S. Moran, J. A. R. Rodrigues, *Tetrahedron: Asymmetry*, 14 (2003) 43–45.
68. G. J. A. Conceição, P. J. S. Moran, J. A. R. Rodrigues, *Arquivoc (Part 10)* (2003) 500–506.

Napredak u biokatalitičkoj asimetričnoj redukciji acetofenona i α,β -nezasićenih karbonilnih spojeva

Sažetak

Cijele stanice živih organizama, posebice stanice kvasaca, koristile su se kao pouzdani biokatalizatori pri provođenju redoks-reakcija raznih funkcionalnih skupina. U radu se posebna pozornost posvetila mogućnostima tih cijelih stanica za redukciju acetofenona i α,β -nezasićenih karbonilnih spojeva (aldehida i ketona) proizvodeći relevantne kiralne spojeve za proizvodnju finih kemikalija i za potrebe farmaceutske industrije.