

Deracemization of Secondary Alcohols through a Concurrent Tandem Biocatalytic Oxidation and Reduction**

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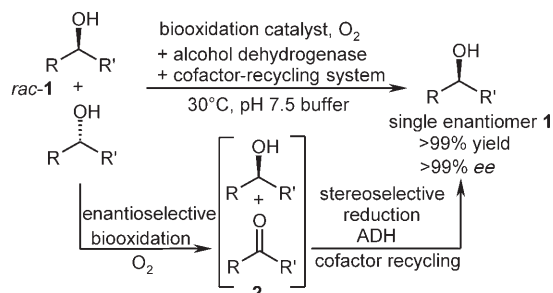
The aim to obtain a highly valuable enantiomerically pure product in 100 % yield and with 100 % *ee* from a cheap racemic substrate in a one-pot process is currently a hot topic in one-pot multiple catalysis.^[1,2] In one-pot sequential catalysis, the reaction conditions can be adjusted for each step; however, concurrent catalysis is more demanding: The steps must be balanced carefully to ensure that the catalytic processes run at comparable rates and, probably most importantly, that the different catalytic reactions do not interfere with one another. Such processes in which multiple catalysts operate concurrently circumvent the often time-intensive and yield-reducing isolation and purification of intermediates in multiple-step syntheses.

For the deracemization^[3] of racemic alcohols through a chemical oxidation–reduction sequence, only sequential processes with one^[4] or two catalysts^[5] have been reported recently. In particular the combination of reaction sequences that involve chemical oxidation and reduction steps with tandem catalysis represents an almost impossible challenge owing to the diverging reaction conditions required. In contrast to the dynamic kinetic resolution^[6] of secondary alcohols through the racemization of the alcohol moiety followed by enzymatic kinetic resolution, no general protocol for the deracemization of alcohols through chemical oxidation and simultaneous reduction of the corresponding ketone has been reported. As oxidation and reduction processes occur simultaneously in living cells, the application of enzymes in concurrent oxidation–reduction sequences might be feasible. Deracemization through the stereoinversion of one alcohol enantiomer was observed in the presence of fermenting or resting microorganisms;^[7,8] however, the application of this method was limited to specific substrates, and only moderate substrate concentrations were possible.

In a first approach to the one-pot deracemization of secondary alcohols, we tested the commercially available microorganisms^[9] for which deracemization through stereoinversion has been described, as well as the strains from our own culture collection. The results confirmed the observations described previously, such as high substrate specificity, the requirement for low substrate concentrations, and

impractically long reaction times. Surprisingly, we observed that the strains of interest showed a high oxidation activity; thus, a significant amount of the ketone was detected along with the alcohol. The best oxidizing strain was found in our own culture collection: Both lyophilized and resting cells of *Alcaligenes faecalis* DSM 13975 catalyzed the enantioselective oxidation of the *R* enantiomer of *rac*-2-octanol (*rac*-1a) to yield optically pure (*S*)-2-octanol ((*S*)-1a; > 99 % *ee*) within 22 h at a substrate concentration of 60 mM. The relative amount of the ketone formed was 29–41 %; therefore, the high *ee* value can not be attributed exclusively to a kinetic resolution, in which case the ketone would need to be formed in a relative amount of 50 % for the alcohol to have an *ee* value of 99 %. We found subsequently in a separate experiment that only negligible oxidation occurred when oxygen was excluded and the reaction was carried out in an argon atmosphere. On the other hand, when the reaction was carried out in an oxygen-saturated environment at an oxygen pressure of 2 bar, the reaction rate of the oxidation increased. Therefore, we concluded that molecular oxygen, one of the most environmentally benign oxidants, is required for this oxidation.^[10]

Such mild and selective oxidation methods are gaining importance.^[11] Oxidative enzymes (more precisely, amine oxidases) are employed for the deracemization of chiral amines, as optimized by Turner and co-workers,^[12] who coupled the enantioselective oxidation of chiral amines with nonstereoselective reduction to give overall deracemization. To date, no general comparable process has been reported for the deracemization of secondary alcohols as a result of the lack of an applicable *sec*-alcohol oxidase.^[13,14] We envisaged that we might couple our oxidation reaction with a highly stereoselective enzymatic reduction step (Scheme 1), as opposed to the nonstereospecific reduction described for amines. We expected that the use of a stereoselective reduction step would result in a more efficient process, as



Scheme 1. Tandem biocatalysis for the deracemization of racemic secondary alcohols through an oxidation–reduction sequence.

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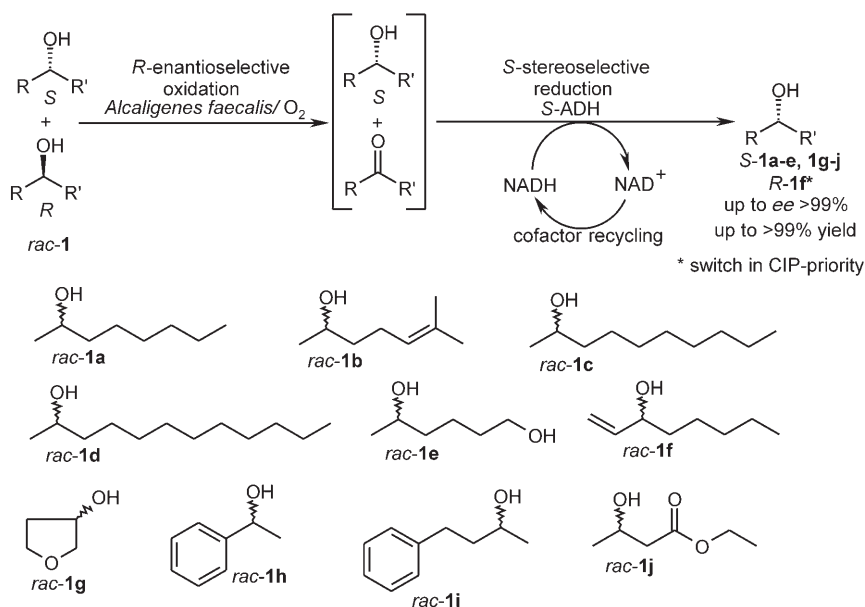
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only 0.5 equivalents, rather than 1 equivalent, of the reagents for the reduction and the oxidation would be required.

Initial explorative experiments in which we attempted to combine lyophilized cells of *Alcaligenes faecalis* DSM 13975 for the oxidation with the commercial *S*-selective alcohol dehydrogenase ADH-“A” from *Rhodococcus ruber* DSM 44541^[15] for the reduction and the cofactor-recycling system glucose dehydrogenase (GDH)/glucose were unsuccessful. In fact, when enantiomerically pure substrates were used, racemization was observed. As lyophilization increases the permeability of the cells, we suspected that a sharp separation of the oxidation and reduction steps was required and might be achieved by using freshly harvested cells with an intact cell membrane. Indeed, the use of freshly harvested cells of *Alcaligenes faecalis* and ADH-“A” with cofactor recycling led finally to a successful system for concurrent deracemization (Scheme 2).

Racemic secondary alcohols, such as *rac*-2-octanol (*rac*-1a) and *rac*-sulcatol (*rac*-1b), could be deracemized by this system within 4 h to yield the enantiomerically pure *S* alcohol (>99% *ee*) with no trace of the ketone (Table 1, entries 1 and 2). These results indicated that the reduction step is the faster step of the reaction. If the reducing enzyme and the cofactor-recycling system were excluded, a significant amount of the ketone was formed (Table 1, entries 3 and 4).

When a different alcohol dehydrogenase, RE-ADH (from *Rhodococcus erythropolis*), was used, similar excellent results were obtained (Table 1, entries 5 and 6). With a different cofactor-recycling system, namely, 2-propanol with ADH-“A” instead of glucose/GDH, almost complete deracemization was observed within 1 h (93–96% *ee*; Table 1, entries 7 and 8). We investigated the deracemization of a range of further substrates, *rac*-1c–1j, with the cofactor-recycling system GDH/glucose. In all cases, the reduction step was sufficiently fast that no trace of the



Scheme 2. Concurrent oxidation and reduction for the deracemization of racemic secondary alcohols to yield the Prelog enantiomer. NADH is the reduced form of nicotinamide adenine dinucleotide (NAD⁺).

Table 1: Biocatalytic deracemization through a tandem stereoselective oxidation–reduction sequence with *Alcaligenes faecalis* DSM 13975 as the catalyst for the *R*-enantioselective oxidation step.

Entry	Substrate ^[a]	Reduction catalyst ^[b]	Cofactor-recycling system ^[c]	<i>t</i> [h]	1 [%] ^[d]	2 [%] ^[e]	<i>ee</i> [%]
1	<i>rac</i> -1a	ADH-“A”	GDH	4	>99	<0.1	>99 (<i>S</i>)
2	<i>rac</i> -1b	ADH-“A”	GDH	4	>99	<0.1	>99 (<i>S</i>)
3	<i>rac</i> -1a	–	–	22	62	38	>99 (<i>S</i>)
4	<i>rac</i> -1b	–	–	22	59	41	>99 (<i>S</i>)
5	<i>rac</i> -1a	RE-ADH	GDH	4	>99	<0.1	>99 (<i>S</i>)
6	<i>rac</i> -1b	RE-ADH	GDH	4	>99	<0.1	>99 (<i>S</i>)
7	<i>rac</i> -1a	ADH-“A”	2-propanol	1	96	4	93 (<i>S</i>)
8	<i>rac</i> -1b	ADH-“A”	2-propanol	1	97	3	96 (<i>S</i>)
9	<i>rac</i> -1c	RE-ADH	GDH	8	>99	<0.1	>99 (<i>S</i>)
10	<i>rac</i> -1c	ADH-“A”	GDH	8	>99	<0.1	>99 (<i>S</i>)
11	<i>rac</i> -1d	RE-ADH	GDH	8	>99	<0.1	>99 (<i>S</i>)
12	<i>rac</i> -1d	ADH-“A”	GDH	8	>99	<0.1	>99 (<i>S</i>)
13	<i>rac</i> -1e	RE-ADH	GDH	16	>99	<0.1	89 (<i>S</i>)
14	<i>rac</i> -1f	RE-ADH	GDH	16	>99	<0.1	20 (<i>R</i>) ^[f]
15	<i>rac</i> -1g	RE-ADH	GDH	16	>99	<0.1	30 (<i>S</i>)
16	<i>rac</i> -1h	RE-ADH	GDH	16	>99	<0.1	10 (<i>S</i>)
17	<i>rac</i> -1i	RE-ADH	GDH	16	>99	<0.1	>99 (<i>S</i>)
18	<i>rac</i> -1i	ADH-“A”	GDH	16	>99	<0.1	>99 (<i>S</i>)
19	<i>rac</i> -1j	RE-ADH	GDH	16	>99	<0.1	96 (<i>S</i>)

[a] Substrate concentration: 60–80 mM. [b] Highly *S*-selective enzymes: ADH-“A” = alcohol dehydrogenase from *Rhodococcus ruber* 44541; RE-ADH = alcohol dehydrogenase from *Rhodococcus erythropolis*. [c] GDH: glucose dehydrogenase, glucose (100 mM), and NAD⁺ (0.5 mM); 2-propanol: 2-propanol (5% v/v; 0.6 M) and NAD⁺ (0.5 mM; the cofactor is recycled by ADH-“A”). [d] Relative amount of the alcohol 1. [e] Relative amount of the ketone 2. [f] Switch in CIP (Cahn–Ingold–Prelog) priority.

ketone was detected, and the enantiomerically enriched alcohols were obtained within 8–16 h. The deracemization system can be applied to alcohol substrates that contain additional functionalities, such as a C=C double bond (in 1b

and **1f**), a primary alcohol (in **1e**), a cyclic ether (in **1g**), or an ester moiety (in **1j**). Furthermore, no other side products were detected. Thus, the reaction was essentially clean: The alcohol was detected exclusively when GDH/glucose was used for recycling. This efficient deracemization system could be used to access the *S* enantiomer even at a substrate concentration of 100 g L⁻¹.

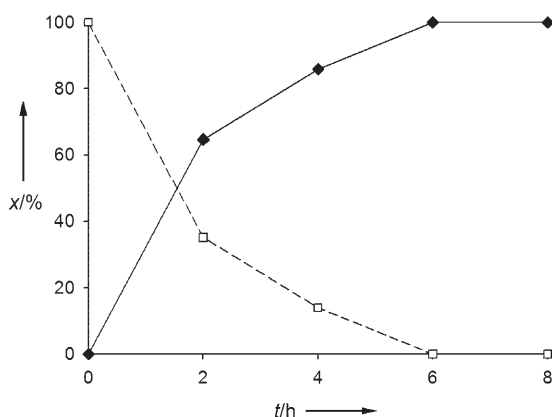


Figure 1. Relative amounts, *x*, of the enantiomers of **1a** in the stereo-inversion of (*R*)-2-octanol ((*R*)-**1a**, □) to (*S*)-**1a** (♦) in the presence of *Alcaligenes faecalis* DSM 13975, RE-ADH, and a cofactor-recycling system (GDH, glucose, and NAD⁺).

As the deracemization was so efficient, we applied our method to the stereoinversion of a chiral secondary alcohol. We monitored the course of the reaction with respect to time for the enantiomerically pure substrate (*R*)-2-octanol ((*R*)-**1a**) with the system *Alcaligenes faecalis*/RE-ADH/GDH/glucose. The alcohol (*R*)-**1a** underwent complete inversion within 6 h to yield (*S*)-**1a** (Figure 1).

To demonstrate that the opposite enantiomer (the *R* enantiomer) is also accessible with a related system, we tested further microorganisms for their ability to oxidize the *S* alcohol. The bacterial strain 0091B,^[16] which was characterized by the German culture collection DSMZ to be identical to *Rhodococcus erythropolis* DSM 43066, showed the desired preference but with significantly lower activity than that of *Alcaligenes faecalis* DSM 13975 (Table 2, entries 1 and 2). To access the *R* enantiomer, oxidation with *Rhodococcus erythropolis* DSM 43066 was coupled in a concurrent tandem reaction with a stereoselective reduction catalyzed by the anti-Prelog-selective alcohol dehydrogenase LK-ADH from *Lactobacillus kefir*.

Deracemization to access the anti-Prelog enantiomer occurred, and the amount of ketone was maintained below the detection limit (Table 2, entries 3–8, 10–12). Surprisingly, in contrast to the result with the first deracemization system (Table 1), *rac*-1-octen-3-ol (*rac*-**1f**) proved to be an excellent substrate, with the highly enantiomerically enriched *S* enantiomer (94% *ee*; Table 2, entry 8) formed within 16 h with no detectable trace of the ketone.

Table 2: Biocatalytic deracemization through a tandem stereoselective oxidation–reduction sequence with *Rhodococcus erythropolis* DSM 43066 as the catalyst for the *S*-enantioselective oxidation step.

Entry	Substrate ^[a]	Reduction catalyst ^[b]	<i>t</i> [h]	1 [%] ^[c]	2 [%] ^[d]	<i>ee</i> [%]
1	<i>rac</i> - 1a	–	24	89	11	26 (<i>R</i>)
2	<i>rac</i> - 1b	–	24	75	25	49 (<i>R</i>)
3	<i>rac</i> - 1a	LK-ADH	16	> 99	< 0.1	43 (<i>R</i>)
4	<i>rac</i> - 1b	LK-ADH	16	> 99	< 0.1	80 (<i>R</i>)
5	<i>rac</i> - 1c	LK-ADH	16	> 99	< 0.1	70 (<i>R</i>)
6	<i>rac</i> - 1d	LK-ADH	16	> 99	< 0.1	55 (<i>R</i>)
7	<i>rac</i> - 1e	LK-ADH	16	> 99	< 0.1	75 (<i>R</i>)
8	<i>rac</i> - 1f	LK-ADH	16	> 99	< 0.1	94 (<i>S</i>) ^[e]
9	<i>rac</i> - 1f	–	16	83	17	34 (<i>S</i>) ^[e]
10	<i>rac</i> - 1g	LK-ADH	16	> 99	< 0.1	<i>rac</i>
11	<i>rac</i> - 1h	LK-ADH	16	> 99	< 0.1	60 (<i>R</i>)
12	<i>rac</i> - 1i	LK-ADH	16	> 99	< 0.1	80 (<i>R</i>)

[a] Substrate concentration: 60–80 mM. [b] An *R*-selective enzyme: LK-ADH = alcohol dehydrogenase from *Lactobacillus kefir*. The cofactor-recycling system used contained glucose dehydrogenase, glucose, (100 mM), and NAD⁺ (0.5 mM). [c] Relative amount of the alcohol **1**. [d] Relative amount of the ketone **2**. [e] Switch in CIP priority.

Finally, we demonstrated the applicability of this deracemization method on a preparative scale. We subjected *rac*-4-phenyl-2-butanol (*rac*-**1i**; 0.5 mL, 485 mg) to deracemization with *Alcaligenes faecalis* DSM 13975 combined with RE-ADH and the NADH-recycling system GDH/glucose. After 16 h of shaking at 30 °C, enantiomerically pure (*S*)-4-phenyl-2-butanol ((*S*)-**1i**; > 99% *ee*) was isolated in 91% yield (441 mg) without any trace of the ketone or any other side product (for a GC chromatogram, see the Supporting Information).

Herein, we have described the identification of *Alcaligenes faecalis* DSM 13975 as a highly active and enantioselective catalyst for the oxidation of secondary alcohols and have demonstrated its application in concurrent tandem oxidation–reduction sequences for the deracemization of secondary alcohols. The most innocuous oxidant, molecular oxygen, is required for the oxidation step, and a commercially available stereoselective alcohol dehydrogenase is used for the reduction step. Furthermore, we showed that the opposite enantiomers are accessible with a similar system, although improved catalysts will be required to generate the products with higher *ee* values. Owing to the increasing importance of biocatalytic transformations in asymmetric organic synthesis,^[17] we expect that this type of deracemization system will gain increasing significance, especially in cases in which the alcohol is more readily accessible or cheaper than the corresponding ketone, or when the ketone has low stability. We have demonstrated the efficient deracemization of racemic secondary alcohols by the stereoinversion of one enantiomer in a tandem reaction sequence in which only glucose and molecular oxygen are required as complementary reagents.

Experimental Section

Typical procedure: The racemic alcohol (5 mg) was added to a mixture of ADH-“A” (10 μL, 0.7 U), glucose (9 mg, 100 mM), GDH

(5 μL , 2.5 U), NAD^+ (0.17 mg, 0.5 mM), and resting cells of *Alcaligenes faecalis* DSM 13975 (wet-cell weight: 100 mg) in Tris-HCl buffer (500 μL , 50 mM, pH 7.5; Tris = tris(hydroxymethyl)aminomethane). The resulting mixture was shaken at 30°C and 350 rpm with an Eppendorf Thermoshaker for the specified time (4–16 h), and then the biotransformation was stopped by the addition of ethyl acetate (600 μL) and centrifugation (13000 rpm, 5 min). The organic phase was dried (Na_2SO_4), and derivatives of the alcohol were formed for chiral analysis by the addition of acetic anhydride (250 μL , 2.5 mM) and a catalytic amount of 4-dimethylaminopyridine (0.02 mM). This reaction mixture was shaken at room temperature (25°C) for 1 h at 170 rpm. Water (300 μL) was then added, as well as a solution of 1-decanol in ethyl acetate (50 mg mL^{-1} ; 1 mg, 20 μL) as an internal standard, and the resulting solution was centrifuged (2 min). The organic phase was dried (Na_2SO_4) and analyzed by GC.

In alternative experiments, ADH-“A” was substituted for RE-ADH (5 mg, 0.17 U) or LK-ADH (1 mg, 0.4 U). For the enantio-complementary system, *Alcaligenes faecalis* DSM 13975 was substituted for *Rhodococcus erythropolis* DSM 43066 (wet-cell weight: 100 mg).

Preparative scale: *rac*-4-Phenyl-2-butanol (**1i**; 500 μL , 485 mg, 3.2 mmol) was added to a mixture of RE-ADH (250 mg, 8.5 U), resting cells of *Alcaligenes faecalis* DSM 13975 (wet-cell weight: 10 g), glucose (100 mM), GDH (480 μL , 240 U), and NAD^+ (17 mg, 0.5 mM) in Tris-HCl buffer (50 mL, 50 mM, pH 7.5) in a centrifuge beaker (volume: 440 mL). The resulting mixture was shaken at 30°C and 170 rpm for 16 h, and then the biotransformation was stopped by the addition of ethyl acetate (50 mL) and centrifugation (10 min, 10000 rpm). The organic phase was dried (Na_2SO_4), and the solvent was evaporated to afford enantiomerically pure (*S*)-**1i** (441 mg, 91%, > 99% ee). $[\alpha]_{\text{D}}^{20} = +18.5 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ ($c = 0.016 \text{ g cm}^{-3}$, CHCl_3 ; lit.^[18] $[\alpha]_{\text{D}}^{20} = +17.4 \text{ deg cm}^3 \text{ g}^{-1} \text{ dm}^{-1}$ ($c = 0.018 \text{ g cm}^{-3}$, CHCl_3)).

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- [1] For recent reviews, see: a) T. J. J. Müller, *Metal Catalyzed Cascade Reactions*, Springer, Heidelberg, **2006**; b) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; c) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302–312; d) J.-A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666–4683; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583; e) A. Ajamian, J. L. Gleason, *Angew. Chem.* **2004**, *116*, 3842–3848; *Angew. Chem. Int. Ed.* **2004**, *43*, 3754–3760.
- [2] For selected recent examples, see: a) A. S. Goldman, A. H. Roy, Z. Huang, R. Ahuja, W. Schinski, M. Brookhart, *Science* **2006**, *312*, 257–261; b) G. Onodera, Y. Nishibayashi, S. Uemura, *Angew. Chem.* **2006**, *118*, 3903–3906; *Angew. Chem. Int. Ed.* **2006**, *45*, 3819–3822; c) B. M. Trost, M. R. Machacek, B. D. Faulk, *J. Am. Chem. Soc.* **2006**, *128*, 6745–6754; d) S. Shekhar, B. Trantow, A. Leitner, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 11770–11771; e) D. M. D'Souza, F. Rominger, T. J. J. Müller, *Angew. Chem.* **2005**, *117*, 156–161; *Angew. Chem. Int. Ed.* **2005**, *44*, 153–158; f) C. J. Kressierer, T. J. J. Müller, *Angew. Chem.* **2004**, *116*, 6123–6127; *Angew. Chem. Int. Ed.* **2004**, *43*, 5997–6000.
- [3] K. Faber, *Chem. Eur. J.* **2001**, *7*, 5004–5010.
- [4] a) G. R. A. Adair, J. M. J. Williams, *Chem. Commun.* **2007**, 2608–2609; b) G. R. A. Adair, J. M. J. Williams, *Chem. Commun.* **2005**, 5578–5579.
- [5] Y. Shimada, Y. Miyake, H. Matsuzawa, Y. Nishibayashi, *Chem. Asian J.* **2007**, *2*, 393–396.
- [6] a) O. Pàmies, J.-E. Bäckvall, *Trends Biotechnol.* **2004**, *22*, 130–135; b) O. Pàmies, J.-E. Bäckvall, *Chem. Rev.* **2003**, *103*, 3247–3261; c) B. Schnell, K. Faber, W. Kroutil, *Adv. Synth. Catal.* **2003**, *345*, 653–666; d) H. Pellissier, *Tetrahedron* **2003**, *59*, 8291–8327; e) M.-J. Kim, Y. Ahn, J. Park, *Curr. Opin. Biotechnol.* **2002**, *13*, 578–587.
- [7] For reviews, see: a) C. C. Gruber, I. Lavandera, K. Faber, W. Kroutil, *Adv. Synth. Catal.* **2006**, *348*, 1789–1805; b) K. Nakamura, T. Matsuda, T. Harada, *Chirality* **2002**, *14*, 703–708; c) R. N. Patel, *Curr. Opin. Biotechnol.* **2001**, *12*, 587–604; d) R. Azerad, D. Buisson, *Curr. Opin. Biotechnol.* **2000**, *11*, 565–571; e) A. J. Carnell, *Adv. Biochem. Eng./Biotechnol.* **1999**, *63*, 57–72; for recent examples, see: f) S. K. Padhi, D. Titu, N. G. Pandian, A. Chadha, *Tetrahedron* **2006**, *62*, 5133–5140; g) Y. Nie, Y. Xu, X. Q. Mu, *Org. Process Res. Dev.* **2004**, *8*, 246–251; h) T. Vijayananthi, A. Chadha, *Tetrahedron: Asymmetry* **2007**, *18*, 1077–1084.
- [8] It was reported to be less efficient to employ simultaneously two different microorganisms, one for oxidation and one for reduction, than to carry out two separate steps: a) G. Fantin, M. Fogagnolo, P. P. Giovannini, A. Medici, P. Pedrini, *Tetrahedron: Asymmetry* **1995**, *6*, 3047–3053; b) E. Takahashi, K. Nakamichi, M. Furui, *J. Ferment. Bioeng.* **1995**, *80*, 247–250.
- [9] We used the strains *Geotrichum candidum* NBRC 5767, *Candida parapsilosis* NBRC 0708 (or ATCC 7330), and *Sphingomonas paucimobilis* NBRC 13934 (equivalent to ATCC 10829, NCIB 8195, NRRL B-54); for details of the results, see the Supporting Information; for *G. candidum*, see, for example: a) K. Nakamura, M. Fujii, Y. Ida, *Tetrahedron: Asymmetry* **2001**, *12*, 3147–3153; b) D. Buisson, R. Azerad, C. Sanner, M. Larcheveque, *Biocatalysis* **1992**, *5*, 249–265; for *C. parapsilosis*, see, for example: Ref. [7g]; c) J. Hasegawa, M. Ogura, S. Tsuda, S. Maremoto, H. Kutsuki, T. Ohashi, *Agric. Biol. Chem.* **1990**, *54*, 1819–1828; d) S. K. Padhi, A. Chadha, *Tetrahedron: Asymmetry* **2005**, *16*, 2790–2798; for *S. paucimobilis*, see: e) G. R. Allan, A. J. Carnell, *J. Org. Chem.* **2001**, *66*, 6495–6497.
- [10] For reviews on the oxidation of alcohols with oxygen, see: a) D. Lenoir, *Angew. Chem.* **2006**, *118*, 3280–3284; *Angew. Chem. Int. Ed.* **2006**, *45*, 3206–3210; b) B.-Z. Zhan, A. Thompson, *Tetrahedron* **2004**, *60*, 2917–2935.
- [11] a) *Modern Oxidation Methods* (Ed.: J.-E. Bäckvall), Wiley-VCH, Weinheim, **2004**; b) G.-J. ten Brink, I. W. C. E. Arends, R. A. Sheldon, *Chem. Rev.* **2004**, *104*, 4105–4123; c) R. Noyori, M. Aoki, K. Sato, *Chem. Commun.* **2003**, 1977–1986; d) M. Poliakov, J. M. Fitzpatrick, T. R. Farren, P. T. Anastas, *Science* **2002**, *297*, 807–810; e) K. Sato, M. Hyodo, M. Aoki, X.-Q. Zheng, R. Noyori, *Tetrahedron* **2001**, *57*, 2469–2476.
- [12] a) N. J. Turner, *Curr. Opin. Biotechnol.* **2003**, *14*, 401–406; b) C. L. Dunsmore, R. Carr, T. Fleming, N. J. Turner, *J. Am. Chem. Soc.* **2006**, *128*, 2224–2226; c) M. Alexeeva, A. Enright, M. J. Dawson, M. Mahmoudian, N. J. Turner, *Angew. Chem.* **2002**, *114*, 3309–3312; *Angew. Chem. Int. Ed.* **2002**, *41*, 3177–3180; d) R. Carr, M. Alexeeva, A. Enright, T. S. C. Eve, M. J. Dawson, N. J. Turner, *Angew. Chem.* **2003**, *115*, 4955–4958; *Angew. Chem. Int. Ed.* **2003**, *42*, 4807–4810; e) J. W. Huh, K. Yokoigawa, N. Esaki, K. Soda, *J. Ferment. Bioeng.* **1992**, *74*, 189–190.
- [13] The only substrate-specific example is the deracemization of lactate by oxidation with a lactate oxidase in combination with the nonselective reduction with sodium borohydride of the pyruvate thus obtained: T. Oikawa, S. Mukoyama, K. Soda, *Biotechnol. Bioeng.* **2001**, *73*, 80–82.
- [14] Deracemization through stereoinversion in the presence of isolated enzymes was only possible in two separate steps: a) W. Hummel, B. Riebel, *Ann. N. Y. Acad. Sci.* **1996**, *799*, 713–716; b) W. Adam, M. Lazarus, B. Boss, C. R. Saha-Möller, H. U. Humpf, P. Schreier, *J. Org. Chem.* **1997**, *62*, 7841–7843; c) W.

- Adam, M. Lazarus, C. R. Saha-Möller, P. Schreier, *Tetrahedron: Asymmetry* **1998**, 9, 351–355.
- [15] ADH-“A” is available from Biocatalytics Ltd.; see: K. Edegger, C. C. Gruber, T. M. Poessl, S. R. Wallner, I. Lavandera, K. Faber, F. Niehaus, J. Eck, R. Oehrlein, A. Hafner, W. Kroutil, *Chem. Commun.* **2006**, 2402–2404.
- [16] The strain, which was provided by C. A. G. M. Weijers and J. A. M. de Bont, was first denoted as *Arthrobacter* T2, 091B: J. Sikkema, J. A. M. de Bont, *Biodegradation* **1991**, 2, 15–23.
- [17] a) H. E. Schoemaker, D. Mink, M. G. Wubbolts, *Science* **2003**, 299, 1694–1697; b) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Kessler, R. Stürmer, T. Zelinski, *Angew. Chem.* **2004**, 116, 806–843; *Angew. Chem. Int. Ed.* **2004**, 43, 788–824.
- [18] K. Nakamura, Y. Inoue, T. Matsuda, I. Misawa, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2397–2402.
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