Stereoselective Formation of Bis(α-hydroxy ketones) via Enzymatic Carboligation

Thomas Dünnwald and Michael Müller*

Institut für Biotechnologie 2, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany

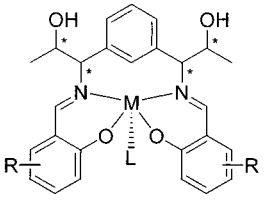
mi.mueller@fz-juelich.de

Received July 8, 2000

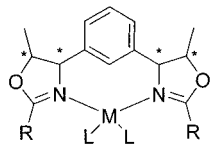
The enzymatic approach to a novel class of chiral bis(α-hydroxy ketones) of type **5** and **8**, which enable the synthesis of new multidentate ligands for asymmetric transition metal catalysis, is described. The key step is the second benzoylformate decarboxylase catalyzed C−C-bond formation between an aromatic dialdehyde and acetaldehyde, which proceeds with complete stereocontrol. Transformation of enantiomerically enriched monoadduct (*S*)-**4** (ee 88%) and (*S*)-**7** (ee 79%) resulted in optical pure (*S*,*S*)-**5** and (*S*,*S*)-**8** besides minor amounts of the corresponding diastereomeric *meso*-forms.

Introduction

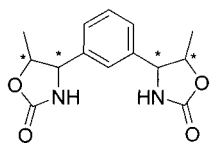
In a former study we reported on the benzoylformate decarboxylase (BFD) catalyzed formation of 2-hydroxy ketones.[1] BFD[2,3] belongs to the class of thiamin diphosphate (ThDP) dependent enzymes which have been of increasing interest during the past decade.[4,5] Although the main reaction catalyzed by BFD is the nonoxidative decarboxylation of benzoyl formate,[6] we could demonstrate this biocatalyst to be suitable for the preparative synthesis of (*S*)-2-hydroxypropanones[7] and (*R*)-benzoins[8] in high optical purity (Scheme 1) via C−C-coupling reactions. Therefore, we want to extend this strategy by subjecting bifunctionalized substrates to this benzoin condensation type reaction with the aim to enable the synthesis of new chiral transition metal complexes of type **1** and **2a** for catalytic asymmetric processes[9] and chiral auxiliaries of type **2b**. Due to its functional groups, **1**



1



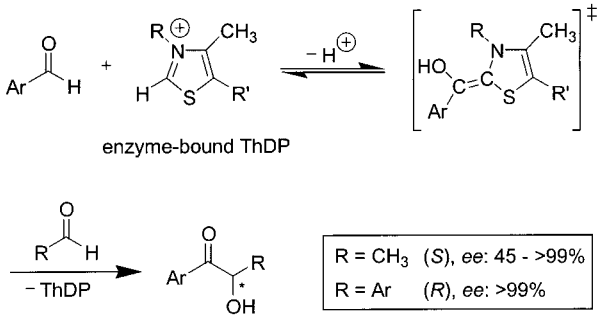
2a



2b

resembles a modified salen complex which might be used, for example, for asymmetric ring opening of *meso*-epoxides with TMS-N_3. Jacobsen and co-workers found this reaction to be dependent on a second-order kinetics with regard to the catalyst. It would be advantageous to obtain covalently linked dimeric salen complexes which can be synthesized by connecting the hydroxy moieties of two molecules of **1** via, for example, polyether spacers.[10] Especially compounds with C_2 symmetry often exhibit a higher capacity as stereochemical promotors compared to those lacking totally in symmetry.[11] Thus C_2-symmetric chiral bis(oxazoline) copper(II) complexes such as **2a** are effective promotors of enantioselective Diels−Alder, aldol, ene, Michael, and amination reactions,[12] whereas chiral bis(oxazolidinones)[13] such as **2b** may be used as chiral auxiliaries.

Scheme 1. Mechanism of BFD-Mediated Carboligation of Aromatic Aldehydes and Acetaldehyde



* To whom correspondence should be addressed. Phone: +49(0)2461/613374. Fax: +49(0)2461/613870.

(1) Iding, H.; Dünnwald, T.; Greiner, L.; Liese, A.; Müller, M.; Siegert, P.; Grötzinger, J.; Demir, A. S.; Pohl, M. *Chem. Eur. J.* **2000**, *6*, 1483.

(2) Ward, O. P.; Wilcocks, R.; Prosen, E.; Collins, S.; Dewdney, N. J.; Hong, Y. In *Microbial Reagents in Organic Synthesis*; Servi, A.; Ed., NATO ASI Ser., Kluwer Acad. Publ.: New York, 1992; Vol. 67.

(3) Wilcocks, R.; Ward, O. P.; Collins, S.; Dewdney, N. J.; Hong, Y.; Prosen, E. *Appl. Environ. Microbiol.* **1992**, *58*, 1699.

(4) Sprenger, G. A.; Pohl, M. *J. Mol. Catal. B: Enzymol.* **1999**, *6*, 145.

(5) Schörken, U.; Sprenger, G. A. *Biochim. Biophys. Acta* **1998**, *1385*, 229.

(6) Iding, H.; Siegert, P.; Mesch, K.; Pohl, M. *Biochim. Biophys. Acta* **1998**, *1385*, 307.

(7) Dünnwald, T.; Demir, A. S.; Siegert, P.; Pohl, M.; Müller, M. *Eur. J. Org. Chem.* **2000**, 2161.

(8) Demir, A. S.; Iding, H.; Pohl, M.; Dünnwald, T.; Müller, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4769.

(9) Type, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 275.

(10) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780.

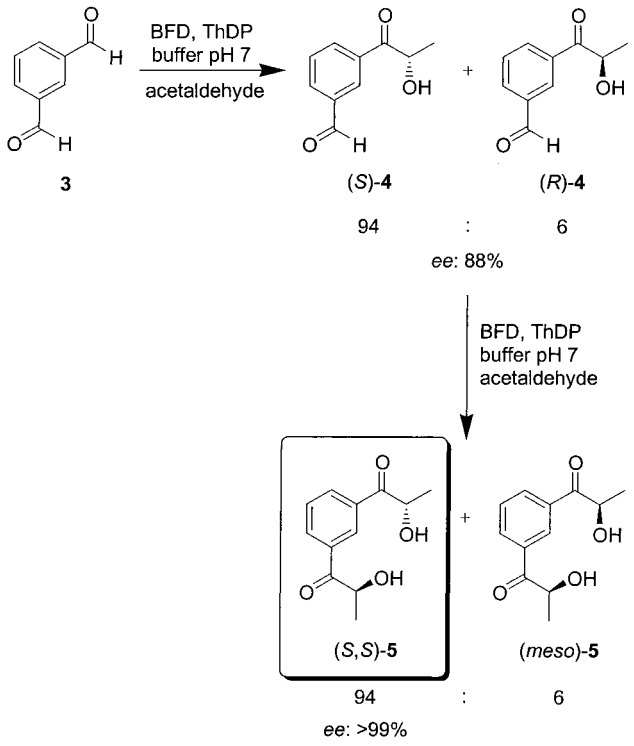
(11) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(12) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(13) Lee, S.; Lim, C. W.; Kim, D. C.; Lee, J. K. *Tetrahedron: Asymmetry* **2000**, *11*, 1455.

10.1021/jo0010274 CCC: $19.00 © 2000 American Chemical Society
Published on Web 11/21/2000

Scheme 2. BFD-Mediated Carboligation of Isophthalaldehyde and Acetaldehyde Yielding (*S*)-4 and (*S,S*)-5



Results and Discussion

In former work we observed that *meta*-substituted aromatic aldehydes provide the highest ee values in good to excellent conversion rates in the BFD-catalyzed coupling reaction with acetaldehyde. *Para*-substituted benzaldehyde derivatives afforded 2-hydroxy ketones with lower ee values and simultaneous lower conversion rates, in general. *Ortho*-substituted aromatic aldehydes, except 2-fluorobenzaldehyde, are not accepted as substrates at all.[7] With this knowledge we subjected isophthalaldehyde (**3**), which comprises a 1,3-substitution pattern, to this biotransformation. Due to the presence of two carbaldehyde functionalities, we expected the formation of bis(α-hydroxy ketones) as products for this kind of substrate. GCMS analysis proved the formation of two products generated by the reaction of **3** and acetaldehyde. These products were assigned to the structures **4** and **5** (Scheme 2) by evaluation of mass data. Determination of conversion rates depending on reaction time (Figure 1) indicated the feasibility of the 2-fold reaction for such substrates in general. It should be possible to isolate either the mono- or the diadduct of isophthalaldehyde and acetaldehyde in high yield by variation of the reaction time or substrate feed strategies. The yield of **4** passes through a maximum of 75% after 7 h, whereas compound **5** is formed in 10% yield. Prolonged reaction time led to an increase of **5** to 65% yield with concomitant decrease of monoadduct **4**. Transferring this strategy to preparative scale synthesis the biotransformation was performed in a simple batch reactor by dissolving isophthalaldehyde and acetaldehyde in aqueous buffer solution containing ThDP with subsequent addition of BFD. Depending on the reaction time, we could isolate both **4** (0.4 g scale) and **5** (1 g scale), in 58% and 82% yield, respectively. The second enzymatic coupling reaction affording **5** was performed in situ without a requirement for isolation of intermediate **4**. To evaluate the stereoselectivity of both enzymatic reaction steps, we had to synthesize racemic standard samples. These were available by reaction of **3** with trimethylsilyl cyanide ("Umpolung"),[14] deprotonation with LDA, and subsequent quenching[15] with acetaldehyde (Scheme 3). The separation of all stereoisomers of both **4** and **5** was performed by chiral phase HPLC using a Chiralpak AD column. Due to symmetry reasons, bis(α-hydroxy ketone) **5** consists of two enantiomers, (*S,S*)- and (*R,R*)-isomer, and one diastereomeric *meso*-form. When comparing the chromatograms of both, the enzymatically and chemically (racemic) prepared **4** and **5** (Scheme 3), we observed that enzymatically synthesized monoadduct **4** exhibited an enantiomeric excess of about 88−90% at the maximum of product formed (Figure 1). The absolute configuration of (*S*) was assigned by mechanistical studies[1] and comparison of HPLC data with already known 2-hydroxy ketones.[7] It is noteworthy that the ee of (*S*)-**4** increases with a progressive in situ formation of bisadduct **5** (Figure 1). For that reason it can be concluded that BFD accepts both enantiomers of **4** as substrate. Therefore, in that case it is not possible to use BFD for kinetic racemate resolution, if the first stereocenter is generated chemically in racemic form. However, the second reaction step proceeds within detection limits completely stereospecific. Monoadduct (*S*)-**4** is converted to (*S,S*)-**5** in optical pure form (ee >99%), whereas the minor enantiomer (*R*)-**4** leads to (*meso*)-**5** which is the diastereomeric form of the former one. No formation of (*R,R*)-**5** could be detected by chiral phase HPLC. Separation of (*S,S*)-**5** and *meso*-**5** using several different methods resulted only in slight partition of the two diastereomeric forms on silica HPLC phases, and no baseline separation has been achieved so far.

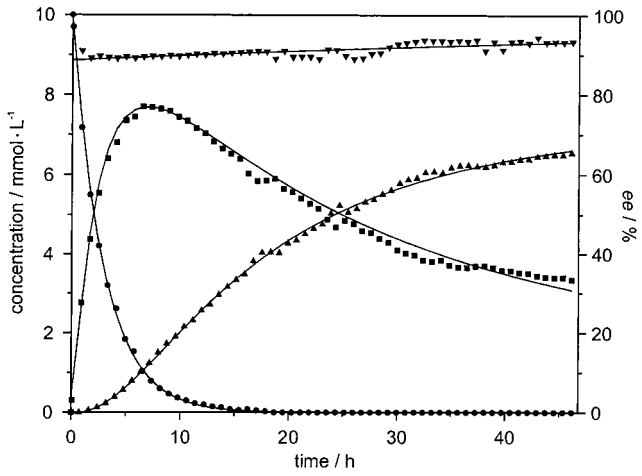
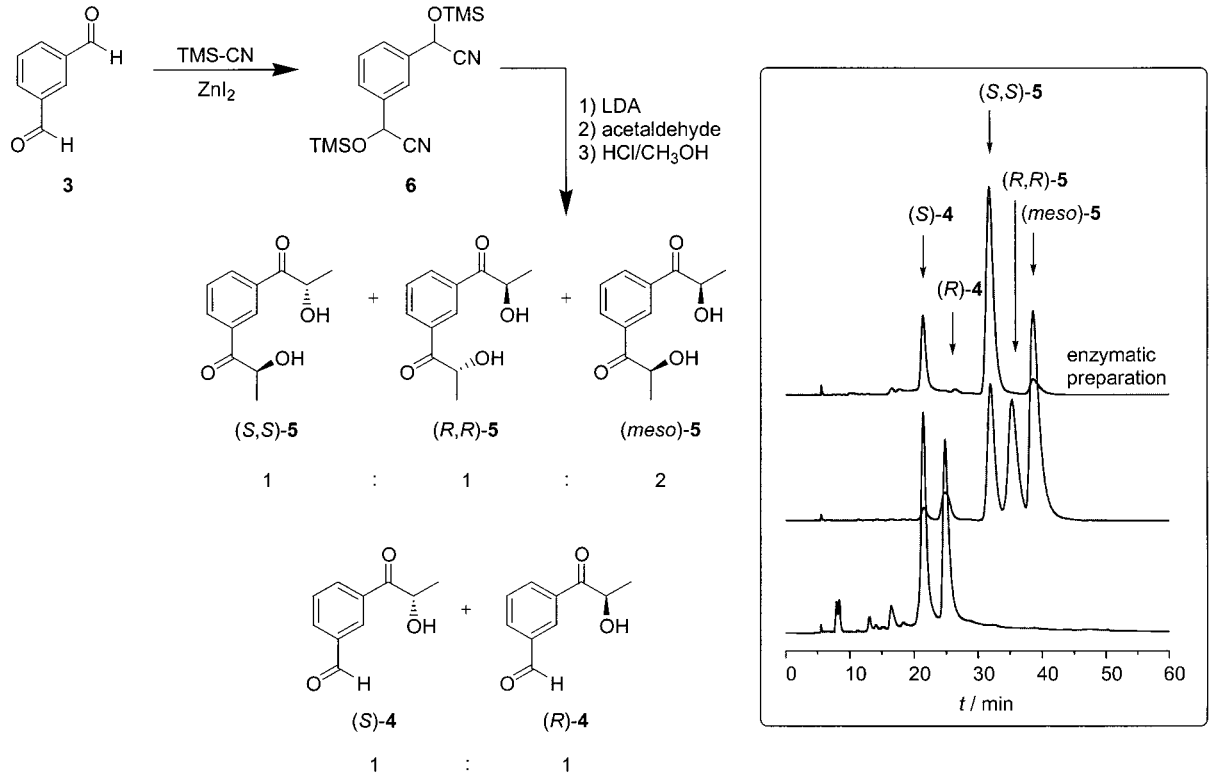


Figure 1. Progress of BFD-mediated carboligation of isophthalaldehyde (**3**) and acetaldehyde yielding (*S*)-**4** and (*S,S*)-**5**; concentration of **3** (●), (*S*)-**4** (■), (*S,S*)-**5** (▲), and ee of (*S*)-**4** (▼) are shown.

Encouraged by this results, we swapped the 1,3-substitution pattern of the substrate for the BFD-catalyzed C−C-bond forming reaction for an 1,4-aromatic dicarboxaldehyde (terephthalaldehyde). In fact, first experiments on an analytical scale indicated the general applicability of terephthalaldehyde as substrate in con-

(14) Cf. Deuchert, K.; Hertenstein, U.; Hünig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2045.
(15) Cf. Hünig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2062.

Scheme 3. Chemical Synthesis of All Stereoisomers of 4 and 5. HPLC Chromatograms of *rac*-4 (bottom), *rac*/*meso*-5 (middle) and Enzymatically Prepared 4 and 5 (top) Are Shown



junction with acetaldehyde, although the reaction time, especially for the second coupling step, had to be increased significantly. Preparative enzymatic conversion of terephthalaldehyde and acetaldehyde yielded **7** and **8** in moderate yield (23% and 14%, respectively). Even elongation of reaction time to three weeks did not result in increased product formation. Nevertheless, the bis-adduct (*S*,*S*)-**8** was obtained, besides diastereomeric *meso*-**8**, in optically pure form from (*S*)-**7** (ee = 79%) (Figure 2). For determination of stereoisomers by chiral phase HPLC (Chiralcel OB), racemic **8** was synthesized using the same protocol as for *rac*-**5**.

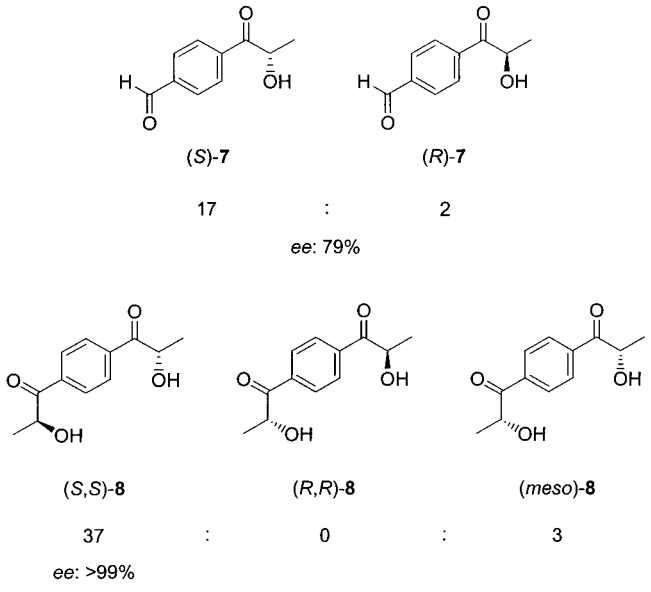


Figure 2. All stereoisomers of 2-hydroxy ketone **7** and bis-(2-hydroxy ketone) **8** resulting from chemical (racemic) synthesis. Product ratio and ee of products prepared enzymatically from terephthalaldehyde and acetaldehyde are given.

In summary we have developed a new enzymatic strategy to a novel class of C_2-symmetric chiral bis(α-hydroxy ketones) comprising two stereogenic centers. The enzymatic approach functioned well with aromatic dialdehydes in an effective manner, particularly when applying 1,3-disubstituted substrates. This method enables the synthesis of novel multidentate complex ligands and chiral auxiliaries of type **1** and **2** by diastereoselective reductive amination of (*S*,*S*)-**5** and (*S*,*S*)-**8**, respectively.

Experimental Section

General Methods. All reagents were used in analytical grade. Isophthalaldehyde (**3**) and terephthalaldehyde were purchased from Aldrich. Solvents were dried and distilled by standard methods if necessary. BFD was used as a recombinant enzyme elongated with a hexahistidine tail (BFD-His) expressed in *E. coli*.[1] Purification of the enzyme is described in the supplement. BFD activity is related to the catalytic decarboxylase activity which was determined in a coupled photometric assay. One unit is defined as the amount of enzyme that decarboxylates 1 μmol of benzoyl formate per minute at 30 °C in potassium phosphate buffer (50 mmol·L^{-1}, pH 6.0). Enzymatic syntheses were performed in standard buffer consisting of potassium phosphate (50 mmol·L^{-1}, pH 7.0) containing $MgSO_4$ (0.5 mmol·L^{-1}) and ThDP (0.5 mmol·L^{-1}). Prior to product workup reaction mixtures containing enzyme were filtered using an ultrafiltration membrane (Amicon YM10, cut off 10000 Da) in order to remove proteins. TLC was carried out on aluminum sheets precoated with silica gel 60F_{254} (Merck), and the spots were visualized with UV light ($\lambda = 254$ nm). Preparative column chromatography was carried out on silica gel 60 (mesh size 40−63 μm). NMR spectra were recorded as $CDCl_3$ solutions at 300 MHz (^{1}H) and 75.5 MHz (^{13}C, DEPT135), respectively. Chemical shifts (δ) are reported in ppm relative to C*H*Cl_3 (^{1}H, $\delta = 7.26$) and *C*DCl_3 (^{13}C, $\delta = 77.0$)

as internal standard. GCMS spectra were determined on a HP-5MS capillary column (5% phenyl methyl siloxane, 30 m × 250 μm; T_{GC}(injector) = 250 °C, T_{MS}(ion source) = 200 °C, time program (oven): $T_{0\ min}$ = 60 °C, $T_{3\ min}$ = 60 °C, $T_{14\ min}$ = 280 °C (heating rate 20 °C·min^{-1}), $T_{19\ min}$ = 280 °C, MS: EI, 70 eV). HPLC was performed on a chiral phase column Chiralpak AD (Daicel Ltd., 250 × 4 mm, equipped with a precolumn, 80 × 4 mm; *i*-hexane:2-propanol = 85:15, flow 0.75 mL·min^{-1}, 10 °C) or Chiralcel OB (Daicel Ltd., 250 ×4 mm, equipped with a precolumn, 80 ×4 mm; *i*-hexane:2-propanol = 80:20, flow 0.75 mL·min^{-1}, 20 °C). Preparative HPLC was carried out using a Kromasil Si-10 column (CS, Germany, 250 × 10 mm; gradient *i*-hexane:2-propanol $T_{0\ min}$ = 99:1, $T_{50\ min}$ = 94:6, $T_{80\ min}$ = 94:6, flow 4 mL·min^{-1}, 4 °C). HRMS (EI) and microanalyses were carried out at the Analytical Department, Chemische Institute der Universität Bonn.

(*S*)-3-(2-Hydroxypropionyl)benzaldehyde ((*S*)-4). Isophthalaldehyde (**3**) (512 mg, 3.8 mmol, 10 mmol·L^{-1}) was dissolved in standard buffer (380 mL). After addition of acetaldehyde (10.7 mL, 0.19 mol, 0.5 mol·L^{-1}), the reaction was started by adding BFD (600 U), and the reaction mixture was allowed to stand at rt for 16 h. Conversion was monitored by HPLC by extracting analytical samples (150 μL) with trichloromethane (150 μL) followed by phase separation by centrifugation (13000 rpm). The reaction mixture was filtered using an ultrafiltration membrane, the filtrate was extracted with ethyl acetate (3 × 60 mL), and the organic layer was dried with Na_2SO_4. Evaporation of the solvent and purification of the crude product by column chromatography (*i*-hexane/ethyl acetate 2:1; R_f = 0.27) afforded (*S*)-**4** as a viscous yellowish oil (396 mg, 58%). ee = 88%. $[\alpha]^{20}_D = -78°$ (*c* = 1.2, $CHCl_3$). HPLC (Chiralpak AD): $t_R(S)$ = 21.5 min; $t_R(R)$ = 25.3 min. ^{1}H NMR: δ = 1.49 (d, *J* = 7.1 Hz, 3H), 3.75 (br, 1H), 5.23 (q, *J* = 7.1 Hz, 1H), 7.72 ('t', *J* = 7.7 Hz, 1H), 8.16 (d't', *J* = 7.7, 1.4 Hz, 1H), 8.21 (d't', *J* = 7.7, 1.4 Hz, 1H), 8.42 ('t', *J* = 1.4 Hz, 1H), 10.12 (s, 1H). ^{13}C NMR: δ = 22.5 (CH_3), 70.0 (CHOH), 130.1, 130.3, 134.5 (CH), 134.6 (C_q), 134.8 (CH), 137.2 (C_q), 191.5 (CHO), 201.9 (CO). GCMS: t_R = 9.7 min; *m*/*z* (%) = 178 (M^+, 1.6), 133 ($M^+ - C_2H_5O$, 100), 105 ($M^+ - C_2H_5O - CO$, 46). HRMS [M^+]; *m*/*z* calcd for $C_{10}H_{10}O_3$ 178.0630; found 178.0622.

(*S*,*S*)-2-Hydroxy-1-[3-(2-hydroxypropionyl)phenyl]propan-1-one ((*S*,*S*)-5). Isophthalaldehyde (**3**) (670 mg, 5.0 mmol, 10 mmol·L^{-1}) was dissolved in standard buffer (500 mL). After addition of acetaldehyde (14.1 mL, 0.25 mol, 0.5 mol·L^{-1}), the reaction was started by adding BFD (1200 U), and the reaction mixture was allowed to stand at rt. Conversion was monitored by HPLC by extracting analytical samples (150 μL) with trichloromethane (150 μL) followed by phase separation by centrifugation (13000 rpm). If conversion stagnated, one more portion of BFD (400 U) was added. After 4 d the reaction mixture was filtered using an ultrafiltration membrane, the filtrate was extracted with ethyl acetate (3 × 60 mL), and the organic layer was dried with Na_2SO_4. Evaporation of the solvent gave a mixture (1.04 g) consisting of (*S*)-**4** (18%), (*S*,*S*)-**5** (75%), and *meso*-**5** (7%). Purification of the crude product by either column chromatography (CH_2Cl_2/ethyl acetate 3:1; R_f = 0.19) or preparative HPLC on Kromasil Si-10 afforded a mixture of (*S*,*S*)-**5** (94%, ee >99%) and *meso*-**5** (6%) as a viscous yellowish oil. $[\alpha]^{20}_D = -90°$ (*c* = 1.4, $CHCl_3$). HPLC (Chiralpak AD): $t_R(S,S)$ = 31.1 min; t_R(*meso*) = 38.4 min. Preparative HPLC (Kromasil Si-10): t_R((*S*,*S*)-**5**) = 49.6 min; t_R(*meso*-**5**) = 51.9 min. ^{1}H NMR: δ = 1.50 (d, *J* = 7.0 Hz, 6H), 3.71 (br, 2H), 5.22 (q, *J* = 7.0 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 8.17 (dt, *J* = 7.6, 1.7 Hz, 2H),), 8.48 (t, *J* = 1.7 Hz, 1H). ^{13}C NMR: δ = 22.50, 22.52 (meso) (CH_3) 70.0 (CHOH), 129.0, 129.1 (meso), 130.1, 133.9, 134.0 (meso) (CH), 134.5 (C_q), 201.88 (meso), 201.93 (CO). GCMS: t_R = 11.1 min; *m*/*z* (%) = 177 ($M^+ - C_2H_5O$, 82), 162 ($M^+ - C_2H_5O - CH_3$, 46), 133 ($M^+ - C_4H_9O_2$, 100), 105 ($M^+ - C_4H_9O_2 - CO$, 96). HRMS [$M^+ - C_2H_5O$]; *m*/*z* calcd for $C_{10}H_9O_3$ 177.0552; found 177.0550.

(*S*)-4-(2-Hydroxypropionyl)benzaldehyde ((*S*)-7) and (*S*,*S*)-2-Hydroxy-1-[4-(2-hydroxypropionyl)phenyl]propan-1-one ((*S*,*S*)-8). (*S*)-**7** and (*S*,*S*)-**8** were prepared according to the procedure for (*S*,*S*)-**5** dissolving terephthalaldehyde (268 mg, 2 mmol, 10 mmol·L^{-1}), acetaldehyde (5.6 mL, 0.1 mol, 0.5 mol·L^{-1}), and BFD (2000 U) in standard buffer (200 mL). After 14 d the reaction was stopped and the resulting crude product purified by column chromatography (*i*-hexane/ethyl acetate 2:1) to yield (*S*)-**7** (81 mg, 23%; R_f = 0.35) and (*S*,*S*)-**8** (60 mg, 14%; R_f = 0.13). The second fraction consisting of (*S*,*S*)-**8** as main product contained 7.5% of *meso*-**8**. Unreacted substrate was recovered.

(*S*)-**7:** ee = 79%. $[\alpha]^{20}_D = -37°$ (*c* = 0.3, $CHCl_3$). HPLC (Chiralcel OB): $t_R(S)$ = 25.1 min; $t_R(R)$ = 41.3 min. ^{1}H NMR: δ = 1.43 (d, *J* = 7.2 Hz, 3H), 3.85 (br, 1H), 5.18 (q, *J* = 7.1 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 2H), 8.06 (d, *J* = 7.8, 2H),), 10.08 (s, 1H). ^{13}C NMR: δ = 22.2 (CH_3), 70.2 (CHOH), 129.6, 130.4 (CH), 138.2, 139.9 (C_q), 191.9 (CHO), 202.4 (CO). GCMS: t_R = 10.1 min; *m*/*z* (%) = 178 (M^+, 0.5), 133 ($M^+ - C_2H_5O$, 100), 105 [$M^+ - C_2H_5O - CO$, 57). HRMS [$M^+ - C_2H_5O$]; *m*/*z* calcd for $C_8H_5O_2$ 133.0290; found 133.0289.

(*S*,*S*)-**8:** ee >99%. $[\alpha]^{20}_D = -29°$ (*c* = 0.4, $CHCl_3$). HPLC (Chiralpak OB): $t_R(S,S)$ = 23.0 min; t_R(*meso*) = 32.7 min. ^{1}H NMR: δ = 1.40 (d, *J* = 7.1 Hz, 6H), 3.79 (br, 2H), 5.18 (q, *J* = 7.1 Hz, 2H), 8.04 (s, 4H). ^{13}C NMR: δ = 22.2 (CH_3) 70.2 (CHOH), 129.4 (CH), 137.7 (C_q), 202.2 (CO). GCMS: t_R = 11.9 min; *m*/*z* (%) = 177 ($M^+ - C_2H_5O$, 100), 133 ($M^+ - C_4H_9O_2$, 18), 105 ($M^+ - C_4H_9O_2 - CO$, 30). HRMS [$M^+ - C_2H_5O$]; *m*/*z* calcd for $C_{10}H_9O_3$ 177.0552; found 177.0543.

[3-(Cyanotrimethylsilanyloxymethyl)phenyl]trimethylsilanyloxyacetonitrile (6).[14] Isophthalaldehyde (**3**) (1.88 g, 14 mmol) was added slowly to a mixture of trimethylsilyl cyanide (2.98 g, 30 mmol) and anhydrous ZnI_2 (catalytic amount). The reaction mixture was heated to 95 °C for 2 h. The resulting crude product was fractionated in vacuo, yielding pure **6** (3.95 g, 85%) as a colorless liquid. $Bp_{0.02\ mbar}$ 108 °C. ^{1}H NMR: δ = 0.27 (s, 18H), 5.55 (s, 2H), 7.51 (m, 3H), 7.58 (s, 1H). ^{13}C NMR: δ = 0.2 ($Si(CH_3)_3$), 63.7 (*C*HCN), 119.3 (CN), 124.5, 127.6, 130.1 (CH), 137.7 (C_q). GCMS: t_R = 12.3 min; *m*/*z* (%) = 332 (M^+, 0.1), 317 ($M^+ - CH_3$, 47), 218 ($M^+ - C_4H_8$-NOSi, 100).

***rac*-3-(2-Hydroxypropionyl)benzaldehyde (*rac*-4).** A solution of LDA (3 mmol) in dry THF (10 mL) was added dropwise to **6** (1 g, 3 mmol) dissolved in dry THF (5 mL) at −55 °C. The resulting red-colored solution was stirred for 30 min at −55 °C, whereupon dry acetaldehyde (0.4 mL, 7 mmol) was added at this temperature. The reaction mixture was warmed to rt within 4 h and subsequently quenched with saturated NH_4Cl-solution (20 mL). After an additional 5 min of stirring at rt, the mixture was extracted with diethyl ether (3 × 10 mL) and the organic layer dried with Na_2SO_4 and evaporated to dryness. The resulting crude TMS-ether of *rac*-**4** was stirred in a mixture of hydrochloric acid (2 N, 10 mL) and methanol (5 mL) for 15 h. After addition of water (10 mL), the crude product was extracted with ethyl acetate (3 × 10 mL), the organic layer washed with aqueous NaOH (1 N, 10 mL) and dried with Na_2SO_4. Purification by column chromatography (*i*-hexane/ethyl acetate 2:1; R_f = 0.27) afforded *rac*-**4** as a viscous yellowish oil (270 mg, 51%). HPLC (Chiralpak AD): $t_R(S)$ = 21.5 min; $t_R(R)$ = 25.3 min. All analytical data are in accordance with enzymatically prepared (*S*)-**4**.

***rac*/*meso*-2-Hydroxy-1-[3-(2-hydroxypropionyl)phenyl]propan-1-one (*rac*/*meso*-5).** A solution of **6** (1 g, 3 mmol) in dry THF (5 mL) was added dropwise to a solution of LDA (6.2 mmol) in dry THF (20 mL) at −55 °C. The resulting dark red-colored solution was stirred for 30 min at −55 °C, whereupon dry acetaldehyde (1.0 mL, 17.5 mmol) was added at this temperature. The reaction mixture was warmed to rt within 4 h and subsequently quenched with saturated NH_4Cl solution (20 mL). After an additional 5 min of stirring at rt, the mixture was extracted with diethyl ether (3 × 10 mL), the organic layer dried with Na_2SO_4 and evaporated to dryness. The resulting crude TMS-ether of *rac*/*meso*-**5** was stirred in a mixture of hydrochloric acid (2 N, 20 mL) and methanol (10 mL) for 15 h. After addition of water (30 mL), the crude product was extracted with ethyl acetate (3 × 20 mL), the organic layer washed with aqueous NaOH (1 N, 15 mL) and dried with Na_2SO_4. Purification by column chromatography (CH_2Cl_2/ethyl acetate 3:1; R_f = 0.19) afforded *rac*/*meso*-**5** as a viscous yellowish oil (354 mg, 53%). HPLC (Chiralpak AD): $t_R(S,S)$ =

31.1 min; $t_R(R,R)$ = 34.5 min; $t_R(meso)$ = 38.4 min. All analytical data are in accordance with enzymatically prepared (*S*,*S*)-**5** and *meso*-**5**.

[4-(Cyanotrimethylsilanyloxymethyl)phenyl]trimethylsilanyloxyacetonitrile (9). 9 was prepared according to the procedure for **6** using terephthalaldehyde (1.88 g, 14 mmol), trimethylsilyl cyanide (2.98 g, 30 mmol), and anhydrous ZnI_2 (catalytic amount). The crude product was fractionated in vacuo yielding pure **9** (3.83 g, 82%) as a colorless liquid. $Bp_{0.03\ mbar}$ 128 °C. ^{1}H NMR: δ = 0.28 (s, 18H), 5.53 (s, 2H), 7.54 (s, 4H). ^{13}C NMR: δ = 0.2 ($Si(CH_3)_3$), 63.6 (*C*HCN), 119.3 (CN), 127.3 (CH), 137.9 (C_q). GCMS: t_R = 11.9 min; *m*/*z* (%) = 332 (M^+, 1.6), 317 ($M^+ - CH_3$, 100), 218 ($M^+ - C_4H_8NOSi$, 65).

***rac*/*meso*-2-Hydroxy-1-[4-(2-hydroxypropionyl)phenyl]-propan-1-one (*rac*/*meso*-8).** *rac*/*meso*-**8** was prepared according to the procedure for *rac*/*meso*-**5** using **9** (1 g, 3 mmol), LDA (6.2 mmol), and dry acetaldehyde (1 mL, 17.5 mmol). Purification of the crude product by column chromatography (*i*-hexane/ethyl acetate 1:1; R_f = 0.27) afforded *rac*/*meso*-**8** as a viscous yellowish oil (208 mg, 31%). HPLC (Chiralpak OB): $t_R(S,S)$ = 23.0 min; $t_R(meso)$ = 32.7 min; $t_R(R,R)$ = 39.5 min. All analytical data are in accordance with enzymatically prepared (*S*,*S*)-**8** and *meso*-**8**.

Acknowledgment. This work has been supported by the Deutsche Forschungsgemeinschaft in the scope of SFB 380. The skillful technical assistance of Ms. Lydia Walter is gratefully acknowledged. We thank Dr. Martina Pohl and Dipl.-Chem. Petra Siegert (Institut für Enzymtechnologie, Heinrich-Heine-Universität Düsseldorf, Germany) for providing the biocatalyst.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds (*S*)-**4**, (*S*,*S*)-**5**, (*S*)-**7**, and (*rac*/*meso*)-**8** as well as the method for the preparation of the enzyme. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0010274