Enantioselective Synthesis of α-Hydroxy Ketones via Benzaldehyde Lyase-Catalyzed C–C Bond Formation Reaction

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Abstract: (*R*)-Benzoins and (*R*)-2-hydroxypropiophenone derivatives are formed on a preparative scale by benzaldehyde lyase (BAL)-catalyzed C–C bond formation from aromatic aldehydes and acetaldehyde in aqueous buffer/DMSO solution with remarkable ease in high chemical yield and high optical purity. The substrate range of this thiamin diphosphate-dependent enzyme was examined with respect to a broad applicability of this benzoin condensation-type reaction in stereoselective synthesis.

Keywords: benzoin condensation; biocatalyst; carboligation; hydroxy ketones; thiamin diphosphate.

Introduction

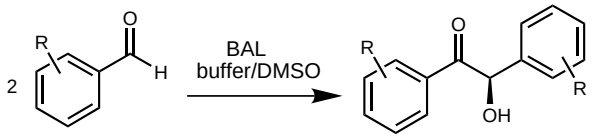
The benzoin reaction,[1] one of the oldest C–C bond-forming reactions in organic chemistry, has been developed for classical organic synthesis using non-chiral catalysts[2] and for asymmetric synthesis using chiral thiazolium and triazolium salts as catalyst.[3] Numerous other chemical methods for the enantioselective synthesis of 2-hydroxy ketones, which are not based on C–C bond formation, have been evolved.[4] As an alternative to chemical methods, enantiomerically pure 2-hydroxy ketones are prepared enzymatically[5] by reduction of the corresponding α-diketone with baker's yeast[6] or an enzymatic kinetic resolution of the racemate of either 2-peroxo,[7] 2-hydroxy[8] or 2-acetoxy ketones.[9] In addition to these methods enzymatic acyloin condensation furnishing α-hydroxy ketone functionality in one step has recently gained increasing attention.[10]

In our ongoing studies, we established that aromatic aldehydes can be converted into acyloins by a benzoyl formate decarboxylase (BFD)-catalyzed reaction. The reaction affords (*R*)-benzoins and (*S*)-2-hydroxypropiophenone [(*S*)-2-HPP] derivatives with high enantiomeric excess and in good chemical yields. However, only *meta*- and *para*-substituted benzaldehydes could be used as substrates.[11] In a preliminary communication we reported the ability of benzaldehyde lyase (BAL), another thiamin diphosphate (ThDP)-dependent enzyme, for the enantioselective formation of (*R*)- and (*S*)-benzoins and (*R*)-2-HPP derivatives via C–C bond cleavage and C–C bond formation.[12] In this paper we focus on the synthetic potential of BAL with regard to the ability to catalyze C–C bond formation on a preparative scale for the synthesis of enantiopure 2-hydroxy ketones. Another aim of this work was to give a broad survey of the substrate and product range of the BAL-catalyzed C–C bond formation in order to gain information about the structural importance of substituents of the substrate aldehydes with regard to enzyme activity and enantiomeric excess.

Results and Discussion

Benzaldehyde lyase (BAL, EC 4.1.2.38) from *Pseudomonas fluorescens* Biovar I was first reported by Gonzáles and Vicuña.[13] They showed that this strain can grow on benzoin as a sole carbon and energy source due to the ability of BAL to catalyze the cleavage of the acyloin linkage of benzoin yielding benzaldehyde. The enzyme used in this study was expressed and purified from a recombinant *Escherichia coli* strain. For easier purification a hexahistidine tag was cloned to the C-terminus of the enzyme.[12]

We investigated the potential of BAL for catalyzing C–C bond formation. As shown in Scheme 1, performing the carboligation reaction with BAL by using benzaldehyde as a sole substrate in potassium phosphate buffer [(50 mmol L^{-1}, pH 7.0) containing $MgSO_4$ (2.5 mmol L^{-1}) and ThDP (0.15 mmol L^{-1})] at 21 °C and monitoring of the reaction by HPLC using a chiral stationary phase column with authentic samples as reference showed the formation of (*R*)-benzoin with an ee > 99%, however only in low to moderate yield. The low solubility of the aromatic substrate in aqueous buffer solution can be regarded as a fundamental problem. With other ThDP-dependent enzymes, e.g., benzoyl formate decarboxylase (BFD) from *Ps. putida*, we observed that addition of cyclodextrin or DMSO as cosolvent facilitates the formation of acyloins in high yield starting from hydrophobic substrates.[11c]



1 **2** (ee 91% to >99%)

Scheme 1. BAL-mediated benzoin condensation.

Accordingly, addition of DMSO (20%, v/v) to the aqueous medium containing BAL resulted in the formation of (*R*)-benzoin starting from benzaldehyde. This conversion worked almost quantitatively and (*R*)-benzoin was obtained in optically pure form (ee > 99%). During the reaction most of the benzoin precipitates from the reaction mixture. A small amount of benzaldehyde was present at the end of the reaction (1–2%).

The reaction was carried out on a semipreparative scale with different aromatic and heteroaromatic aldehydes and the corresponding (*R*)-benzoins **2a–s** were obtained in high yield and mostly in enantiomerically pure form (Table 1). The enantiomeric excess of the products was determined by HPLC on a chiral stationary phase column compared to racemic products, which were synthesized using classical chemical benzoin synthesis methodology.[14] The absolute configuration of the benzoins **2a**, **b**, **i**, **k–o**, **r**, **s** was assigned to be *R* according to a correlation of the optical rotation value of benzoins with data from the literature and to HPLC data of commercially available enantiomers of benzoins. The absolute configuration of **2c–h**, **j**, **p**, **q** was assigned assuming a uniform reaction mechanism. As can be seen from Table 1, BAL is able to activate and dimerize a broad range of aromatic aldehydes, substituted with electron-releasing as well as electron-withdrawing properties, and heteroaromatic aldehydes. In contrast to BFD, BAL accepts aromatic aldehydes substituted at the *ortho*-position as well, e.g., compounds **1b–e.** Only a few aromatic aldehydes such as pyridine-3- and -4-carbaldehyde, 4-hydroxybenzaldehyde and pyrrole-2-carbaldehyde as well as sterically demanding aldehydes like vanillin, isovanillin and 3,4-dimethoxybenzaldehyde gave either very low yield or no benzoin condensation.

In some cases, e.g., for the halogenated compounds, we observed the formation of trace amounts of the corresponding benzils, a known side reaction which is probably due to oxidation of benzoins by oxygen.[15]

To further demonstrate the usefulness of BAL-catalyzed reactions on a preparative scale the synthesis of (*R*)-3,3′-dimethoxybenzoin (**2i**) was performed in a repetitive batch mode. Starting from 2 × 1.62 g (24 mmol) 3-methoxybenzaldehyde and 60 U BAL, after 6 hours at room temperature the enantiopure product **2i** was isolated in 93% yield.

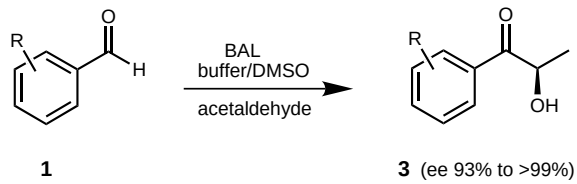
The BAL-catalyzed transformation of benzaldehyde in the presence of acetaldehyde afforded (*R*)-benzoin (**2a**) and (*R*)-2-HPP **3a** in enantiomerically pure form. We observed that the benzaldehyde/acetaldehyde ratio is very important for the product distribution, since excess acetaldehyde resulted in high yield formation of (*R*)-2-HPP, whereas a 1:1 ratio of benzaldehyde/acetaldehyde gave an almost equimolar mixture of (*R*)-benzoin and (*R*)-2-HPP.

As expected from the above-mentioned results, a wide range of aromatic aldehydes substituted at *ortho*-, *meta*-, and *para*-position and heteroaromatic aldehydes were accepted as donor substrates for the formation of (*R*)-2-HPP analogues **3a–p** (Table 2). In general *ortho*-substituted aromatic aldehydes afforded HPPs **3** in lower yields than the *meta*-, and *para*-substituted aldehydes. 2-Chlorobenzaldehyde and 2-methylbenzaldehyde gave no 2-HPP formation. The preference of BAL for aromatic substrates is underlined by the observation that 2,2′-disubstituted benzoins were formed with remarkable ease, e.g., compound **2e**, whereas the corresponding 2-HPP derivative **3c** was formed in moderate yield even after prolonged reaction time. Interestingly, even sterically demanding aromatic aldehydes were accepted as donor substrates in the presence of acetaldehyde (**3m–o**, Table 2). Enantiomeric excess of 2-HPP derivatives **3** was determined by chiral phase HPLC analysis using racemic compounds **3c**, **o**[16] or (*S*)-acyloins **3a**, **d–l** prepared by BFD-catalyzed reaction[11a,c] as references. The absolute configuration of the acyloins **3a**, **b**, **d, e**, **g**, **h**, **j–l**, **p** was assigned to be *R* according to the correlation of the optical rotation of acyloins with data from the literature and to HPLC data of the (*S*)-enantiomers. The absolute

Table 1. BAL-catalyzed carboligation of aromatic aldehydes to the corresponding (*R*)-benzoins **2.**

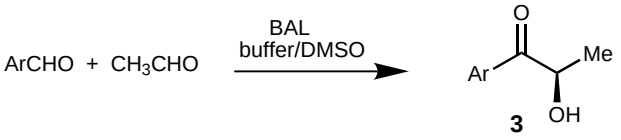
(*R*)-benzoins **2**	Ar	yield [%]	ee [%][a]
a	Ph	96	> 99
b	2-FC_6H_4	68	96
c	2-ClC_6H_4	80	97
d	2-BrC_6H_4	90	> 99
e	2-$MeOC_6H_4$	87	> 99[b]
f	3-FC_6H_4	80	97
g	3-ClC_6H_4	94	> 99
h	3-BrC_6H_4	94	> 99
i	3-$MeOC_6H_4$	93	> 99
j	3-HOC_6H_4	84	n.d.[c]
k	4-FC_6H_4	89	> 99
l	4-ClC_6H_4	95	> 99
m	4-BrC_6H_4	83	> 99
n	4-$MeOC_6H_4$	95	> 99[d]
o	4-MeC_6H_4	94	> 99
p	2,4-$F_2C_6H_3$	87	> 99
q	2-naphthalenyl	98	> 99[e]
r	2-furanyl	88	92
s	2-thienyl	73	91

[a] Enantiomeric excess of benzoins **2** was determined by chiral phase HPLC analysis (Chiralpak AD column, UV detection at 254 nm, eluent: *n*-hexane/2-propanol = 90:10, flow 0.80 mL min^{-1}, 20 °C) using racemic compounds as references.
[b] Eluent: *n*-hexane/2-propanol = 98:2, flow 0.90 mL min^{-1}, 20 °C.
[c] Not determined.
[d] Eluent: *n*-hexane/2-propanol = 75:25, flow 0.95 mL min^{-1}, 20 °C.
[e] Eluent: *n*-hexane/2-propanol = 10:90, flow 0.95 mL min^{-1}, 20 °C.



Scheme 2. BAL-mediated carboligation of aromatic aldehydes and acetaldehyde to the corresponding (*R*)-2-hydroxypropiophenone derivatives **3.**

Table 2. BAL-catalyzed carboligation of aromatic aldehydes and acetaldehyde to the corresponding (*R*)-2-hydroxypropiophenone derivatives **3.**



(*R*)-2-HPP derivatives **3**	Ar	yield [%]	ee [%][a]
a	Ph	94	>99[b]
b	2-FC_6H_4	64	97[b]
c	2-$MeOC_6H_4$	63	>99[c]
d	3-FC_6H_4	85	95
e	3-ClC_6H_4	94	>99[c]
f	3-BrC_6H_4	88	93
g	3-$MeOC_6H_4$	80	>99[d]
h	4-ClC_6H_4	88	>99
i	4-BrC_6H_4	86	>99
j	4-$MeOC_6H_4$	64	>99
k	2,4-$F_2C_6H_3$	65	97[b]
l	3,5-$F_2C_6H_3$	67	>99
m	3-HO-4-$MeOC_6H_3$	80	n.d.[e]
n	3-MeO-4-HOC_6H_3	90	n.d.[e]
o	3,4,5-$(MeO)_3C_6H_2$	92	>99[f]
p	2-furanyl	61	>99[d]

[a] Enantiomeric excess of 2-HPP derivatives **3** was determined by chiral phase HPLC analysis (Chiralcel OB column, UV detection at 254 nm, eluent:isohexane/2-propanol = 95:5, flow 0.75 mL min^{-1}, 20 °C) using racemic compounds or (*S*)-acyloins (prepared by BFD-catalyzed reaction) as references.[11]

[b] Chiralpak AD, eluent: isohexane/2-propanol = 90:10, flow 0.80 mL min^{-1}, 20 °C.

[c] Chiralcel OB column, eluent: isohexane/2-propanol = 98:2, flow 0.75 mL min^{-1}, 20 °C.

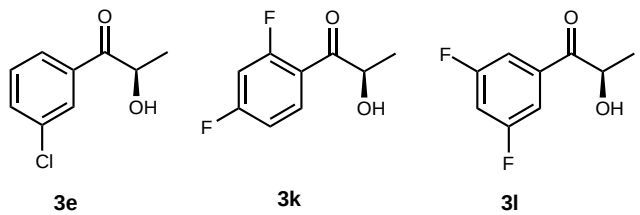
[d] Chiralcel OB column, eluent: isohexane/2-propanol = 90:10, flow 0.75 mL min^{-1}, 20 °C.

[e] Not determined.

[f] Chiralpak AD column, eluent: isohexane/2-propanol = 95:5, flow 0.75 mL min^{-1}, 20 °C.

configuration of **3c**, **f**, **i**, **m – o** was assigned assuming a uniform reaction mechanism.

Recently, several chiral 2-HPP derivatives became of interest as starting material for the stereoselective syntheses of biologically active substances, especially for pharmaceuticals possessing antifungal properties. The 2-HPP derivatives, (*R*)-1-(3-chlorophenyl)-2-hydroxypropan-1-one (**3e**), starting material for Bupropion,[17] (*R*)-1-(2,4-difluorophenyl)-2-hydroxypropan-1-one (**3k**), starting material for Ro 09-3355[18] and SM 8668/Sch 39304,[19] and (*R*)-1-(3,5-difluorophenyl)-2-hydroxypropan-1-one (**3l**), potential starting material for 1555U88,[20] were synthesized on a preparative scale. From the viewpoint of the organic-preparative chemist, it is important to mention that a crude cell extract of the recombinant *E. coli* strain overexpressing the BAL gene[21] is sufficient for catalysis hence purification of the enzyme is not necessary. As shown for the synthesis of **3k**, it is important to remove the major fraction of protein by ultrafiltration (cut-off 10 kDa) in order to facilitate product isolation. In doing so, the desired (*R*)-2-HPP **3k** was isolated in 65% yield on a 3-gram scale. As described for the benzoins, oxidation of acyloins to diketones was observed in some cases as a side reaction during work-up or even in aqueous buffer after prolonged reaction time.



Scheme 3.

The results presented are in accord with mechanistic investigations of other ThDP-dependent enzymes.[11a,22] Since structural information about BAL is still lacking, a structure-based discussion of the observed stereocontrol is not yet possible. Nevertheless, the carboligation must be a consequence of a selective attack of an enamine intermediate to an acceptor aldehyde yielding (*R*)-benzoins and (*R*)-2-HPP analogues in optically pure form. We expect that our investigations concerning the substrate and product range of this valuable biocatalyst will be helpful for elucidation of the catalytic cycle.

Conclusion

In conclusion, the method described here presents a convenient one-enzyme-catalyzed, highly selective synthesis of (*R*)-benzoins and (*R*)-2-HPP analogues. The reaction works in organic-aqueous medium, overcomes the solubility problem with organic substrates, and opens the way for large-scale preparation. The products are obtained in high yield starting from simple, easily available aromatic aldehydes and acetaldehyde via carboligation reactions. In this way, BAL represents a valuable alternative to BFD concerning the formation of (*R*)-benzoins.[11b] Since these two enzymes are enantiocomplimentary with regard to 2-HPP formation, most members of this class of substances, except for *ortho*-substituted (*S*)-2-HPP derivatives, can be synthesized in either enantiomeric form using these two enzymes.

Experimental Section

General Methods

Enzymatic syntheses were performed in standard buffer consisting of potassium phosphate (50 mmol L^{-1}, pH 7.0) containing $MgSO_4$ (2.5 mmol L^{-1}) and ThDP (0.15 mmol L^{-1}). NMR spectra were recorded on a Bruker DPX 400 or on a Bruker AMX 300. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: δ = 7.27) and $CDCl_3$ (^{13}C: δ = 77.0) or DMSO (^{1}H: δ = 2.49) and DMSO-d_6 (^{13}C: δ = 39.7) as internal standard. Column chromatography was conducted on silica gel 60 (40 – 63 μm). TLC was carried out on aluminium sheets precoated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light (λ = 254 nm). Enantiomeric excesses were determined by HPLC analysis using a Thermo Quest (TSP) GC-LC-MS equipped with an appropriate optically active column, as described in the footnotes of the corresponding Tables. GC-mass spectra were determined on a phenomenex Zebron ZB-5 capillary column (5% phenylmethylsiloxane, 30 m, 250 μm; T_{GC} (injector) = 250° C, T_{MS} (ion source) = 200° C, time program (oven): T_{0min} = 60° C, T_{3min} = 60° C, T_{14min} =

280° C (heating rate 20° C min^{-1}), $T_{19min} = 280°$ C, $T_{20min} = 300°$ C (heating rate 20° C min^{-1}), $T_{25min} = 300°$ C, MS: EI, 70 eV). Optical rotations were measured with a Bellingham & Stanley P20 polarimeter or a Perkin-Elmer 241 polarimeter. Mps were measured on a capillary tube apparatus and are uncorrected. HRMS (EI) and microanalyses were carried out at the Analytical Department, Chemische Institute der Universität Bonn.

Preparation of BAL

Hexahistidine-tagged BAL was obtained from recombinant *E. coli* SG13009 cells following a procedure described previously.[11a] One unit (U) of activity is defined as the amount of enzyme which catalyzes the cleavage of 1 μmol benzoin (1.5 mM) into benzaldehyde in potassium phosphate buffer [50 mmol L^{-1}, pH 7.0, containing $MgSO_4$ (2.5 mmol L^{-1}), ThDP (0.15 mmol L^{-1}) and 15% PEG 400 (v/v)] in 1 min at 30° C.

Representative Example for the Synthesis of (*R*)-Benzoins: (*R*)-2-Hydroxy-1,2-diphenylethan-1-one (2a)

Benzaldehyde (318 mg, 3 mmol) was dissolved in a mixture of dimethyl sulfoxide (20 mL) and potassium phosphate buffer [80 mL, 50 mM, pH 7.0, containing $MgSO_4$ (2.5 mM) and ThDP (0.15 mM)]. After addition of BAL (20 U) the reaction mixture was allowed to stand at 25° C for 48 h before a further 20 U of BAL were added. After 62 h no more benzaldehyde was detected (GC-MS). The reaction mixture was extracted with dichloromethane (250 mL) and the organic layer washed with water (25 mL) and brine (25 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification of the crude product by crystallization afforded (*R*)-2-hydroxy-1,2-diphenylethan-1-one as a colorless solid; yield: 305 mg (96%, >99% ee); mp 133–134° C [Lit.[23], mp 132–133° C for (*R*)-enantiomer]; $[a]_D^{22}$: −113.8 (*c* 1.5, CH_3COCH_3); [Lit.[23] $[a]_D^{22}$: −118.3 (*c* 2.5, CH_3COCH_3) for >99% ee]; HPLC: (Chiralpak AD) R_t (*R*) = 27.1 min; R_t (*S*) = 34.5 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.92 (d, *J* = 7.9 Hz, 2H), 7.29–7.52 (m, 8H), 5.97 (d, *J* = 6.1 Hz, 1H), 4.58 (d, *J* = 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 198.9, 139.6, 134.1, 134.0, 129.5, 129.4, 128.9, 128.8, 128.2, 76.5.

(*R*)-1,2-Bis(2-fluorophenyl)-2-hydroxyethan-1-one (2b)

Colorless solid; yield: 68% (96% ee); mp 61–62° C [Lit.[24], mp 60–62° C for racemic compound]; $[\alpha]_D^{20}$: −264.1 (*c* 0.5, CH_3OH) [Lit.[11b], $[\alpha]_D^{20}$: −266.0, (*c* 0.5, CH_3OH) for >99% ee]; HPLC (Chiralpak AD): R_t (*S*) = 17.8 min; R_t (*R*) = 20.2 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.80–7.91 (m, 1H), 7.55–7.67 (m, 1H), 6.98–7.30 (m, 6H), 5.91 (d, *J* = 5.6 Hz, 1H), 4.33 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 198.6, 164.2 (d, *J* = 253 Hz), 163.5 (d, *J* = 251 Hz), 134.7 (d, *J* = 13 Hz), 134.1 (d, *J* = 12 Hz), 130.6, 131.2, 129.2, 128.9, 124.4, 123.6, 116.2 (d, *J* = 24 Hz), 115.4 (d, *J* = 23 Hz), 75.9.

(*R*)-1,2-Bis(2-chlorophenyl)-2-hydroxyethan-1-one (2c)

Colorless solid; yield: 80% (97% ee); mp 57–61° C [Lit.[30], mp 64° C for racemic compound]; $[\alpha]_D^{20}$: −46.0 (*c* 1.0, $CHCl_3$); HPLC (Chiralpak AD): R_t (*S*) = 21.7 min; R_t (*R*) = 24.1 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.19–7.47 (m, 8H), 6.32 (d, *J* = 5.8 Hz, 1H), 4.35 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 200.8, 136.2, 135.4, 134.2, 133.0, 132.8, 132.3, 131.2, 130.2, 129.6, 129.3, 127.8, 126.7, 75.6; HRMS: *m/z* calcd. for $C_{14}H_{10}O_2Cl_2$ [$M^+ - Cl$]: 245.0375, found: 245.0372; anal. calcd. for $C_{14}H_{10}O_2Cl_2$: C, 59.81; H, 3.59%; found: C, 60.07; H, 3.79%.

(*R*)-1,2-Bis(2-bromophenyl)-2-hydroxyethan-1-one (2d)

Semisolid; yield: 90% (>99% ee); $[\alpha]_D^{20}$: −24.4 (*c* 1.5, $CHCl_3$); HPLC (Chiralpak AD): R_t (*S*) = 23.1 min; R_t (*R*) = 26.4 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 6.97–7.93 (m, 8H), 6.22 (d, *J* = 4.9 Hz, 1H), 4.22 (d, *J* = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 201.6, 138.1, 134.7, 133.7, 133.5, 132.4, 130.5, 129.7, 128.2, 127.9, 127.2, 124.6, 123.6, 77.6.

(*R*)-2-Hydroxy-1,2-bis(2-methoxyphenyl)ethan-1-one (2e)

Colorless solid; yield: 87% (>99% ee); mp 99° C [Lit.[25], mp 98–99° C for racemic compound]; $[\alpha]_D^{20}$: −125.0 (*c* 0.9, $CHCl_3$); HPLC (Chiralpak AD, *n*-hexane/2-propanol = 98:2, flow 0.90 mL min^{-1}, 20 °C): R_t (*R*) = 31.2 min.; R_t (*S*) = 42.2 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 6.63–7.69 (m, 8H), 5.92 (d, *J* = 5.1 Hz, 1H), 4.29 (d, *J* = 5.1 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 201.6, 158.4, 157.6, 134.0, 131.1, 130.3, 129.8, 128.2, 125.8, 120.9, 120.8, 111.4, 111.2, 76.1, 55.5, 55.4.

(*R*)-1,2-Bis(3-fluorophenyl)-2-hydroxyethan-1-one (2f)

Colorless solid; yield: 80% (97% ee); mp 70–71° C [Lit.[24], mp 73–76° C for racemic compound]; $[\alpha]_D^{20}$: −38.2 (*c* 2.5, $CHCl_3$); HPLC (Chiralpak AD): R_t (*R*) = 18.9 min; R_t (*S*) = 23.9 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.67–7.71 (m, 2H), 7.40–7.62 (m, 4H), 6.96–7.32 (m, 2H), 5.77 (d, *J* = 4.8 Hz, 1H), 4.45 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 197.2, 163.0 (d, *J* = 247 Hz), 162.7 (d, *J* = 248 Hz), 140.9 (d, *J* = 7 Hz), 135.5 (d, *J* = 7 Hz), 130.7 (d, *J* = 8 Hz), 130.4 (d, *J* = 7 Hz), 124.8 (d, *J* = 3 Hz), 123.4 (d, *J* = 3 Hz), 121.1 (d, *J* = 21 Hz), 115.9 (d, *J* = 23 Hz), 115.8 (d, *J* = 21 Hz), 114.7 (d, *J* = 21 Hz), 75.7.

(*R*)-1,2-Bis(3-chlorophenyl)-2-hydroxyethan-1-one (2g)

Colorless solid; yield: 94% (>99% ee); mp 76–78° C [Lit.[30], mp 76° C for racemic compound]; $[\alpha]_D^{20}$: −31.0 (*c* 1.2, $CHCl_3$); HPLC (Chiralpak AD): R_t (*R*) = 20.2 min; R_t (*S*) = 26.2 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.09–7.82 (m, 8H), 5.76 (d, *J* = 5.7 Hz, 1H), 4.32 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 197.5, 140.8, 135.7, 135.6, 135.3, 134.4, 130.7, 130.4, 129.5, 129.4, 128.3, 127.5, 126.1, 75.9.

(*R*)-1,2-Bis(3-bromophenyl)-2-hydroxyethan-1-one (2h)

Colorless solid; yield: 94% (>99% ee); mp 75–77° C [Lit.[26], mp 75° C for racemic compound]; $[\alpha]_D^{20}$: −38.0 (*c* 2.0, $CHCl_3$); HPLC (Chiralpak AD): R_t (*R*) = 22.7 min; R_t (*S*) = 28.0 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.31–8.30 (m, 8H), 6.01 (d, *J* = 5.5 Hz, 1H), 4.72 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 197.4, 141.1, 137.2, 137.1, 132.9, 132.6, 132.2, 131.1, 130.9, 130.8, 127.8, 126.6, 123.6, 75.9.

(*R*)-2-Hydroxy-1,2-bis(3-hydroxyphenyl)ethan-1-one (2j)

Colorless solid; yield: 84% (ee not determined); mp 150° C [Lit.[27], mp. 173–175° C for racemic compound]; $[\alpha]_D^{23}$: −144.4 (*c* 1.0, CH_3OH); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.91 (s, 1H), 9.41 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.30 (s, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.79 (t, *J* = 7.7 Hz, 2H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.87 (s, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 199.1, 157.44, 157.41, 141.2, 136.1, 129.7, 129.5, 120.3, 119.8, 118.0, 115.1, 114.7, 114.0, 75.7.

(*R*)-1,2-Bis(4-fluorophenyl)-2-hydroxyethan-1-one (2k)

Colorless solid; yield: 89% (>99% ee); mp 81–82° C [Lit.[24], mp 80–82° C for racemic compound]; $[\alpha]_D^{20}$: −95.2 (*c* 1.1, CH_3OH) [Lit.[3c], $[\alpha]_D^{r.t.}$: −41.2, (*c* 1.0, CH_3OH) for 44% ee]; HPLC (Chiralpak AD): R_t (*S*) = 22.5 min; R_t (*R*) = 26.5 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.84 (m, 2H), 7.25 (m, 2H), 7.12 (m, 2H), 7.09 (m, 2H), 5.86 (d, *J* = 5.4 Hz, 1H), 4.12 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 197.2, 166.7 (d, *J* = 246 Hz), 165.7 (d, *J* = 232 Hz), 135.1, 134.9, 132.1 (d, *J* = 9.6 Hz), 130.2 (d, *J* = 9.4 Hz), 116.8 (d, *J* = 22 Hz), 116.1 (d, *J* = 20 Hz), 75.4.

(*R*)-1,2-Bis(4-chlorophenyl)-2-hydroxyethan-1-one (2l)

Colorless solid; yield: 95% (>99% ee); mp 89° C [Lit.[28,30], mp 87–88° C for racemic compound]; $[\alpha]_D^{20}$: −29.0 (*c* 0.1, CH_3OH) [Lit.[3c], $[\alpha]_D^{r.t.}$: −12.3, (*c* 1.0, CH_3OH) for 29% ee; Lit.[3b], $[\alpha]_D$: 32.0, (CH_3OH) for 76% ee (*S*)]; HPLC (Chiralpak AD): R_t (*R*) = 26.7 min; R_t (*S*) = 31.5 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.75 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 5.75 (d, *J* = 5.2 Hz, 1H), 4.32 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 197.5, 141.1, 137.7, 135.2, 132.0, 130.8, 129.8, 129.5, 129.4, 75.8.

(*R*)-1,2-Bis-(4-bromophenyl)-2-hydroxyethan-1-one (2m)

Colorless solid; yield: 83% (>99% ee); mp 85–87° C [Lit.[29], mp 95–98° C for racemic compound]; $[\alpha]_D^{20}$: −13.0 (*c* 0.5, CH_3OH) [Lit.[3c], $[\alpha]_D^{r.t.}$: −2.3, (*c* 1.0, CH_3OH) for 20% ee; Lit.[11b], $[\alpha]_D^{20}$: −12.0, (*c* 0.5, CH_3OH) for >99% ee]; HPLC (Chiralpak AD): R_t (*R*) = 32.4 min; R_t (*S*) = 36.5 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.65 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 5.72 (d, *J* = 6.1 Hz, 1H), 4.29 (d, *J* = 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 197.6, 138.1, 132.7, 132.5, 132.0, 130.6, 129.8, 129.7, 123.4, 75.8.

(*R*)-2-Hydroxy-1,2-bis(4-methoxyphenyl)ethan-1-one (2n)

Colorless solid; yield: 95% (>99% ee); mp 112° C [Lit.[2c], mp 109–110° C for racemic compound]; $[\alpha]_D^{20}$: −90.4 (*c* 1.0, CH_3OH) [Lit.[3c], $[\alpha]_D^{r.t.}$: −76.2, (*c* 1.1, CH_3OH) for 86% ee]; HPLC (Chiralpak AD, *n*-hexane/2-propanol = 75:25, flow 0.95 mL mL min^{-1}, 20 °C): R_t (*R*) = 25.4 min; R_t (*S*) = 30.2 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.85 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.84 (d, *J* = 5.7 Hz, 1H), 4.46 (d, *J* = 5.7 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 197.3, 164.2, 159.9, 132.4, 131.9, 129.4, 126.8, 114.8, 114.7, 75.5, 55.5, 55.3.

(*R*)-2-Hydroxy-1,2-bis(4-methylphenyl)ethan-1-one (2o)

Colorless solid; yield: 94% (>99% ee); mp 90° C [Lit.[30], mp 89° C for racemic compound]; $[\alpha]_D^{20}$: −150.0 (*c* 0.7, CH_3OH) [Lit.[3c], $[\alpha]_D^{r.t.}$: −130.8, (*c* 1.0, CH_3OH) for 82% ee; Lit.[3b], $[\alpha]_D$: 107.0, (CH_3OH) for 82.5% ee (*S*)]; HPLC (Chiralpak AD): R_t (*R*) = 30.2 min; R_t (*S*) = 36.0 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.83 (d, *J* = 8.1 Hz, 2H), 7.18–7.22 (m, 4H), 7.16 (d, *J* = 8.1 Hz, 2H), 5.88 (d, *J* = 5.8 Hz, 1H), 4.52 (d, *J* = 5.8 Hz, 1H), 2.36 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 198.5, 144.7, 138.3, 136.9, 131.5, 130.0, 129.7, 129.6, 128.1, 76.1, 22.1, 21.6.

(*R*)-1,2-Bis(2,4-difluorophenyl)-2-hydroxyethan-1-one (2p)

Semisolid; yield: 87% (>99% ee); $[\alpha]_D^{20}$: −102.4 (*c* 2.0, $CHCl_3$); HPLC (Chiralpak AD): R_t (*R*) = 17.3 min; R_t (*S*) = 18.3 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.82–7.97 (m, 2H), 6.86–7.10 (m, 4H), 5.87 (s, 1H), 4.18 (br.s, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 195.2 (d, *J* = 5 Hz), 166.3 (dd, *J* = 12, 257 Hz), 162.9 (dd, *J* = 12, 250 Hz), 161.9 (dd, *J* = 12, 257 Hz), 160.9 (dd, *J* = 12, 251 Hz), 132.9 (dd, *J* = 4, 11 Hz), 130.7 (dd, *J* = 5, 10 Hz), 121.5 (dd, *J* = 3, 14 Hz), 118.8 (dd, *J* = 4, 13 Hz), 112.5 (dd, *J* = 3, 21 Hz), 111.6 (dd, *J* = 4, 21 Hz), 105.2 (dd, *J* = 26 Hz), 104.7 (dd, *J* = 25 Hz), 72.9 (d, *J* = 7 Hz).

(*R*)-2-Hydroxy-1,2-di(2-naphthalenyl)ethan-1-one (2q)

Colorless solid; yield: 98% (>99% ee); mp 127° C [Lit.[31], mp 125–126° C for racemic compound]; $[\alpha]_D^{20}$: 21.0 (*c* 1.1, $CHCl_3$); HPLC (Chiralpak AD, *n*-hexane/2-propanol = 10:90, flow 0.95 mL min^{-1}, 20 °C): R_t (*R*) = 18.5 min; R_t (*S*) = 30.0 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 6.71–7.76 (m, 14H), 5.92 (d, *J* = 6.1 Hz, 1H), 4.86 (d, *J* = 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 198.9, 137.3, 136.5, 134.5, 134.4, 132.9, 131.5, 129.7, 129.2, 128.9, 128.3, 127.9, 127.2, 126.4, 124.7, 122.9, 76.7.

(*R*)-1,2-Di(2-furanyl)-2-hydroxyethan-1-one (2r)

Brown solid; yield: 88% (92% ee); mp 136° C [Lit.[2c], mp 135–136° C for racemic compound]; $[\alpha]_D^{20}$: −21.6 (*c* 0.1, CH_3OH) [Lit.[32], $[\alpha]_D^{20}$: −22.0, (*c* 0.01, CH_3OH) for 94% ee]; HPLC (Chiralpak AD): R_t (*S*) = 22.8 min; R_t (*R*) = 28.6 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.90–7.91 (m, 1H), 7.51–7.52 (m, 1H), 7.44 (d, *J* = 3.6 Hz, 1H), 6.60 (dd, *J* = 1.5, 3.6 Hz, 1H), 6.32–6.36 (m, 2H), 5.84 (d, *J* = 5.6 Hz, 1H), 3.98 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 185.2, 152.6, 149.9, 148.5, 143.3, 120.6, 112.7, 110.9, 108.8, 69.7.

(*R*)-1,2-Di(2-thienyl)-2-hydroxyethan-1-one (2s)

Colorless solid; yield: 73% (91% ee); mp 107° C [Lit.[33], mp 108–109° C for racemic compound]; $[\alpha]_D^{20}$: −392.0 (*c* 0.1, $CHCl_3$) [Lit.[32], $[\alpha]_D^{20}$: −380.0, (*c* 0.1, $CHCl_3$) for 95% ee]; HPLC (Chiralpak AD): R_t (*R*) = 35.0 min; R_t (*S*) = 40.6 min; ^{1}H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.10–7.40 (m, 4H), 6.41–6.60 (m, 2H), 5.81 (d, *J* = 5.8 Hz, 1H), 4.14 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 196.2, 148.1, 143.5, 124.7, 119.6, 119.2, 113.1, 112.1, 110.2, 75.4.

Synthesis of (*R*)-2-Hydroxy-1,2-bis(3-methoxyphenyl)ethan-1-one (2i) on a Preparative Scale

To a suspension of 3-methoxybenzaldehyde (1.62 g, 12 mmol) in dimethyl sulfoxide (40 mL) and potassium phosphate buffer [160 mL, 50 mM, pH 7.0, containing $MgCl_2$ (2.5 mM) and ThDP (0.15 mM)] BAL (0.3 U/mL) was added and the reaction-mixture stirred at 21° C. After a reaction-time of 3 h the product, which accumulates as a yellow oil, was separated by centrifugation and 3-methoxybenzaldehyde (1.62 g, 12 mmol) was added to the buffer solution. The reaction-mixture was stirred for an additional 3 h at 21° C before extraction with dichloromethane (3 x 50 mL) was carried out. After drying the collected organic phase over Na_2SO_4, removal of the solvent under reduced pressure gave the crude product. Crystallization at −18° C from isohexane/ethyl acetate afforded the pure product as a white solid; yield: 3.03 g (93%, >99% ee); mp 55° C [Lit.[34], mp 55° C for racemic compound]; $[\alpha]_D^{20}$: −156.0 (*c* 1.0, CH_3OH) [Lit.[3c], $[\alpha]_D^{r.t.}$: −105.9, (*c* 1.0, CH_3OH) for 66% ee]; HPLC (Chiralpak AD, *n*-hexane/2-propanol = 90:10, flow 0.90 mL min^{-1}, 20 °C): R_t (*R*) = 41.0 min; R_t (*S*) = 54.1 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.51 (m, 2H), 7.22–7.34 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 6.9 Hz, 1H), 6.86 (t, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.90 (d, *J* = 6.1 Hz, 1H), 4.54 (d, *J* = 6.1 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 198.9, 160.3, 159.9, 140.6, 134.9, 130.4, 129.9, 122.0, 120.7, 120.3, 114.3, 113.5, 113.3, 76.4, 55.6, 55.4.

Representative Example for the Synthesis of (*R*)-2-Hydroxy-1-phenylpropan-1-one Derivatives: (*R*)-2-Hydroxy-1-phenylpropan-1-one [(*R*)-2-HPP] (3a)

Benzaldehyde (212 mg, 2 mmol) was dissolved in a mixture of dimethyl sulfoxide (20 mL) and potassium phosphate buffer [80 mL, 50 mM, pH 7.0, containing $MgSO_4$ (2.5 mM) and ThDP (0.15 mM)]. To this solution 88 mg (2 mmol) acetaldehyde was added. After addition of BAL (20 U) the reaction mixture was allowed to stand at 25° C. After 24 h 20 U of BAL and 176 mg (4 mmol) of acetaldehyde were added. This was repeated every 24 h. After 96 h the conversion was determined as 97% (GC-MS). Work-up according to the former procedure afforded (*R*)-2-HPP as a viscous oil; yield: 285 mg (94%, >99% ee); $[\alpha]_D^{22}$: 85.1 (*c* 2.0, $CHCl_3$), [Lit.[9a] $[\alpha]_D^{20}$: 82.2 (*c* 2.0, $CHCl_3$) for 96% ee; Lit.[35] $[\alpha]_D^{20}$: −80.9 (*c* 2.0, $CHCl_3$) for >95% ee (*S*)]; HPLC (Chiralpak AD, isohexane/2-propanol = 90:10, flow 0.80 mL min^{-1}, 20 °C): R_t (*S*) = 12.1 min; R_t (*R*) = 14.3 min; ^{1}H NMR (400 MHz, $CDCl_3$/CCl_4): δ = 7.90 (dd, *J* = 1.4, 8.2 Hz, 2H), 7.40–7.60 (m, 3H), 5.13 (q, *J* = 6.0 Hz, 1H), 3.80 (br.s, 1H), 1.41 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CCl_4): δ = 202.7, 134.4, 134.0, 128.9, 128.7, 69.2, 22.0.

(*R*)-1-(2-Fluorophenyl)-2-hydroxypropan-1-one (3b)

Viscous oil; yield: 64% (97% ee); $[\alpha]_D^{20}$: 105.3 (*c* 0.5, $CHCl_3$); HPLC (Chiralpak AD, isohexane/2-propanol = 90:10, flow 0.80 mL min^{-1}, 20 °C): R_t (*S*) = 9.7 min; R_t (*R*) = 11.1 min; ^{1}H NMR (400 MHz, $CDCl_3$/CCl_4): δ = 7.81–7.90 (m, 1H), 7.56–7.67 (m, 1H), 7.12–7.31 (m, 2H), 4.96 (q, *J* = 6.8 Hz, 1H), 3.72 (br.s, 1H), 1.29 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CCl_4): δ = 198.2, 163.8 (d, *J* = 251 Hz), 134.5 (d, *J* = 12 Hz), 131.3, 129.9, 124.5, 115.9 (d, *J* = 23 Hz), 72.2, 21.1.

(*R*)-2-Hydroxy-1-(2-methoxyphenyl)propan-1-one (3c)

Viscous oil; yield: 63% (>99% ee); $[\alpha]_D^{20}$: 143.0 (*c* 0.8, $CHCl_3$); HPLC (Chiralcel OB, isohexane/2-propanol = 98:2, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 34.9 min; R_t (*R*) = 42.7 min; ^{1}H NMR (400 MHz, $CDCl_3$/CCl_4): δ = 7.70–7.78 (m, 1H), 7.39–7.51 (m, 1H), 6.91–7.01 (m, 2H), 5.05 (q, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 3.68 (br.s, 1H),1.42 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CCl_4): δ = 203.7, 158.2, 134.5, 131.3, 125.1, 121.1, 111.3, 72.9, 55.2, 20.7; HR-MS: *m/z*: calcd. for $C_{10}H_{12}O_3$ [$M^+ - C_2H_3O$]: 135.0454; found: 135.0450; anal. calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%; found: C, 66.27; H, 6.64%.

(*R*)-1-(3-Fluorophenyl)-2-hydroxypropan-1-one (3d)

Viscous oil; yield: 85%; (95% ee); $[\alpha]_D^{20}$: 107.5 (*c* 0.5, $CHCl_3$); (Chiralcel OB, isohexane/2-propanol = 95:5, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 16.5 min; R_t (*R*) = 25.8 min; ^{1}H NMR (400 MHz, $CDCl_3$/CCl_4): δ = 7.71–7.76 (m, 1H), 7.59–7.66 (m, 1H), 7.41–7.50 (m, 1H), 7.22–7.31 (m, 1H), 4.92 (q, *J* = 6.8 Hz, 1H), 3.71 (br.s, 1H), 1.41 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CCl_4): δ = 198.8, 164.1 (d, *J* = 246 Hz), 134.2 (d, *J* = 7 Hz), 130.2 (d, *J* = 7 Hz), 124.3 (d, *J* = 3 Hz), 114.1 (d, *J* = 23 Hz), 113.8 (d, *J* = 22 Hz), 71.8, 21.4.

(*R*)-1-(3-Chlorophenyl)-2-hydroxypropan-1-one (3e)

Viscous oil; yield: 94% (>99% ee); $[\alpha]_D^{20}$: 73.0 (*c* 1.1, CH_2Cl_2); HPLC (Chiralcel OB, isohexane/2-propanol = 98:2, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 28.5 min; R_t (*R*) = 48.2 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.43 (dd, *J* = 8.0 Hz, 1H), 5.12 (q, *J* = 7.0 Hz, 1H), 3.70 (br. s, 1H), 1.41 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CCl_4): δ = 200.9, 135.7, 133.8, 130.6, 130.3, 129.1, 126.9, 69.7, 22.2; HR-MS *m/z* calcd. for $C_9H_9O_2Cl$ [M^+]: 184.0291, found: 184.0272; anal. calcd. for $C_9H_9O_2Cl$: C, 58.55; H, 4.91%; found: C, 58.23; H, 5.16%.

(*R*)-1-(3-Bromophenyl)-2-hydroxypropan-1-one (3f)

Viscous oil; yield: 88%; (93% ee); $[\alpha]_D^{20}$: 22.1 (*c* 1.5, $CHCl_3$); HPLC (Chiralcel OB, isohexane/2-propanol = 95:5, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 23.0 min; R_t (*R*) = 33.7 min; ^{1}H NMR (400 MHz, $CDCl_3$/CCl_4): δ = 8.04–8.05 (m, 1H), 7.82–7.84 (m, 1H), 7.73–7.75 (m, 1H), 7.36–7.40 (m, 1H), 5.09 (q, *J* = 6.9 Hz, 1H), 3.78 (br.s, 1H), 1.41 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CCl_4): δ = 200.3, 141.3, 136.7, 132.0, 130.4, 126.4, 123.4, 69.8, 24.2.

(*R*)-2-Hydroxy-1-(3-methoxyphenyl)propan-1-one (3g)

Viscous oil; yield: 80% (>99% ee); $[\alpha]_D^{20}$: 67.8 (*c* 1.0, $CHCl_3$) [Lit.[11c], $[\alpha]_D^{20}$: −65.2 (*c* 1.1, $CHCl_3$) for 96% ee (*S*)]; HPLC (Chiralcel OB, isohexane/2-propanol = 90:10, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 12.9 min; R_t (*R*) = 14.4 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.47 (m, 4H), 5.14 (q, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 3.78 (d, *J* = 6.8 Hz, 1H), 1.45 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CCl_4): δ = 201.9, 160.2, 135.2, 130.1, 121.9, 121.6, 113.4, 69.5, 55.5, 22.5.

(*R*)-1-(4-Chlorophenyl)-2-hydroxypropan-1-one (3h)

Viscous oil; yield: 88% (>99% ee); $[\alpha]_D^{20}$: 18.3 (*c* 0.5, $CHCl_3$) [Lit.[9c], $[\alpha]_D^{20}$: 15.2 (*c* 1.0–2.0, $CHCl_3$) for 83% ee]; HPLC (Chiralcel OB, isohexane/2-propanol = 95:5, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 17.5 min; R_t (*R*) = 28.9 min.; ^{1}H NMR (400 MHz, $CDCl_3$/CCl_4): δ = 7.83 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 4.98 (q, *J* = 6.7 Hz, 1H), 3.59 (br.s, 1H), 1.42 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CCl_4): δ = 199.5, 134.6, 132.5, 130.9, 129.1, 69.5, 22.1.

(*R*)-1-(4-Bromophenyl)-2-hydroxypropan-1-one (3i)

Viscous oil; yield: 86% (>99% ee); $[\alpha]_D^{20}$: 61.3 (*c* 0.5, $CHCl_3$); HPLC (Chiralcel OB, isohexane/2-propanol = 95:5, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 19.2 min; R_t (*R*) = 27.6 min; ^{1}H NMR (400 MHz, $CDCl_3$/CCl_4): δ = 7.73 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 4.96 (q, *J* = 7.0 Hz, 1H), 3.57 (br.s, 1H), 1.40 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CCl_4): δ = 200.4, 137.1, 133.0, 131.4, 129.4, 71.4, 22.4.

(*R*)-2-Hydroxy-1-(4-methoxyphenyl)propan-1-one (3j)

Viscous oil; yield: 64% (>99% ee); $[\alpha]_D^{20}$: 43.4 (*c* 1.0, CH_3OH) [Lit.[4f], $[\alpha]_D^{20}$: 32.8 (*c* 1.4, CH_3OH) for 99% ee; Lit.[36], $[\alpha]_D^{20}$: −33.4 (*c* 1.05, CH_3OH) for 98% ee (*S*); Lit.[4b], $[\alpha]_D^{28}$: −41.1 (*c* 1.12, CH_3OH) for 92% ee (*S*)]; HPLC (Chiralcel OB, isohexane/2-propanol = 95:5, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 26.9 min; R_t (*R*) = 36.4 min; ^{1}H NMR (400 MHz, $CDCl_3$/CCl_4): δ = 7.92 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 5.11 (q, *J* = 7.0 Hz, 1H), 3.89 (s, 3H), 3.52 (br.s, 1H), 1.44 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/CCl_4): δ = 200.6, 164.1, 130.9, 125.9, 114.0, 68.8, 55.5, 22.6.

(*R*)-1-(3,5-Difluorophenyl)-2-hydroxypropan-1-one (3l)

Viscous oil; yield: 67% (>99% ee); $[\alpha]_D^{20}$: 71.0 (*c* 1.0, $CHCl_3$); HPLC (Chiralcel OB, isohexane/2-propanol = 95:5, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 12.7 min; R_t (*R*) = 16.7 min; ^{1}H NMR (400 MHz, $CDCl_3$/CCl_4): δ = 7.78–8.18 (m, 1H), 6.70–7.31 (m, 2H), 4.99 (q, *J* = 6.6 Hz, 1H), 3.36 (br.s, 1H), 1.42 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 201.3, 163.5 (d, *J* = 252 Hz), 136.5, 112.0 (d, *J* = 17 Hz), 109.6 (t, *J* = 25 Hz), 70.1, 22.3.

(*R*)-2-Hydroxy-1(3-hydroxy-4-methoxyphenyl)propan-1-one (3m)

Colorless oil; yield: 80%; (ee not determined); $[\alpha]_D^{20}$: 40.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ=7.52 (s, 1H), 7.47 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 5.82 (br.s, 1H), 5.11 (q, J = 7.1 Hz, 1H), 3.97 (s, 3H), 3.80 (br.s, 1H), 1.44 (d, J=7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 201.6, 153.5, 146.6, 131.5, 124.8, 114.8, 113.2, 71.9, 56.3, 23.8; HR-MS: *m/z*: calcd. for $C_{10}H_{12}O_4$ [M^+]: 196.0735; found: 196.0735.

(*R*)-2-Hydroxy-1(4-hydroxy-3-methoxyphenyl)propan-1-one (3n)

Colorless oil; yield: 90%; (ee not determined); $[\alpha]_D^{20}$: 42.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 6.35 (br.s, 1H), 5.10 (q, J = 7.0 Hz, 1H), 3.93 (br. s, 4H), 1.44 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 201.4, 151.9, 147.6, 126.5, 124.7, 114.8, 111.1, 69.5, 56.8, 23.6; HR-MS: *m/z*: calcd. for $C_{10}H_{12}O_4$ [M^+]: 196.0736; found: 196.0741; anal. calcd. for $C_{10}H_{12}O_4$: C, 61.22, H, 6.16%; found: C, 61.00, H, 5.95%.

(*R*)-2-Hydroxy-1(3,4,5-trimethoxyphenyl)propan-1-one (3o)

Colorless oil; yield: 92% (>99% ee); $[\alpha]_D^{20}$: 54.3 (*c* 1.0, $CHCl_3$); HPLC (Chiralpak AD, isohexane/2-propanol = 95:5, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 28.5 min; R_t (*R*) = 36.4 min; ^1H NMR (300 MHz, $CDCl_3$): δ=7.11 (s, 2H), 5.07 (q, J = 7.1 Hz, 1H), 3.81 (s, 9H), 3.72 (br. s, 1H), 1.45 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 201.5, 153.5, 143.5, 128.9, 106.4, 69.4, 56.6, 56.4, 23.6; HR-MS: *m/z*: calcd. for $C_{12}H_{16}O_5$ [M^+]: 240.0992; found: 240.0995; anal. calcd. for $C_{12}H_{16}O_5$: C, 59.99, H, 6.71%; found: C, 59.84, H, 6.76%.

(*R*)-1-(2-Furanyl)-2-hydroxypropan-1-one (3p)[37]

Viscous oil; yield: 61%; (>99% ee); $[\alpha]_D^{20}$: 18.0 (*c* 0.2, $CHCl_3$); HPLC (Chiralcel OB, isohexane/2-propanol = 90:10, flow 0.75 mL min^{-1}, 20 °C): R_t (*S*) = 13.7 min; R_t (*R*) = 16.9 min; ^1H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.40 (m, 1H), 6.55 (d, J = 3.4 Hz, 1H), 6.36 (dd, J = 1.7, 3.4 Hz, 1H), 5.01 (q, J = 6.7 Hz, 1H), 3.66 (br.s, 1H), 1.45 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3/CCl_4$): δ = 196.2, 150.3, 144.1, 111.6, 110.4, 71.2, 21.8.

Representative Example for the Synthesis of (*R*)-2-Hydroxy-1-phenylpropan-1-one Derivatives on a Preparative Scale: (*R*)-1-(2,4-Difluorophenyl)-2-hydroxypropan-1-one (3k)

2,4-Difluorobenzaldehyde (4.2 g, 29.7 mmol) was dissolved in a mixture of dimethyl sulfoxide (100 mL) and potassium phosphate buffer [380 mL, 50 mM, pH 7.0, containing $MgSO_4$ (2.5 mM) and ThDP (0.15 mM)]. After addition of acetaldehyde (2.6 g, 60.0 mmol) the reaction was started by adding 480 U of BAL (7.5 g of wet cells of *E. coli* recBAL,[21] suspended in 20 mL standard buffer, were disrupted by sonification and centrifuged to afford 20 mL of a solution containing 480 U BAL) and the reaction mixture was smoothly stirred at 25° C. Conversion was monitored by GC-MS by extracting analytical samples with dichloromethane followed by phase separation by centrifugation. After 38 h (99% conversion) the reaction mixture was filtered using a folded filter and an ultrafiltration membrane (cut-off 10 kDa, Sartocon Micro module, Sartorius AG, Göttingen). Then, 100 g sodium chloride and 200 mL ethyl acetate were added to the permeate. The organic layer was separated, dried with Na_2SO_4 and concentrated under vacuum to give **3k** as a yellow oil; yield: 3.6 g (65%, 97% ee); $[\alpha]_D^{20}$: 66.9 (*c* 1.0, $CHCl_3$) [Lit.[19c], $[\alpha]_D^{20}$: 73.0 (*c* 1.0, $CHCl_3$) for >98% ee; Lit.[19f], $[\alpha]_D^{25}$: −67.1 (*c* 1.17, $CHCl_3$) for >99.5% ee (*S*)]; HPLC (Chiralpak AD, isohexane/2-propanol = 90:10, flow 0.80 mL min^{-1}, 20 °C): R_t (*S*) = 8.8 min; R_t (*R*) = 10.9 min; ^1H NMR (400 MHz, $CDCl_3/CCl_4$): δ = 7.91 – 8.05 (m, 1H), 6.83 – 7.10 (m, 2H), 5.02 (q, J = 6.5 Hz, 1H), 3.76 (br. s, 1H), 1.42 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 199.5, 166.4 (d, J = 259 Hz), 162.2 (d, J = 259 Hz), 133.2, 118.7, 113.0 (d, J = 21 Hz), 105.1 (dd, J = 27 Hz), 72.7, 20.8; HR-MS: *m/z* calcd. for $C_9H_8O_2F_2$ [M^+]: 186.0493, found: 186.0520.

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