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Baker's yeast-mediated synthesis of (*R*)- and (*S*)-heteroaryl-ethane-1,2-diols

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ABSTRACT

Baker's yeast-mediated enantioselective bioreduction of 1-(heteroaryl)-2-hydroxyethanones and 2-acetoxy-1-(hetero-aryl)ethanones was used for the enantioselective synthesis of both (*R*)- and (*S*)-benzofuranyl-, benzo[*b*]thiophenyl- and benzo[*d*]thiazolyl-ethane-1,2-diols.

1. Introduction

Optically active terminal 1,2-diols are important chiral building blocks in organic synthesis with numerous applications as chiral auxiliaries or ligands for asymmetric synthesis.[1] Among the chemical methods known for their enantioselective synthesis, the asymmetric dihydroxylation of olefins or the reduction of α-hydroxy ketones protected as their silyl ethers in a CBS system[2] seems to be most common. However, these procedures suffer from inherent drawbacks. Dihydroxylation involves the use of toxic OsO_4, while the CBS-oxazaborolidine-catalyzed borane reduction of protected α-hydroxy ketones requires two extra steps of protection and deprotection.

Thus, many biocatalytic methodologies[3] based on the enantiomer selective kinetic resolution of racemates and enantioselective transformation of prochiral substrates were developed for an efficient, economical and environmentally friendly synthesis of optically active 1,2-diols.

Epoxide hydrolases[4,5] mediate the hydrolytic oxirane ring opening of many racemic epoxides and lipases,[6,7] and assist the stereoselective acylation of various racemic diols, are important enzymes used for the synthesis of both stereoisomers of terminal 1,2-diols. The main drawback of these reactions is that the maximum conversion for the desired enantiomer can be only 50%; this can be overcome by performing enantioselective enzymatic reactions. The use of monooxygenases for enantioselective asymmetrization of prochiral alkenes[8] provides with a 100% theoretical yield the desired enantiopure epoxides, which are high value intermediates for the synthesis of enantiopure vicinal diols. However, their use in biocatalysis is rather limited, as they show not only a strict enantioselectivity, but are also specific for one or a few substrates, thus having limited utility. Lipase-mediated enantioselective epoxidation with hydrogen peroxide of variously substituted styrenes has recently been developed,[9] but the enantiomeric excess for the isolated products was lower than 81%.

The bioreduction of ketones is one of the most important and practical reactions for producing chiral alcohols.[10] Baker's yeast reduction of hydroxymethyl ketones and acetoxymethyl ketones proved to be useful for the production of both enantiomeric forms of 1,2-diols with 100% theoretical yield. Ketones with a relatively small and hydrophilic hydroxymethyl group were all reduced from the same face, whereas for the acetoxymethyl ketones baker's yeast gave an opposite enantiotopic face preference. Our previous results[11] demonstrate that enantioselective bioreduction of 1-(benzofuran-2-yl)-2-hydroxyethanones and 2-acetoxy-1-(benzofuran-2-yl)-ethanones provided both enantiomeric forms of diols with high enantiomeric purity (ee 84–93%). These results encouraged us to investigate baker's yeast-mediated biotransformation of other α-substituted heteroaryl-ketones for the synthesis of (*R*)- and (*S*)-heteroaryl diols.

2. Results and discussions

2.1. Chemical synthesis

The synthesis of the substrates was performed in accordance with a chemoenzymatic method as developed by us.[12] Thus, as general starting materials, heteroaryl ethanones **1a–d** were used (Scheme 1a), which were α-brominated using cuprous bromine in ethyl acetate for **1a** or pyridinium tribromide in glacial acetic acid for **1b–d**. The bromo-ketones **2a–d** were subsequently, quantitatively transformed into α-acetoxymethylketones **3a–d** with sodium acetate in dry dioxane using 18C6 crown ether as phase transfer catalyst. Furthermore, the enzymatic ethanolysis of the α-acetoxymethylketones **3a–d** provided with excellent yields the α-hydroxymethyl ketones **4a–d**. Finally the latter compounds were reduced with sodium borohydride into *rac*-heteroaryl-ethane-diols *rac*-**5a–d** (Scheme 1a).

2.2. Cellular biotransformations

To investigate the stereoselectivity for baker's yeast-mediated reduction of ketones **3**,**4a–d**, the chromatographic separation of

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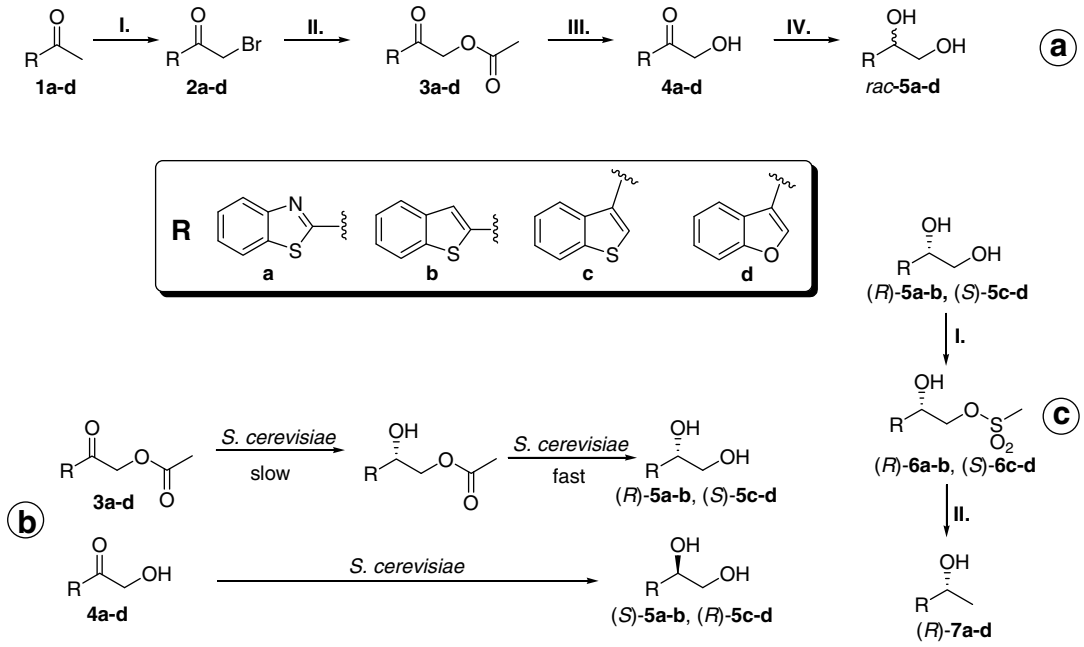

Scheme 1. (a) Chemoenzymatic synthesis of the prochiral ketones **3**,**4a–d** and racemic heteroaryl-ethanediols *rac*-**5a–d**; (b) Baker's yeast-mediated stereoselective biotransformation of ketones **3**,**4a–d**; (c) retrosynthetic pathway for the absolute configuration of enantiomerically enriched heteroaryl-ethane-1,2-diols produced. Reagents and conditions: (**a**) (**Ia**) $CuBr_2/CH_3COOC_2H_5$, reflux; (**Ib–d**) pyridinium tribromide/CH_3COOH, 50 °C; (**II**) $CH_3COO^-Na^+$, 18C6/dioxane, reflux; (**III**) Novozym 435/EtOH; (**IV**) $NaBH_4$/MeOH; (**c**) (**I**) CH_3SO_2Cl, Et_3N/THF, −20 °C; (**II**) $LiAlH_4$/THF.

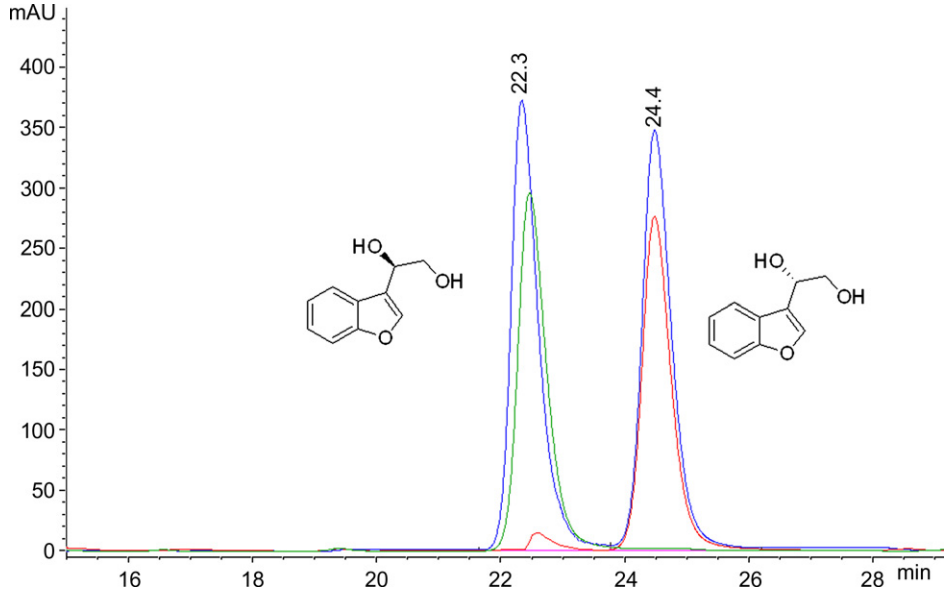

Figure 1. Elution diagram of the racemic 1-(benzofuran-3-yl)ethane-1,2-diol (*rac*-**5d**) as reference (blue trace), of (*R*)-**5d** obtained by the bioreduction of ketone **4d** (green trace) and of (*S*)-**5d** isolated from baker's yeast-mediated biotransformation of ketone **3d** (red trace).

the enantiomers of the reaction products *rac*-**5a–d** was first established (Fig. 1, blue trace).

The analytical scale reduction of ketones **3**,**4a–d** was performed under fermenting and non-fermenting conditions. Samples were taken every 6 h over 2 days and analyzed chromatographically with HPLC. As we expected, the biotransformation of 2-(heteroaryl)-2-oxoethyl acetates **3a–d** and 1-(heteroaryl)-2-hydroxyethanones **4a–d** takes place with opposite enantiopreference, as shown in Figure 1 (green and red trace) and Scheme 1b. It is important to note that the enantiopurity of the isolated optically active 1-(heteroaryl)-ethane-1,2-diols remained constant during the reaction time. In case of the biotransformation of 2-(heteroaryl)-2-oxoethyl acetates **3a–d**, the corresponding 1-(heteroaryl)-ethane-1,2-diols **5a–d** could be detected as reaction products. These facts indicate that the optically active 2-hydroxy-2-heteroarylethyl acetates, the products of the enzymatic reduction of 2-(heteroaryl)-2-oxoethyl acetates **3a–d**, are good substrates for the hydrolases present in baker's yeast cells (Scheme 1b).

In contrast to most of the earlier reported results, the selectivity of the reactions was higher when fermenting baker's yeast was

used as a biocatalyst. However, the enantiopurity of the produced 1-(heteroaryl)-ethane-1,2-diols from ketones **3c**, **4a** and **4b** (see Table 1, entries 3, 5 and 6) was not satisfactory.

Table 1
Ee (%) for (*R*)- and (*S*)-1-(heteroaryl)-ethane-1,2-diols obtained by cellular biotransformation

Entry	Substrate	Product	Enantiomeric excess	
			Fermenting system	Nonfermenting system
1	**3a**	(*R*)-**5a**	99	99
2	**3b**	(*R*)-**5b**	96	83
3	**3c**	(*S*)-**5c**	73	62
4	**3d**	(*S*)-**5d**	95	60
5	**4a**	(*S*)-**5a**	<5	<5
6	**4b**	(*S*)-**5b**	88	85
7	**4c**	(*R*)-**5c**	99	99
8	**4d**	(*R*)-**5d**	99	99

It is known that various additives could significantly influence the selectivity of baker's yeast-mediated reactions.[10] While the fermenting as well as the non-fermenting bioreduction of ketone **4a** in presence of six different additives is almost non-selective, the ee was increased for (*S*)-**5b** from 88% to 96% in presence of L-cysteine (Table 2, entry 5) and from 73% to 89% in the presence of allyl alcohol for (*S*)-**5c**, respectively (Table 2, entry 3).

Table 2
The influence of various additives upon the stereoselectivity of bioreduction of ketones **3c** and **4b**

Entry	Additive(s) (amount)	ee (%)	
		(*S*)-**5b**	(*S*)-**5c**
1	Without additives	88	73
2	Ethyl chloroacetate (0.5%)	73	67
3	Allyl alcohol (0.5%)	79	89
4	Hexane (1:1, v:v)	62	59
5	L-Cysteine (0.5%)	96	78
6	$MgCl_2$ (0.5%)	87	79
7	$MnCl_2$ (0.5%)	87	79

With these results in our hands, the preparative scale synthesis of (*S*)-**5b–d** and (*R*)-**5a–d** was performed (Table 3). The dilutions and substrate–biocatalyst ratio were the same as in the case of the analytical scale reactions. For the biotransformation of ketones **3c** and **4b**, the above-mentioned additives were used in the same concentration.

Table 3
Baker's yeast-mediated preparative scale reduction of heteroaryl-ketones **3a–d** and **4b–d**

Entry	Substrate	Product	ee (%)	Reaction time (days)[c]	Yield (%)	$[\alpha]_D^{20}$ (10 mg mL^{-1})
1	**3a**	(*R*)-**5a**	99	5	92	+18.2, MeOH
2	**3b**	(*R*)-**5b**	96	6	92	+12.5, MeOH
3	**3c**	(*S*)-**5c**	89[a]	3	94	+44.8, MeOH
4	**3d**	(*S*)-**5d**	95	2	93	+25.15, MeOH
5	**4b**	(*S*)-**5b**	96[b]	5	91	−12.5, MeOH
6	**4c**	(*R*)-**5c**	99	2	92	−50.1, MeOH
7	**4d**	(*R*)-**5d**	99	2	94	−25.3, MeOH

[a] Fermenting system with L-cysteine (0.5%).
[b] Fermenting system with allyl alcohol (0.5%).
[c] Reaction time for the complete transformation of the substrates.

The reactions were stopped when the entire quantity of the substrate was consumed. The yield for the isolated and purified reaction products was more than 90% and the ee values were the same as those found for the small scale reactions.

2.3. The absolute configuration of the synthesized heteroaryl-ethanediols

Since the absolute configurations of the produced diols were unknown, diols (+)-**5a–d** prepared by the biotransformation with *Saccharomyces cerevisiae* from 2-(heteroaryl)-2-oxoethyl acetates **3a–d** were converted into (*R*)-1-heteroaryl-ethanols (*R*)-**7a–d** (Scheme 1c) using the procedure described earlier by us.[11] For this, the diols (+)-**5a–d** were selectively mesylated at the primary hydroxyl group. The reduction with $LiAlH_4$ of the resulting optically active mesylates **6a–d**, provided (*R*)-heteroaryl-ethanols (*R*)-**7a–d.** The found (*R*)-configuration of the latest compounds was confirmed by measuring their specific rotations, which were consistent with literature values.[13]

3. Conclusions

Herein, the usability of *S. cerevisiae* cells for the preparation of both highly enantiomerically enriched (*R*)- and (*S*)-heteroaryl-ethane-1,2-diols. When the enantiopurity of the products was not satisfactory, in most of the cases, the presence of a certain additive in the fermenting cell suspension raised the enantiopurity of the isolated products.

4. Experimental

4.1. Analytical methods

The ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 300 MHz and 75 MHz, respectively, at 25 °C. Chemical shifts are expressed in ppm values from TMS as internal standard. Electron impact mass spectra (EI-MS) were taken on a VG 7070E mass spectrometer operating at 70 eV. IR spectra were recorded in KBr pellets on a Jasco 615 FT-IR spectrometer and the wavenumbers are given in cm^{-1}. High performance liquid chromatography (HPLC) analyses were conducted with an Agilent 1200 instrument using a Chiralpak IB column (0.46 cm × 25 cm) and a mixture of hexane and 2-propanol, 90:10 (v/v) as eluent for enantiomeric separation of *rac*-**5a**,**c** and 95:5 (v/v) for enantiomeric separation of *rac*-**5b**,**d**, respectively, both at 1 mL/min. flow rate. For all chiral compounds, high resolution enantiomeric separation was performed. Retention times for (*R*)- and (*S*)-**5a–d** are presented in Table 4. Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60F_{254} sheets. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating. Preparative chromatographic separations were performed using column chromatography on Merck Kieselgel 60 (63–200 μm). Melting points were determined by hot plate method and are uncorrected. Optical rotations were measured with a Perkin–Elmer 201 polarimeter, and $[\alpha]_D^{20}$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

Table 4
Retention times of the enantiomers of (*rac*)-**5a–d**

Entry	*Rac.* ethanediols	t_R for (*S*)-isomer	t_R for (*R*)-isomer
1	*rac*-**5a**	11.5	15.0
2	*rac*-**5b**	29.5	31.6
3	*rac*-**5c**	16.7	13.9
4	*rac*-**5d**	24.4	22.3

4.2. Reagents and solvents

Pyridinium tribromide, sodium acetate, phase transfer catalyst 18C6, all inorganic reagents and solvents were products of Aldrich or Fluka. All solvents were purified and dried by standard methods

as required. Novozyme 435 (lipase B from *Candida antarctica*) was purchased from Novozymes, Denemark. Baker's yeast produced as wet cakes by Budafok Ltd, Hungary, was from a local store.

4.3. Chemoenzymatic synthesis of the prochiral ketones

4.3.1. Synthesis of heteroaryl-2-bromoethanones

4.3.1.1. Synthesis of 1-(benzo[*d*]thiazol-2-yl)-2-bromoethanone 2a. A mixture of anhydrous cuprous bromide (6 g, 45 mmol) and ketone **1a** (5.3 g, 30 mmol) in ethyl acetate (50 mL) was refluxed for 24 h. After cooling, the precipitate was filtered and washed with ethyl acetate (3 × 5 mL). The solvent was removed by distillation from the combined solutions and the crude product was suspended in CH_2Cl_2 (50 mL). The mixture was stirred for 30 min and filtered. The solid was washed with CH_2Cl_2 (3 × 5 mL) and CH_2Cl_2 was distilled in vacuo from the combined solutions. The crude product was purified by preparative vacuum-chromatography using CH_2Cl_2 as eluent. Yield = 78%; mp 193 °C from ethanol; ^{1}H NMR ($CDCl_3$): δ = 4.86 (s, 2H), 7.58–7.63 (m, 2H), 8.00 (d, 1H), 8.23 (d, 1H); ^{13}C NMR ($CDCl_3$): δ = 31.0, 122.5, 125.7, 127.3, 128.2, 137.6, 153.2, 163.0, 186.2; IR: $\tilde{\nu}$ = 3436, 2937, 2360, 1704, 1592, 1550, 1479, 1388, 1322, 1292, 1272, 1182, 1130, 1066, 939, 767, 734, 701, 644, 582, 433.

4.3.1.2. Synthesis of 1-(heteroaryl)-2-bromoethanones 2b–d. Pyridinium tribromide (3.8 g, 12 mmol) in small portions was added into the solution of heteroaryl-ketones **1b–d** (10 mmol) in acetic acid (20 mL). The mixture was stirred at 50 °C for 0.5 h and then at the room temperature for 1 h. The deposited solid was filtered and the filtrate was evaporated in vacuo. The combined crude solids were dissolved in CH_2Cl_2 (20 mL), washed with saturated sodium bicarbonate solution (3 × 5 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by preparative vacuum-chromatography using CH_2Cl_2 as eluent.

4.3.1.2.1. 1-(Benzo[b]thiophen-2-yl)-2-bromoethanone **2b**. Yield = 63%; mp 115 °C from toluene (115 °C from benzene, petroleum ether[14]) ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 4.47 (s, 2H); 7.42–7.54 (m, 2H); 7.87–7.94 (m, 2H); 8.06 (s, 1H); ^{13}C NMR (75 MHz): δ = 30.4; 123.0; 125.3; 126.3; 128.1; 130.9; 138.8; 140.1; 142.9; 185.9; IR: (KBr) (cm^{-1}): $\tilde{\nu}$ = 3446, 3326, 3066, 2994, 2950, 2362, 1673, 1590, 1513, 1425, 1380, 1292, 1249, 1209, 1166, 931, 862, 842, 752, 725, 646, 576, 457.

4.3.1.2.2. 1-(Benzo[b]thiophen-3-yl)-2-bromoethanone **2c**. Yield = 61%; mp 139 °C from ethanol; ^{1}H NMR ($CDCl_3$): δ = 4.47 (s, 2H), 7.44–7.57 (m, 2H), 7.88 (d, 1H), 8.42 (s, 1H), 8.77 (d, 1H); ^{13}C NMR ($CDCl_3$): δ = 31.8, 122.3, 125.6, 125.8, 126.2, 131.8, 136.5, 138.6, 139.6, 185.9; IR: $\tilde{\nu}$ = 3448, 3077, 2996, 2368, 1793, 1671, 1488, 1455, 1421, 1388, 1363, 1261, 1199, 1141, 1114, 1056, 871, 821, 755, 732, 655, 543, 470.

4.3.1.2.3. 1-(Benzofuran-3-yl)-2-bromoethanone **2d**. Yield = 60%; mp 135 °C from ethanol (135–136 °C from CCl_4[15]); ^{1}H NMR ($CDCl_3$): δ = 4.34 (s, 2H), 7.40–7.43 (m, 2H), 7.55–7.59 (m, 1H), 8.21–8.25 (m, 1H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 31.5, 111.6, 119.4, 122.8, 123.9, 124.9, 126.1, 151.9, 155.5, 186.6; IR: $\tilde{\nu}$ = 3114, 3062, 2996, 2942, 2360, 1673, 1544, 1477, 1448, 1297, 1265, 1197, 1126, 1087, 946, 856, 746, 678, 622, 420.

4.3.2. Synthesis of 2-(heteroaryl)-2-oxo-ethyl-acetates 3a–d

A mixture of anhydrous sodium acetate (2.46 g, 30 mmol), inter-phase catalyst crown ether 18C6 (50 mg, 0.3 mmol) and one of the heteroaryl-bromoethanones **2a–d** (10 mmol) in dioxane (20 mL) was refluxed until the reaction was completed (controlled by TLC, approx. 4 h). After cooling, the precipitate was filtered and washed with dioxane (3 × 5 mL). The dioxane was removed by distillation from the combined solutions and the crude product was purified by preparative vacuum-chromatography using CH_2Cl_2 as eluent.

4.3.2.1. 2-(Benzo[*d*]thiazol-2-yl)-2-oxoethyl acetate 3a. Yield = 94%; mp 102 °C from ethanol HRMS: M^+ found (M^+ calculated for $C_{11}H_9NO_3S$): 235.03052 (235.03031); MS: *m/z* (%) = 236 (M+1, 1), 235 (M^+, 6), 193 (22), 163 (3), 162 (15), 136 (4), 135 (22), 134 (14), 108 (6), 107 (3), 90 (9), 82 (4), 81 (2), 76 (2), 75 (3), 74 (2), 73 (4), 69 (7), 64 (4), 63 (10), 51 (2), 50 (5), 45 (6), 43 (100), 42 (7), 39 (6), 38 (2); ^{1}H NMR ($CDCl_3$): δ = 2.26 (s, 3H), 5.62 (s, 2H), 7.52–7.62 (m, 2H), 7.99 (d, 1H), 8.16 (d, 1H); ^{13}C NMR ($CDCl_3$): δ = 20.5, 66.1, 122.4, 125.5, 127.2, 128.1, 136.8, 153.3, 162.9, 170.3, 187.4; IR: $\tilde{\nu}$ = 3469, 2360, 2343, 1743, 1712, 1477, 1382, 1317, 1268, 1216, 1083, 1062, 916, 790, 765, 732, 457, 424.

4.3.2.2. 2-(Benzo[*b*]thiophen-2-yl)-2-oxoethyl acetate 3b. Yield = 95%; mp 83 °C from ethanol HRMS: M^+ found (M^+ calculated for $C_{12}H_{10}O_3S$): 234.03533 (234.03506); MS: *m/z* (%) = 236 (M+2, 1), 235 (M+1, 2), 234 (M^+, 13), 161 (90), 147 (4), 133 (18), 93 (3), 90 (5), 89 (48), 82 (3), 74 (4), 69 (8), 63 (15), 51 (3), 50 (4), 45 (6), 43 (100), 39 (11); ^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 3H), 5.34 (s, 2H), 7.40–7.52 (m, 2H), 7.87–7.92 (m, 2H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 20.5, 65.7, 122.9, 125.2, 126.1, 127.8, 129.2, 138.8, 139.7, 142.3, 170.3, 186.9; IR: $\tilde{\nu}$ = 3446, 3050, 2989, 2931, 2360, 2343, 1922, 1760, 1739, 1685, 1513, 1457, 1417, 1375, 1332, 1278, 1261, 1241, 1220, 1176, 1081, 1066, 1045, 912, 871, 840, 781, 748, 725, 649, 578, 468, 460, 418.

4.3.2.3. 2-(Benzo[*b*]thiophen-3-yl)-2-oxoethyl acetate 3c. Yield = 96%; mp 63 °C from ethanol HRMS: M^+ found (M^+ calculated for $C_{12}H_{10}O_3S$): 234.03527 (234.03506); MS: *m/z* (%) = 236 (M+2, 1), 235 (M+1, 2), 234 (M^+, 18), 161 (100), 147 (4), 133 (23), 93 (4), 90 (5), 89 (55), 74 (3), 69 (7), 63 (14), 51 (3), 50 (4), 45 (6), 43 (73), 39 (8); ^{1}H NMR ($CDCl_3$): δ = 2.26 (s, 3H), 5.31 (s, 2H), 7.41–7.53 (m, 2H), 7.88 (d, 1H), 8.29 (s, 1H), 8.72 (d, 1H); ^{13}C NMR ($CDCl_3$): δ = 20.6, 66.0, 122.2, 125.4, 125.8, 126.0, 131.9, 136.4, 136.5, 139.4, 170.5, 187.3; IR: $\tilde{\nu}$ = 3446, 3093, 2940, 2364, 1735, 1687, 1492, 1459, 1430, 1380, 1288, 1243, 1201, 1145, 1074, 1056, 908, 871, 852, 792, 763, 736, 455.

4.3.2.4. 2-(Benzofuran-3-yl)-2-oxoethyl acetate 3d. Yield = 96%; mp 56–57 °C from ethanol HRMS: M^+ found (M^+ calculated for $C_{12}H_{10}O_4$): 218.05821 (218.05791); MS: *m/z* (%) = 219 (M+1, 2), 218 (M^+, 14), 176 (4), 145 (100), 131 (3), 117 (4), 103 (2), 90 (4), 89 (37), 88 (3), 77 (6), 74 (2), 63 (25), 62 (10), 51 (5), 50 (4), 43 (73), 42 (5), 39 (13); ^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 3H), 5.16 (s, 2H), 7.37–7.41 (m, 2H), 7.53–7.56 (m, 1H), 8.18–8.21 (m, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 20.5, 66.4, 111.5, 119.2, 122.7, 123.8, 124.8, 126.0, 150.6, 155.3, 170.3, 188.2; IR: $\tilde{\nu}$ = 3463, 3133, 3081, 2983, 2935, 2362, 1959, 1741, 1689, 1556, 1481, 1452, 1425, 1386, 1373, 1278, 1241, 1128, 1070, 1043, 925, 856, 836, 798, 757, 617, 453, 420.

4.3.3. Synthesis of 1-(heteroaryl)-2-hydroxyethanones 4a–d

A mixture of Novozyme 435 (100 mg) and one of the heteroaryl-oxoethyl-acetates **3a–d** (100 mg) in ethanol (10 mL) was shaken at 1000 rpm and room temperature until the ethanolysis of the substrates was completed (checked by TLC, approx. 24 h). Then the enzyme was filtered and washed with ethanol (2 × 5 mL). The solvent was removed by distillation from the combined solutions and the crude product was purified by preparative vacuum-chromatography using CH_2Cl_2 as eluent.

4.3.3.1. 1-(Benzo[*d*]thiazol-2-yl)-2-hydroxyethanone 4a. Yield = 96%; mp 148 °C from ethanol; HRMS: M^+ found (M^+ calculated for $C_{19}H_7NO_2S$): 193.01997 (193.01975); MS: *m/z* (%) = 193

(M^+, 3), 164 (9), 163 (41), 162 (29), 136 (22), 135 (100), 134 (57), 109 (9), 108 (37), 107 (12), 91 (10), 90 (30), 82 (17), 81 (8), 76 (9), 75 (11), 74 (9), 69 (41), 64 (20), 63 (41), 51 (14), 50 (27), 45 (22), 39 (32), 38 (16), 31 (94); ^{1}H NMR ($CDCl_3$): δ = 3.08 (s, 1H), 5.18 (s, 2H), 7.55–7.65 (m, 2H), 8.02 (d, 1H), 8.20 (d, 1H); ^{13}C NMR ($CDCl_3$): δ = 66.5, 122.4, 125.5, 127.3, 128.1, 136.8, 153.3, 162.4, 193.7; IR: $\tilde{\nu}$ = 3478, 3396, 1697, 1484, 1415, 1319, 1240, 1220, 1106, 1068, 916, 765, 734, 431.

4.3.3.2. 1-(Benzo[*b*]thiophen-2-yl)-2-hydroxyethanone 4b. Yield = 97%; mp 151 °C from ethanol; HRMS: M^+ found (M^+ calculated for $C_{10}H_8O_2S$): 192.02464 (192.0245); MS: *m/z* (%) = 192 (M^+,2), 190 (15), 161 (85), 133 (35), 106 (4), 93 (10), 90 (9), 89 (100), 82 (7), 69 (18), 63 (44), 51 (7), 50 (14), 45 (9), 39 (29), 38 (12), 32 (5); ^{1}H NMR (DMSO-d_6): δ = 3.41 (s, 1H), 4.82 (s, 2H), 7.44–7.55 (m, 2H), 8.01–8.07 (m, 2H), 8.35 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 65.9, 123.5, 125.7, 126.7, 128.1, 130.6, 139.5, 140.7, 141.5, 194.7. IR: $\tilde{\nu}$ = 3399, 3056, 2917, 2898, 2522, 2360, 2343, 1656, 1590, 1556, 1515, 1427, 1407, 1259, 1236, 1187, 1170, 1103, 1020, 910, 869, 840, 771, 746, 740, 725, 707, 607, 582, 460, 420.

4.3.3.3. 1-(Benzo[*b*]thiophen-3-yl)-2-hydroxyethanone 4c. Yield = 95%; mp 84–85 °C from ethanol; HRMS: M^+ found (M^+ calculated for $C_{10}H_8O_2S$): 192.02471 (192.0245); MS: *m/z* (%) = 194 (M+2, 1), 193 (M+1, 3), 192 (M^+, 20), 161 (100), 133 (34), 106 (2), 93 (7), 90 (8), 89 (77), 82 (5), 69 (12), 63 (25), 51 (5), 50 (8), 45 (9), 39 (12), 31 (38); ^{1}H NMR ($CDCl_3$): δ = 3.87 (s, 1H), 4.78 (s, 2H), 7.33–7.45 (m, 2H), 7.77 (d, 1H), 8.10 (s, 1H), 8.64 (d, 1H); ^{13}C NMR ($CDCl_3$): δ = 65.6, 122.3, 125.1, 125.7, 126.0, 131.3, 136.2, 137.0, 139.5, 193.3; IR: $\tilde{\nu}$ = 3482, 3407, 3070, 2360, 1668, 1492, 1457, 1423, 1309, 1228, 1211, 1168, 1091, 1056, 908, 867, 763, 752, 728, 709, 470.

4.3.3.4. 1-(Benzofuran-3-yl)-2-hydroxyethanone 4d. Yield = 97%; mp 98–99 °C from ethanol; HRMS: M^+ found (M^+ calculated for $C_{10}H_8O_3$): 176.04756 (176.04734); MS: *m/z* (%) = 176 (M^+,2), 174 (12), 146 (10), 145 (100), 117 (8), 90 (9), 89 (96), 88 (9), 74 (6), 63 (75), 62 (36), 61 (13), 51 (7), 50 (14), 44 (3), 39 (46), 38 (12), 32 (5); ^{1}H NMR ($CDCl_3$): δ = 3.20 (s, 1H), 4.77 (s, 2H), 7.39–7.45 (m, 2H), 7.55–7.59 (m, 1H), 8.15–8.19 (m, 1H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 66.1, 111.7, 118.7, 122.4, 123.5, 124.9, 126.0, 150.7, 155.4, 193.8; IR: $\tilde{\nu}$ = 3399 3338, 3120, 3068, 2913, 2360, 2341, 1668, 1548, 1477, 1448, 1411, 1317, 1290, 1143, 1132, 1105, 1083, 935, 858, 740, 647, 624, 424.

4.3.4. Synthesis of *rac*-1-(heteroaryl)-ethane-1,2-diols *rac*-5a–d

To a stirred solution of ketone **4a–d** (100 mg) in methanol (4 mL), $NaBH_4$ (38 mg, 1 mmol) was added in small portions at room temperature, until the entire amount of the ketone was transformed. The progress of the reaction was followed by thin layer chromatography, using CH_2Cl_2 as eluent. Then the reaction mixture was treated with 1 M HCl (400 μL) and the methanol was removed in vacuo. The crude product was treated with a mixture of CH_2Cl_2–water = 1:1 (v/v), the organic layer was separated, dried over anhydrous $MgSO_4$ and the CH_2Cl_2 was removed in vacuo. The crude product was purified by column chromatography, using CH_2Cl_2–acetone = 9:1 (v/v) as eluent. The pure racemic alcohols *rac*-**5a–d** were used as reference for the chiral HPLC separation.

4.3.4.1. *rac*-1-(Benzo[*d*]thiazol-2-yl)-ethane-1,2-diol *rac*-5a. Yield = 93%; mp 142 °C from $CHCl_3$; HRMS: M^+ found (M^+ calculated for $C_9H_9NO_2S$): 195.03563 (195.0354); MS: *m/z* (%) = 196 (M+1, 2), 195 (M^+, 6), 178 (3), 167 (4), 166 (14), 165 (94), 164 (100), 163 (6), 136 (74), 135 (16), 134 (6), 109 (70), 108 (33), 107 (4), 91 (9), 90 (6), 82 (21), 77 (13), 75 (9), 69 (51), 65 (47), 64 (10), 63 (29), 58 (12), 51 (16), 50 (17), 45 (25), 43 (13), 39 (27), 38 (12), 31 (75); ^{1}H NMR (CD_3OD): δ = 3.84–4.04 (m, 2H), 4.06–5.09 (m, 1H), 7.38–7.53 (m, 2H), 7.92–7.99 (m, 2H); ^{13}C NMR (CD_3OD): δ = 65.8, 72.7, 121.6, 121.9, 124.7, 125.8, 134.5, 152.9, 176.2; IR: $\tilde{\nu}$ = 3262, 2929, 2360, 1508, 1436, 1324, 1317, 1182, 1112, 1074, 1054, 968, 759, 730, 615, 443.

4.3.4.2. *rac*-1-(Benzo[*b*]thiophen-2-yl)ethane-1,2-diol *rac*-5b. Yield = 93%; mp 113 °C from $CHCl_3$; HRMS: M^+ found (M^+ calculated for $C_{10}H_{10}O_2S$): 194.04028 (194.04015); MS: *m/z* (%) = 196 (M+2, 2), 195 (M+1, 4), 194 (M^+, 32), 176 (6), 165 (6), 164 (12), 163 (100), 147 (29), 136 (11), 135 (75), 134 (28), 115 (7), 102 (8), 92 (9), 91 (91), 90 (11), 89 (29), 77 (10), 69 (20), 63 (20), 51 (16), 50 (10), 45 (18), 39 (18), 32 (5), 31 (51); ^{1}H NMR (CD_3OD): δ = 3.80 (d, 2H), 4.99 (t, 1H), 7.25–7.35 (m, 3H), 7.71–7.74 (m, 1H), 7.80–7.82 (m, 1H); ^{13}C NMR (CD_3OD): δ = 66.9; 70.9, 120.2, 121.8, 123.0, 123.6, 123.8, 139.3, 139.7, 146.6; IR: $\tilde{\nu}$ = 3253, 3052, 2927, 2873, 2406, 1683, 1455, 1443, 1361, 1348, 1249, 1159, 1089, 1052, 935, 871, 838, 742, 725, 674, 590, 576, 441.

4.3.4.3. *rac*-1-(Benzo[*b*]thiophen-3-yl)ethane-1,2-diol *rac*-5c. Yield = 93%; mp 103 °C from $CHCl_3$; HRMS: M^+ found (M^+ calculated for $C_{10}H_{10}O_2S$): 194.04034 (194.04015); MS: *m/z* (%) = 194 (M^+, 27), 163 (82), 147 (26), 135 (78), 115 (12), 91 (100), 77 (15), 69 (27), 63 (29), 51 (8), 50 (15), 45 (34), 43 (11), 39 (28), 32 (63), 31 (98); ^{1}H NMR (CD_3OD): δ = 3.75–3.90 (m, 2H), 5.12–5.16 (m, 1H), 7.31–7.41 (m, 2H), 7.53 (s, 1H), 7.85–7.94 (m, 2H); ^{13}C NMR (CD_3OD): δ = 65.9, 70.1, 121.8, 122.3, 122.6, 123.6, 124.0, 136.8, 137.6, 140.7; IR: $\tilde{\nu}$ = 3291, 2923, 2454, 2375, 1457, 1427, 1371, 1251, 1141, 1114, 1076, 1062, 1031, 890, 792, 754, 728, 663, 428.

4.3.4.4. *rac*-1-(Benzofuran-3-yl)ethane-1,2-diol *rac*-5d. Yield = 93%; mp 69 °C from $CHCl_3$; HRMS: M^+ found (M^+ calculated for $C_{10}H_{10}O_3$): 178.06316 (178.06299); MS: *m/z* (%) = 179 (M+1, 2), 178 (M^+, 15), 160 (2), 147 (52), 131 (10), 119 (5), 103 (6), 92 (9), 91 (100), 90 (8), 89 (20), 77 (12), 65 (26), 63 (22), 62 (10), 51 (16), 50 (10), 43 (4), 39 (24), 31 (49); ^{1}H NMR (CD_3OD): δ = 3.83–3.86 (m, 2H), 4.95–4.99 (m 1H), 7.23–7.30 (m, 2H), 7.45–7.48 (m, 1H), 7.71–7.74 (m, 2H); ^{13}C NMR (CD_3OD): δ = 65.6, 67.4, 110.8, 120.2, 121.3, 122.1, 124.0, 126.3, 142.0, 155.6; IR: $\tilde{\nu}$ = 3351, 3228, 2935, 1452, 1373, 1191, 1105, 1027, 896, 750, 734, 630, 420.

4.4. Asymmetric reduction of 2-(heteroaryl)-2-oxo-ethyl-acetates 3a–d and 1-(heteroaryl)-2-hydroxy-ethanones 4a–d by baker's yeast

4.4.1. Analytical scale reduction of the prochiral ketones 3,4a–d

4.4.1.1. Analytical scale non-fermenting reduction of 2-(hetero-aryl)-2-oxo-ethyl-acetates 3a–d and 1-(hetero-aryl)-2-hydroxy-ethanones 4a–d by baker's yeast. Baker's yeast (1.5 g) was suspended in water (3 mL). After stirring for 15 min, 2-(hetero-aryl)-2-oxo-ethyl-acetates **3a–d** and 1-(heteroaryl)-2-hydroxy-ethanones **4a–d** (10 mg) dissolved in methanol (0.2 mL) was added into the resulting cell suspension. Samples (100 μL) were taken periodically every 6 h over 48 h and extracted with ethyl acetate (300 μL). The organic layer was dried over anhydrous $MgSO_4$ and was used for HPLC analysis without further purification.

4.4.1.2. Analytical scale reduction of heteroaryl-oxo-ethyl-acetates 3a–d and heteroaryl-hydroxyethanones 4a–d with fermenting baker's yeast. A fresh wet cake of baker's yeast (1.5 g) and sucrose (0.5 g) was added to water (3 mL) and the resulting suspension was stirred for 30 min. 2-(Heteroaryl)-2-oxo-ethyl-acetates **3a–d** or 1-(heteroaryl)-2-hydroxyethanones **4a–d** (10 mg) dissolved in methanol (0.2 mL) were added into

the suspension. Further experiments were performed as described in the previous section.

4.4.1.3. Analytical scale baker's yeast-mediated reduction of heteroaryl-oxo-ethyl-acetates 3a–d and heteroaryl-hydroxyethanones 4a–d with fermenting baker's yeast in the presence of additives. Experiments were conducted as previously described. Hexane (3 mL) or one of the other additives (15 μg) was introduced into the suspension together with the sucrose.

4.4.2. Preparative scale baker's yeast-mediated synthesis of (*R*)- and (*S*)-heteroaryl-ethanediols

To a suspension of baker's yeast (15 g) in water (30 mL) sucrose (0.5 g) was added, and the mixture was stirred for 30 min. For the biotransformation of **3c** and **4b** as additives, 150 μg of L-cystein and allyl alcohol, respectively, was introduced into the reaction mixture. After that, the solution of 2-(heteroaryl)-2-oxo-ethyl-acetates **3a–d** and 1-(heteroaryl)-2-hydroxyethanones **4b–d** (each 100 mg) in methanol (2 mL) was added into the fermenting cell suspension. The resulting mixture was stirred at room temperature until the transformation of the substrates was completed (checked with TLC) and then extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with saturated NaCl solution (50 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by vacuum-chromatography (CH_2Cl_2–acetone, 10:1, v:v) to give the corresponding (*R*)- and (*S*)-1-(heteroaryl)-ethane-1,2-diols.

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