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Chemoenzymatic synthesis of (*R*)- and (*S*)-1-heteroarylethanols

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ABSTRACT

A chemoenzymatic methodology for the synthesis of highly enantiomerically enriched (*S*)- and (*R*)-1-heteroarylethanols by enantioselective bioreduction with baker's yeast of the corresponding 1-heteroarylethanones followed by three racemization free chemical steps including a Mitsunobu reaction was developed.

1. Introduction

There is a considerable interest in efficient routes for obtaining enantiopure chiral 1-heteroarylalcohols, since they are useful building blocks in the synthesis of more complex structures. Since the need for the production of optically active compounds as single enantiomers is growing rapidly, we have previously studied the lipase-catalyzed enantiomerselective kinetic resolutions of the racemic 1-heteroarylethanols **2a**–**d**.[1,2]

The main drawback of the enantiomer selective reactions is that maximum conversion for the desired enantiomer can only be 50%, which in turn can be overcome by performing an enantioselective transformation, with 100% theoretical conversion.

Enantioselective chemical methods for the synthesis of 1-heteroarylethanols **2b**–**d** have already been described. The enantioselective reduction of the corresponding ketone with (*S*)-2-methyl-CBS-oxazaborolidine yielded the optically active 1-(benzo[*b*]thiophen-2-yl)ethanol ((*R*)-**2b**).[3] The optically active 1-(benzo[*b*]thiophen-3-yl)ethanol ((*R*)-**2d**) was obtained by the addition of $(CH_3)_2Zn$ to the corresponding aldehyde **1d** catalyzed by a commercially available ClCr(Salen).[4] The (*S*)-enantiomer of 1-(benzo[*b*]-furan-3-yl)ethanol (*S*)-**2c** was obtained either by reducing (*S*)-benzo[*b*]furan-3-yl)oxirane with $LiAlH_4$ or by stereoselective reduction of 3-acetylbenzofuran with (−)-DIP-Cl.[5] However, no enzymatic methods for enantioselective preparation of optically active 1-heteroarylethanols **2a**–**d** have been found.

Biotransformations using *Saccharomyces cerevisiae* are very simple because of the availability of biomass and the use of water with or without carbon sources as reaction medium that makes the work-up procedure easy and reduces costs. There are numerous examples of using baker's yeast for asymmetric reductions. Some of the representative reactions are presented in Nakamura's review.[6] According to Prelog's rule, the (*S*)-alcohol is obtained from baker's yeast reduction of a prochiral ketone. In the absence of an appropriate DKR system, for converting the (*S*)-alcohol into the corresponding (*R*)-alcohol with high conversion, the Mitsunobu reaction seems to be an optimal choice for achieving this inversion.

The Mitsunobu reaction is perhaps the most favored method for the inversion of secondary alcohols. This transformation was found to be very efficient for inverting the configuration of chiral secondary alcohols since a clean S_N2 process is generally observed ('Mitsunobu inversion').[7] Chemoenzymatic methods using lipases have already been described for the preparation of different secondary alcohols[8] or their esters.[9] The Mitsunobu reaction allows the synthesis of different derivatives by the stereoselective incorporation of azides, esters, nitriles, phthalimides and sulfonamides with inversion of configuration. Various protocols including a Mitsunobu reaction have been developed for obtaining arylbenzoates,[10] aryl ethers,[11] dialkyl carbonates,[12] thiocarbamates[13] and trithiocarbonates.[14] Some of these procedures have been modified for use on solid-phase supports.[15]

Herein, we report the baker's yeast-catalyzed preparation of the highly enantiomerically enriched (*S*)-1-heteroarylethanols (*S*)-**2a**–**d**, followed by their racemization free chemical transformation into the corresponding (*R*)-heteroarylethanols (*R*)-**2a**–**d** including a Mitsunobu reaction.

2. Results and discussion

The synthesis of the racemic heteroaryl ethanols was first performed. Racemic 1-(benzo[*d*]thiazol-2-yl)ethanol *rac*-**2a** and 1-(benzo[*b*]thiophen-2-yl)ethanol *rac*-**2b** were prepared starting from the corresponding unsubstituted heteroaryl compounds, which were selectively lithiated at the 2-position with *N*-butyl lithium in tetrahydrofuran at −78 °C. The latest compounds were transformed with acetaldehyde into *rac*-**2a**,**b**.[2] For the preparation of *rac*-**2c**,**d** the corresponding aldehydes served as starting materials, which were transformed with methyl magnesium iodide into

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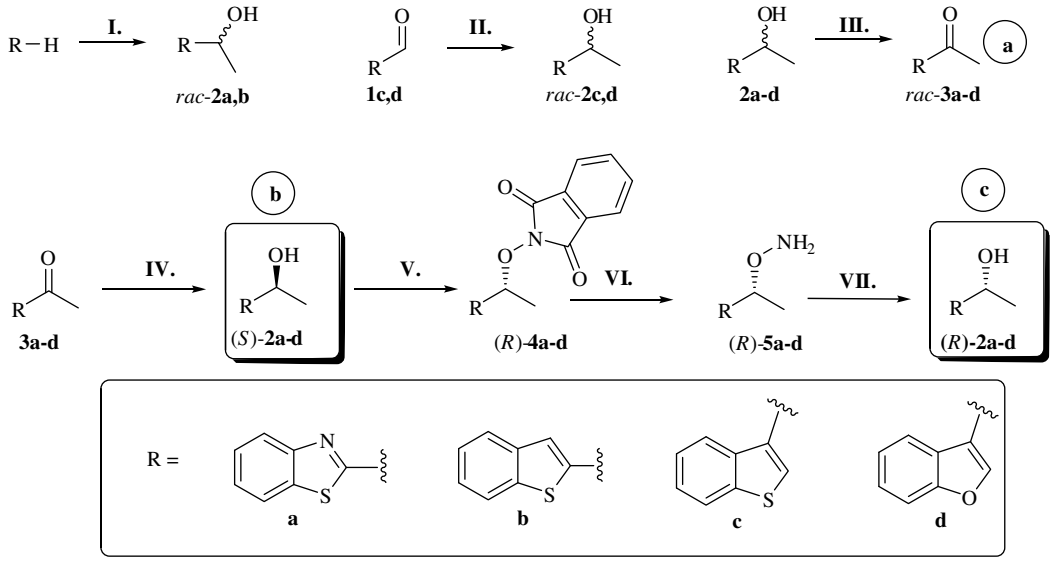

Scheme 1. (a) Synthesis of the racemic 1-heteroarylethanols and prochiral ethanones; (b) baker's yeast-mediated bioreduction and (c) chemical reactions for the total inversion of (*S*)-1-heteroarylethanols. Reagents and conditions: (I) (1) BuLi, −78 °C, 1 h; (2) acetaldehyde, −10 °C, 2 h; (II) CH_3I, Mg/EtOEt; (III). PCC/CH_2Cl_2; (IV) *S. cerevisiae*; (V). DIAD, Ph_3P, *N*-hydroxyphtalimide/THF, −40 °C; (VI) $NH_2NH_2{\cdot}H_2O$, rt; (VII) H_2, Pd/C/MeOH, rt.

the desired products.[2] The prochiral 1-heteroarylethanones **3a–d** were synthesized by the mild oxidation of *rac*-**2a–d** with pyridinium chlorochromate (PCC) in dichloromethane at room temperature (Scheme 1a).

To measure the enantiopurity of both (*R*)- and (*S*)-1-heteroarylethanols obtained by the procedures described below, the chromatographic enantiomeric separation of *rac*-**2a–d** was first established. For all racemates, the base-line separation of the enantiomers was found using a GC Astec B-DM column working in isotherm manner at temperatures described in Section 4.1.

To investigate the baker's yeast-mediated reduction of ketones **3a–d**, the analytical scale reactions were first performed under fermenting and non-fermenting conditions (Scheme 1b). Samples were taken every 12 h over 6 days and analyzed by GC. It was found that the enantiomeric composition of the optically active 1-(heteroaryl)ethanols remained constant during the reaction time. In accordance with the majority of the earlier reported results, the selectivity of the reactions was higher when non-fermenting baker's yeast was used as the biocatalyst (Table 1). Due to the high ee values for the isolated (*S*)-1-heteroarylethanols (ee >98%), further optimization of the bioreduction was not investigated; however, it is known that various additives can significantly influence the selectivity of the bioreduction with baker's yeast.

Table 1
Baker's yeast-mediated reduction of ketones **3a–d** under fermenting and non-fermenting conditions

Entry	Substrate	Product	Enantiomeric excess (%)	
			Fermenting	Non-fermenting
1	**3a**	(*S*)-**2a**	76	98
2	**3b**	(*S*)-**2b**	47	>99.5
3	**3c**	(*S*)-**2c**	>99.5	>99.5
4	**3d**	(*S*)-**2d**	98	>99.5

With these results in our hand, the preparative scale synthesis of (*S*)-**2a–d** was attempted. The dilutions and substrate-biocatalyst ratio were the same as in the case of the analytical scale reactions. 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 ee values were the same as those found for small scale reactions (Table 2).

Table 2
Preparative scale synthesis of (*S*)-**2a–d**

Entry	Product	ee (%)	Yield (%)	$[\alpha]_D^{20}$ (10 mg × mL^{-1})
1	(*S*)-**2a**	98	92	−18.15, CH_3Cl
2	(*S*)-**2b**	>99	92	−21.2, CH_3Cl
3	(*S*)-**2c**	>99	94	−27.1, CH_3Cl
4	(*S*)-**2d**	>99	93	−18.95, CH_3Cl

Furthermore, we tried to transform the previously obtained (*S*)-**2a–d** into the corresponding (*R*)-heteroarylethanols, (*R*)-**2a–d** with the Mitsunobu reaction, using acetic acid as a nucleophile. The racemic 1-acetoxy-1-heteroarylethanes were first synthesized by the chemical acylation of *rac*-**2a–d**. The racemic acetates were used as a chromatographic reference for the detection of the enantiomeric composition for the products of the Mitsunobu reaction. The acetylation of (*S*)-**2a–d** was performed in several organic solvents, varying the nucleophile–substrate ratio between 1 and 2. In each case, the reactions were started at −40 °C, then the reaction mixture was warmed up to room temperature over 8 h. The unsatisfactory yields of the reactions (20–78%) and the low ee values for the acylated products (46–81%) led us to check the conversion of the reaction and the enantiopurity of the acylated products using other nucleophiles, such as propanoic, butyric, chloroacetic and benzoic acid. Unfortunately, no significant enhancement in the yield or ee was observed.

Recently, phthalimide and *N*-hydroxyphthalimide were used successfully in several types of Mitsunobu reactions.[16] Since *N*-hydroxyphthalimide is a bulkier and stronger nucleophile than the above-mentioned carboxylic acids, in our further experiments we used this compound in order to obtain higher yields and selectivity.

First the synthesis of the racemic 2-(1-(heteroaryl)-ethoxy)isoindoline-1,3-diones *rac*-**4a–d** was performed in several organic solvents. Using 1.1 equiv of *N*-hydroxyphthalimide was sufficient for the complete conversion of *rac*-**2a–d** in tetrahydrofuran (checked by TLC). Because the aim of the experiments was the synthesis of (*R*)-heteroarylethanols, (*R*)-**2a–d** from (*S*)-**2a–d**, two extra chemi-

cal steps had to be inserted for the transformation of 2-(1-(heteroaryl)-ethoxy)isoindoline-1,3-diones into 1-(heteroaryl)ethanols. The complete hydrasinolysis of *rac*-**4a–d** yielded the corresponding racemic aminoxy derivatives *rac*-**5a–d**. By the reduction with H_2 gas (1atm) in the presence of Pd on charcoal in methanol at room temperature, the latter compounds were totally converted into *rac*-**2a–d**. Since the global yield for the three-step transformation of *rac*-**2a–d** into itself was around 85%, this method was further used successfully for the conversion, with the total inversion of the configuration, of (*S*)-**2a–d** into (*R*)-**2a–d** with good yields (Table 3).

Table 3
Synthesis of (*R*)-heteroarylethanols by Mitsunobu reaction

Entry	Substrate	Product	ee (%)	Yield (%)	$[\alpha]_D^{20}$ (10 mg × mL^{-1})
5	(*S*)-**2a**	(*R*)-**2a**	98	84	+18.15, CH_3Cl
6	(*S*)-**2b**	(*R*)-**2b**	>99	87	+21.2, CH_3Cl
7	(*S*)-**2c**	(*R*)-**2c**	>99	80	+27.1, CH_3Cl
8	(*S*)-**2d**	(*R*)-**2d**	>99	82	+18.95, CH_3Cl

In addition to the high yields and ee, the absolute configurations of the isolated 1-heteroarylethanols were also confirmed by measuring their optical rotations, which were consistent with the literature values.[2]

3. Conclusions

The present work describes the usability of a chemoenzymatic procedure for the preparation of both, highly enantiomerically enriched, (*R*)- and (*S*)-1-heteroarylethanols. The first enzymatic step was the baker's yeast-mediated reduction of the prochiral ketones which provided the (*S*)-1-heteroarylethanols with more than 90% yield and ee >98%. The latter compounds were converted into the opposite enantiomer by a three-step chemical procedure (approx. 85% yield, ee >98%).

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}. GC analyses were conducted with a Konik HRGC 4000 B gas chromatograph (carrier gas N_2; head pressure: 60 psi, injector: 250 °C; FID detector: 250 °C) on an Astec chiral column (30 m × 0.25 mm, dimethylated-β-cyclodextrin, No. 777023 G0507-30). For all chiral compounds, high resolution enantiomeric separation was performed. Retention times for (*S*) and (*R*)-**2a–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 by 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.

Table 4
Retention times for (*S*) and (*R*)-**2a–d**

Racemic ethanols *rac*-**2a–d**	t_{R_S} (min)	t_{R_R} (min)	*t* (°C) (GC)
2a	44.89	51.82	110
2b	12.92	12.48	140
2c	14.60	15.46	140
2d	24.73	23.30	120

4.2. Reagents and solvents

Commercial chemicals and solvents were purchased from Aldrich or Fluka. All solvents were purified and dried by standard methods. Racemic 1-heteroarylethanols were prepared from the corresponding 2-formylheteroaryl derivatives **1c**,**d** with a Grignard reaction **2c**,**d** or by reaction of the corresponding heteroaryl-2-yl-lithium derivatives with acetaldehyde, in the case of **1a**,**b**. Heteroaryl-ethanones **3a–b** as prochiral substrates were prepared by oxidation of racemic ethanols **2a–d** with pyridinium chlorochromate (PCC).

4.3. Synthesis of 1-heteroarylethanones 3a–d

The mixture of one of the *rac*-1-heteroarylethanols *rac*-**2a–d** (30 mmol) and pyridinium chlorochromate (PCC) (6.5 g) in CH_2Cl_2 (50 mL) was stirred at room temperature for 10 h. The suspension formed was filtered and the precipitate was washed with CH_2Cl_2 (3 × 10 mL). The solvent was removed by distillation in vacuo and the crude solid product was purified by preparative vacuum-chromatography using dichloromethane as eluent, yielding the 1-heteroarylethanones **3a–d** as white solids.

4.3.1. 1-(Benzo[*d*]thiazol-2-yl)ethanone 3a

Yield = 74%; mp 112 °C from ethanol (lit. 108–111 °C from aqueous ethanol[17]); ^1H NMR: (300 MHz, $CDCl_3$): δ 2.85 (s, 3H); 7.53–7.61 (m, 2H); 7.99 (d, 1H, J = 8.5 Hz); 8.21 (d, 1H, J = 8.5 Hz); ^{13}C NMR (75 MHz): δ 26.1; 122.4; 125.4; 127.0; 127.7; 137.4; 153.5; 166.5; 193.1; IR:(KBr) (cm^{-1}): $\tilde{\nu}$ = 3446, 3054, 2364, 1683, 1592, 1548, 1482, 1321, 1268, 1257, 1166, 1079, 1033, 1012, 954, 931, 860, 771, 734, 703, 620, 561, 431; HRMS: M^+ found (M^+ calculated for C_9H_7NOS): 177.02498 (177.02483); MS *m/z* (%): 178(6), 177(M^+, 44), 149(23), 135(53), 108(21), 90(13), 69(24), 63(21), 50(12), 43(100), 39(12).

4.3.2. 1-(Benzo[*b*]thiophen-2-yl)ethanone 3b

Yield = 78%; mp 88 °C from ethanol (87–88 °C from diethyl ether, hexane[18]); ^1H NMR: (300 MHz, $CDCl_3$): δ 2.67 (s, 3H); 7.39–7.50 (m, 2H); 7.85–7.91 (m, 2H); 7.94 (s, 1H); ^{13}C NMR (75 MHz): δ 26.8; 123.0; 125.0; 125.9; 127.4; 129.7; 139.1; 142.6; 143.9; 192.3; IR: (KBr) (cm^{-1}): $\tilde{\nu}$ = 3448, 3056, 2921, 1660, 1508, 1427, 1355, 1330, 1270, 1243, 1224, 1176, 1074, 1020, 950, 927, 846, 757, 728, 609, 566, 551, 464; HRMS: M^+ found (M^+ calculated for $C_{10}H_8OS$): 176.02973 (176.02959); MS *m/z* (%): 178(M+2, 3), 177(M+1, 5), 176(M^+, 45), 163(5), 162(10), 161(100), 147(2), 133(32), 93(8), 90(9), 89(71), 82(7), 74(9), 69(18), 63(35), 62(12), 61(5), 51(10), 50(13), 45(12), 43(57), 39(20), 38(7), 37(4).

4.3.3. 1-(Benzo[*b*]thiophen-3-yl)ethanone 3c

Yield = 74%; mp 65 °C from ethanol (64–65 °C from aqueous ethanol[19]); ^1H NMR: (300 MHz, $CDCl_3$): δ 2.65 (s, 3H); 7.43–7.53 (m, 2H); 7.88 (d, 1H, J = 8.3 Hz); 8.27 (s, 1H); 8.81 (d, 1H, J = 8.3 Hz); ^{13}C NMR (75 MHz): δ 28.2; 122.2; 125.4; 125.7; 125.8; 135.4; 136.4; 137.4; 139.8.; 193.1; IR: (KBr) (cm^{-1}): $\tilde{\nu}$ = 1656, 1490, 1457, 1421, 1371, 1340, 1259, 1205, 1008, 923, 860, 815, 759, 732, 620, 547, 501, 478; HRMS: M^+ found (M^+ calculated for $C_{10}H_8OS$): 176.02973 (176.02959); MS *m/z* (%): 178(M+2, 3), 177(M+1, 6), 176(M^+, 52), 163(5), 162(12), 161(100), 147(2), 133(30), 93(5), 89(53), 82(4), 74(8), 69(10), 63(18), 62(8), 61(4), 51(5), 50(6), 45(8), 43(23), 39(9), 38(4), 37(2).

4.3.4. 1-(Benzofuran-3-yl)ethanone 3d

Yield = 76%; mp 39 °C from ethanol (38 °C from CCl_4[20]); ^{1}H NMR: (300 MHz, $CDCl_3$): δ 2.56 (s, 3H); 7.35–7.41 (m, 2H); 7.51–7.55 (m, 1H); 8.22–8.27 (m, 2H); ^{13}C NMR (75 MHz): δ 28.1; 111.4; 122.6; 122.8; 124.1; 124.5; 125.6; 151.3; 155.6; 193.0; IR: (KBr) (cm^{-1}): $\tilde{\nu} = 1671$, 1554, 1479, 1450, 1382, 1292, 1130, 1101, 943, 858, 844, 771, 748, 671, 605, 422; HRMS: M^+ found (M^+ calculated for $C_{10}H_8O_2$): 160.05284 (160.05243); MS *m/z* (%): 161(M+1, 6), 160(M^+, 45), 146(11), 145(100), 117(7), 102(2), 90(5), 89(41), 88(5), 77(5), 63(25), 62(14), 61(4), 51(6), 50(7), 43(21), 39(11), 38(5), 37(2).

4.4. Asymmetric reduction of 1-heteroarylethanones 3a–d by baker's yeast

4.4.1. Analytical scale reduction of 3a–d

4.4.1.1. Analytical scale non-fermenting reduction of 3a–d. Baker's yeast (1.5 g) was suspended in water (3 mL). After stirring for 15 min, 1-heteroarylethanones **3a**–**d** (10 mg) dissolved in methanol (0.2 mL) were added into the resulting cell suspension. Samples (100 μL) were taken periodically for every 12 h over 6 days and extracted with ethyl acetate (300 μL). The organic layer was dried over anhydrous $MgSO_4$ and used for GC analysis without further purification.

4.4.1.2. Analytical scale fermenting reduction of 3a–d. Fresh wet cakes of baker's yeast (1.5 g) and sucrose (0.5 g) were added to water (3 mL), and the resulting suspension was stirred for 30 min. 1-Heteroarylethanones **3a**–**d** (10 mg) dissolved in methanol (0.2 mL) were added into the suspension. Further experiments were performed as described in the previous section.

4.4.2. Preparative scale non-fermenting reduction of 3a–d

To a suspension of baker's yeast (15 g) in water (30 mL), the solutions of 1-heteroarylethanones **3a**–**d** (each 100 mg) in methanol (2 mL) were added after 15 min. The resulting mixture was stirred at room temperature until the transformation of the substrates was complete (checked with TLC), and was 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 using dichloromethane as eluent to give the corresponding optically active 1-(heteroaryl)ethanols (*S*)-**2a**–**d**.

4.5. Synthesis of (*R*)-heteroaryl alcohols (*R*)-2a–d using Mitsunobu reaction

4.5.1. Mitsunobu reaction

To a solution of (*S*)-heteroaryl alcohols ((*S*)-**2a**–**d**) (3 mmol) dissolved in dry THF (5 mL), PPh_3 (1.1 equiv) and *N*-hydroxy-phthalimide (1.1 equiv) were added. The mixture was cooled to 0–5 °C and DIAD (1.1 equiv) was added. The mixture was stirred at room temperature for 24 h. Evaporation of solvent and purification by column chromatography (eluent: dichloromethane) yielded (*R*)-**4a**–**d**, which were used without further purification in the next step.

4.5.2. Hydrolysis of (*R*)-4a–d

A mixture of compounds (*R*)-**4a**–**d** (0.4 g), 100% hydrazine hydrate (1 equiv) and ethanol (10 mL) was heated at reflux for 4 h. Aqueous HCl (1 M, 3 mL) was added and the mixture was subsequently heated at reflux for 0.5 h. After cooling to room temperature, the mixture was filtered to remove the precipitated solid. The filtrate was evaporated under reduced pressure. Aqueous NaOH (1 M, 5 mL) was added to the residue and the mixture was then extracted with ether (3×25 mL). The combined ether solution was dried with magnesium sulfate, filtered and evaporated in vacuum and the crude product was purified on column chromatography. CH_2Cl_2 afforded the desired compounds (*R*)-**5a**–**d**.

4.5.3. Reduction of (*R*)-5a–d

A 100-mL three-necked round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet and hydrogen inlet was charged with 25 mL methanol and 2.5 g (*R*)-**5a**–**d**. A catalytical quantity on Pd/C was added into solution. A stream of H_2 was passed into the suspension formed until all the aminoxy compound was reduced (checked by TLC). When the reaction was over, the suspension was filtered and the solvent was distilled off from the forming solution by rotatory evaporation. The solid crude product was purified by preparative vacuum-chromatography with dichloromethane as eluent, yielding the (*R*)-heteroarylethanols ((*R*)-**2a**–**d**).

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