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Resolution of 2,2-Disubstituted Epoxides via Biocatalytic Azidolysis

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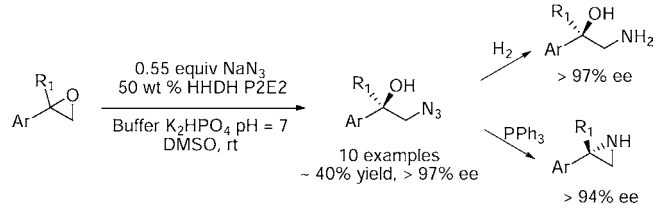
ABSTRACT



A practical procedure for the enzymatic resolution of 2-alkyl-2-aryl-disubstituted epoxides using the Codex HHDH P2E2 enzyme and sodium azide is reported. This method allowed the synthesis of novel regio- and enantioselective 1-azido-2-arylpropan-2-ols in excellent yields. Furthermore, these intermediates were used for the preparation of enantiomerically enriched amino alcohols and aziridines containing a tertiary center.

The growing importance of optically active azido alcohols as intermediates toward the synthesis of aziridines[1] and amino alcohols[2] in organic synthesis and their presence in bioactive molecules has created a need for synthesizing these molecules. Over the past several years, important advances have been made toward these targeted chiral intermediates. Generally, they are synthesized by asymmetric reduction of azido ketones,[3] conversion of chiral diols via cyclic sulfates or sulfites,[4] and asymmetric ring-opening of oxiranes by the azide anion.[5] During the course of our investigations, we became interested in the synthesis of 1-azido-2-arylpropan-2-ols. Although ring-opening of epoxides with azide nucleophiles is among the most frequently used reactions for the formation of azido alcohols, none of the methods describe examples with a 2-alkyl-2-aryl substituent.[6,7] Herein, we

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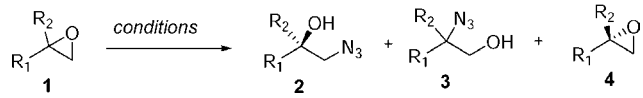
Table 1. Uncatalyzed and Enzyme Catalyzed Azidolysis: Substrate Scope



entry	R_1	R_2	epoxide **1**	conditions[a]	ratio **2**: **3**[b]	yield[c]	% ee **2**[d]	azidoalcohol **2**	% ee **4**[d]	epoxide **4**
1	C_6H_5	Me	**1a**	A	1.6:1	100	0	**2a**		
2	C_6H_5	Me	**1a**	F	>25:1	45	98	**2a**		
3	4-Cl-C_6H_4	Me	**1b**	A	2.4:1	100	0	**2b**		
4	4-Cl-C_6H_4	Me	**1b**	F	>25:1	41	99	**2b**	99	**4b**
5	4-F-C_6H_4	Me	**1c**	A	1.4:1	95	0	**2c**		
6	4-F-C_6H_4	Me	**1c**	F	>25:1	38	>97	**2c**		
7	3,5-diF-C_6H_3	Me	**1d**	A	3:1	95	0	**2d**		
8	3,5-diF-C_6H_3	Me	**1d**	F	>25:1	45	99	**2d**		
9	4-BrC_6H_4	Me	**1e**	A	2.8:1	95	0	**2e**		
10	4-BrC_6H_4	Me	**1e**	B	0	0	0	**2e**		
11	4-BrC_6H_4	Me	**1e**	C	>25:1	40	31	**2e**		
12	4-BrC_6H_4	Me	**1e**	D	>25:1	40	35	**2e**		
13	4-BrC_6H_4	Me	**1e**	E	>25:1	40	45	**2e**		
14	4-BrC_6H_4	Me	**1e**	F	>25:1	43	99	**2e**		
15	4-BrC_6H_4	Et	**1f**	A	12.5:1	96	0	**2f**		
16	4-BrC_6H_4	Et	**1f**	F	>25:1	26	98	**2f**		
17	4-BrC_6H_4	iPr	**1g**	A	>20:1	90	0	**2g**		
18	4-BrC_6H_4	iPr	**1g**	F	n.a.	no rx	n.a.	**2g**		
19	4-BrC_6H_4	CF_3	**1h**	A	>20:1	87	0	**2h**		
20	4-BrC_6H_4	CF_3	**1h**	C	>25:1	22	88	**2h**		
21	4-BrC_6H_4	CF_3	**1h**	F	>25:1	n.d.	34	**2h**		
22	2-naphthyl	Me	**1i**	A	1.4:1	93	0	**2i**		
23	2-naphthyl	Me	**1i**	C	>25:1	19	96	**2i**		
24	2-naphthyl	Me	**1i**	F	>25:1	n.d.	71	**2i**		
25	$PhCH_2CH_2$	Me	**1j**	A	1.6:1	90	0	**2j**		
26	$PhCH_2CH_2$	Me	**1j**	F	>25:1	39	98	**2j**	99	**4j**

[a] Condition A: To a solution of the epoxide in methanol were added ammonium chloride (3 equiv) and sodium azide (3 equiv). The reaction mixture was heated to 60 °C for 1−4 h. General conditions for **B**−**F**: To a solution of the enzyme in aqueous K_2HPO_4 (pH = 7) at rt were added the NaN_3 (0.55 equiv) and a solution of the epoxide in DMSO. Reaction time: 16 h. Condition B: no enzyme. Condition C: enzyme P1H2. Condition D: enzyme P2A12. Condition E: enzyme P2H4. Condition F: enzyme P2E2. [b] Determined by ^{1}H NMR. [c] Isolated yield of **2** + **3**. [d] Determined by HPLC or SFC.

report our findings toward the regio- and enantioselective preparation of synthetically useful 1-azido-2-arylpropan-2-ols through the azidolysis of 2-alkyl-2-aryl-disubstituted epoxides using Codex halohydrin dehalogenase[8] (HHDH) enzymes[9] and show an application toward the preparation of enantiomerically enriched amino alcohols and aziridines containing a tertiary center.

We first investigated the efficiency of different Codex HHDH enzymes[10] for the azidolysis of 2,2-disubstituted epoxides. For this purpose, racemic 2-(4-bromophenyl)-2-methyloxirane (**1e**)[11] was used as a model substrate and treated at rt with sodium azide (0.55 equiv) and the enzyme under a K_2HPO_4-buffered aqueous medium at neutral pH (Table 1 entries 10−14). Our control experiment indicated that in the absence of any enzyme, no product was observed (entry 10). Also, out of a screen of over 96 Codex HHDH enzymes *only four enzymes* (P1H2, P2A12, P2H4, and P2E2) *showed complete regioselectivity* (>25:1) for preparation of isomer **2** with P2E2, in this case giving the highest enantioselectivities (99% ee) (entries 11−14).[12] As a comparison, under standard uncatalyzed azidolysis a 2.8:1 ratio of **2** vs **3** was observed for this substrate (entry 9). We were pleased to note that the complete regio- and enantioselectivity observed was a result of the substrate match with the enzyme active site (entry 14).

Encouraged by these results and to establish the general scope and applicability of this method, we applied the optimized reaction conditions[13,14] to a series of 2-alkyl-2-aryl-substituted epoxides (Table 1).[15] When R_2 = Me,

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(11) All of the 2,2-disubstituted epoxides (except for 2-methyl-2-phenyloxirane) needed for this study were prepared in >85% yield using the Corey−Chaykovsky epoxidation methodology: (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782. (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

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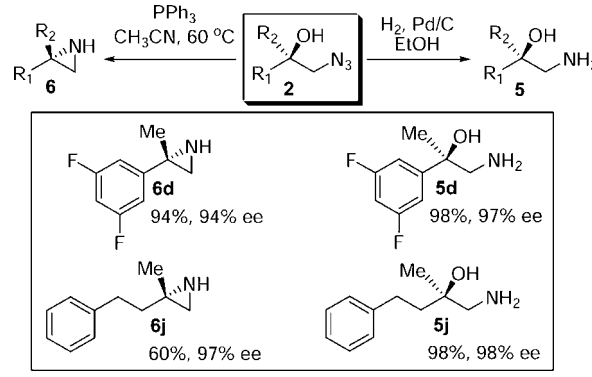
substrates with electron-withdrawing groups on the aryl group were well tolerated as yields of approximately 40% (out of a theoretical maximum of 50%), >25:1 ratios of isomers **2** vs **3**, and >97% enantiomeric excess were observed (entries 2, 4, 6, 8, and 14). The increase in steric bulk at the R_2 position caused a decrease in yields presumably due to a negative interaction with the enzyme catalytic site (entry 14 vs 16, 18, and 20[16]). A lower solubility substrate such as 2-methyl-2-(naphthalen-2-yl)oxirane gave >25:1 regioselectivity and 98% ee albeit in low yield (entry 23). For epoxides **1h** and **1i**, Codex HHDH P1H2 was a better match for the substrate, giving higher enantioselectivities of the corresponding 1-azido-2-arylpropan-2-ols (entries 20 vs 21 and 23 vs 24). Finally, the scope of the reaction was also extended to 2-methyl-2-phenethyloxirane, a 2,2-dialkyl-disubstituted epoxide; excellent yields and selectivities were observed (entry 26).[17]

A direct comparison of the biocatalytic azidolysis of 2,2-disubstituted epoxides was made with a standard uncatalyzed azidolysis for all substrates tested (Table 1).[18] Contrary to literature precedents that suggest preferential opening at the terminal position of monosubstituted epoxides,[18] the uncatalyzed azidolysis of the 2,2-disubstituted epoxides described in this paper produces a mixture of regioisomers **2** and **3** where the ratios varied between 1.4:1 to 3:1 for most substrates (entries 1, 3, 5, 7, 9, and 22) and *only* in strongly sterically or electronically biased systems such as **1f**, **1g**, and **1h** were the ratios of **2** vs **3** >12:1 (entries 15, 17, and 19). These results demonstrate that the HHDH P2E2 enzyme controls *both* the regioselectivity and enantioselectivities of the azide opening.

Because all of the 1-azido-2-arylpropan-2-ols prepared in this paper are new compounds not previously reported in the literature, we determined the stereochemistry of the residual unreacted enantiomerically enriched epoxide for two reactions (entries 4 and 26). The absolute configuration of the residual enantiomerically enriched epoxides **4b** and **4j** was determined to be (*S*) by comparing the sign of optical rotation with the literature data[19a] and was of high optical purity 99% ee as determined by SFC (Table 4).[20] Therefore, the azidolysis occurred selectively on the (*R*) epoxide providing the (*R*)-azido alcohol.

The novel regioselective and enantiomerically enriched 2,2-disubstituted azido alcohols reported in this paper are synthetically valuable chiral building blocks. They can be converted into enantiomerically enriched 2,2-disubstituted unprotected aziridines[21] through a Staudinger reaction in >94% ee and regio- and enantioselective 2,2-disubstituted amino alcohols[22] through simple reduction of the azide as demonstrated by two examples in Scheme 1.

Scheme 1. Novel Enantiomerically Enriched 2,2-Disubstituted Aziridines and 1,2-Disubstituted Amino Alcohols



In conclusion, we have developed a method for the enzymatic resolution of 2-alkyl-2-aryl-disubstituted epoxides

(13) Other azide sources were tested (LiN_3, Me_3SiN_3, Me_3SnN_3, and Bu_4NN_3) which had no influence on the azidolysis: see ref 5a.

(14) The enzyme loading was optimized to 50 wt % or $\sim 2.5 \times 10^{-3}$ mol % of enzyme.

(15) **Representative Procedure: (*R*)-1-Azido-2-phenylpropan-2-ol [(*R*)-2a].** To a solution of the enzyme (HHDH P2E2, 250 mg) in 0.1 M K_2HPO_4 (buffered at pH = 7) (70 mL) at room temperature was added a solution of sodium azide (133 mg, 2.05 mmol) in 0.1 M K_2HPO_4 (25 mL) followed by a solution of the epoxide **1a** (500 mg, 3.73 mmol) in DMSO (5 mL) and the mixture stirred overnight. The reaction mixture was diluted with EtOAc and water, and the layers were separated by centrifugation. The organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture purified by column chromatography on silica gel using hexane/EtOAc (gradient: 0−100% EtOAc) to provide 300 mg (45%) of (*R*)-**2a**. $[\alpha]_D = -27.50$ (*c* 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 7.45−7.38 (m, 2H), 7.37−7.31 (m, 1H), 3.65 (d, $J = 12.1$ Hz, 1H), 3.49 (d, $J = 12.3$ Hz, 1H), 2.33 (s, 1H), 1.64 (s, 3H). The enantiomeric excess was determined by SFC (Chiralcel-OJ, 2 mL/min, 5−40% MeOH at 4%MeOH/min, t_R (major) 6.64min, t_R(minor) 6.37 min (98% ee). SFC (supercritical fluid chromatography) where mobile phases are carbon dioxide and a polar modifier, methanol.

(16) Where $R_2 = CF_3$, a major byproduct for this particular substrate was hydolysis of the epoxide providing the corresponding diol.

(17) In ref 6b, 90% ee was observed for this substrate.

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using the Codex HHDH P2E2 enzyme and sodium azide. Ten examples of novel regio- and enantioselective 1-azido-2-arylpropan-2-ols were reported to give (*R*)-azido alcohols in 19−45% yield and 88−99% ee material. Furthermore, these intermediates were used for the preparation of enantiomerically enriched amino alcohols and aziridines containing a tertiary center.

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Supporting Information Available: Complete experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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