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Synthesis of Chiral 5-Aryl-2-oxazolidinones via Halohydrin Dehalogenase-Catalyzed Enantio- and Regioselective Ring-Opening of Styrene Oxides

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Abstract. An efficient biocatalytic approach for enantio- and regioselective ring-opening of styrene oxides with cyanate was developed by using the halohydrin dehalogenase HheC from *Agrobacterium radiobacter* AD1, generating the corresponding chiral 5-aryl-2-oxazolidinones in up to 47% yield and 90% ee. Additionally, the origin of enantioselectivity and regioselectivity of the HheC-catalyzed cyanate-mediated ring-opening process was uncovered by single enantiomer bioconversions and molecular docking study.

Keywords: Oxazolidinones; Halohydrin dehalogenase; Epoxides; Ring-opening; Cyanate

Oxazolidinones are important five-membered heterocyclic compounds in pharmaceutical chemistry and organic chemistry, which have received significant attention in serving as antibiotics, chiral auxiliaries and synthetic intermediates for a variety of organic transformations.[1] Therefore lots of synthetic methods have been developed for preparing structurally diverse oxazolidinones.[2] Despite significant advancements in this field, the construction of the oxazolidinone scaffolds is still a challenge for organic chemists, due to the involvement of harsh reaction conditions or the use of expensive catalysts in many cases. Recently a growing effort has been devoted to developing environmentally benign methods for oxazolidinone synthesis.[3] Biocatalysis is considered as a green synthetic technology due to its specific selectivity and mild reaction conditions, while very few enzymes are reported for oxazolidinones preparation until now.

Halohydrin dehalogenase (HHDH), a catalytically promiscuous enzyme from short-chain dehydrogenase superfamily, is not only able to catalyze the formation of epoxides via dehalogenation of vicinal halohydrins, but also involves the reverse reaction of ring-opening epoxides in the presence of several anionic nucleophiles.[4] Synthesis of 5-substituted oxazolidinones was achieved for the first time by Janssen and coworkers using a HHDH from *A. radiobacter* AD1 (HheC), which was a milestone for biocatalytic formation of oxazolidinones. This approach starts from the readily available epoxides, in which inorganic cyanate serves as a nucleophile to be catalyzed by HHDH to generate oxazolidinone through [3+2] cycloaddition reaction with epoxides.[5] Although preparation of enantiopure 5-substituted oxazolidinones via HHDH-catalyzed kinetic resolution or dynamic kinetic resolution of epoxides have been achieved, the reactions only focus on alky epoxides, especially for 2,2-disubstituted alkyl epoxide substrates.[5]

Enantiopure 5-aryl-2-oxazolidinones as key building blocks for chiral pharmaceuticals such as tembamide and aegeline,[6] are usually prepared from the corresponding enantiopure β-amino alcohols.[7] Though several efficient methods have been developed to prepare 5-aryl-2-oxazolidinones via highly regioselective ring-opening of ayl airidines using carbon dioxide as a C1 source, the enantioselectivity control in these reactions is still a challenge.[8] One successful methodology to meet this goal was reported by Bartoli and coworkers via a chiral (salen)Co^{II}-catalyzed regio- and enantioselective ring-opening of epoxides with ethyl carbamate (Scheme 1).[9] However, this method requires a subsequent cyclization step after completion of the ring-opening process. In addition, ethyl carbamate used in this reaction is a known genotoxic carcinogen. In this study, we describe a one-step, greener and atom-economic approach for

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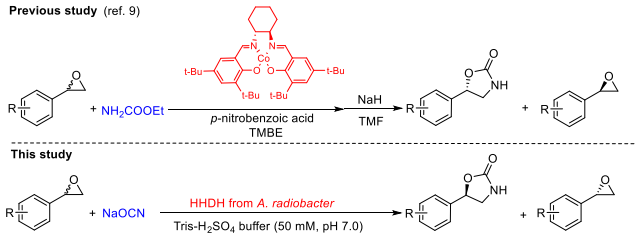
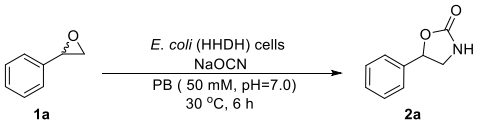
the synthesis of 5-aryl-2-oxazolidinones through the HHDH-catalyzed enantio- and enantioselective ring-opening of aryl epoxides with safer inorganic cyanates (Scheme 1).



Scheme 1. Synthesis of chiral 5-aryl-2-oxazolidinones from aromatic epoxides.

We started our investigation by screening of HHDH biocatalysts for the reaction of model substrate styrene oxide (**1a**) and sodium cyanate. Preliminary screening reactions were performed on analytical scale using cell-free extract of HHDHs. More than twenty recombinant HHDHs from class A to E were examined, while most of them showed no or very low catalytic activity (Table S1). Several HHDHs with relatively good catalytic activity or enantioselectivity were further tested in whole-cell biotransformation. As summarized in Table 1, the HheA10 converted **1a** to 5-phenyloxazolidin-2-one (**2a**) with the enantioselectivity in favor of the (*S*)-enantiomer (Table 1, entry 1), while the HheA11 and HheC exhibited the complementary *R* enantioselectivity (Table 1, entries 2-3). The HheA10 and HheA11 showed low activity in this reaction. Although the HheE and HheE5 exhibited relatively good activity, the enantioselectivity was too low to obtain enantioenriched **2a** (Table 1, entries 4-5). The control reactions revealed the spontaneous and host cell-caused formation of **2a** did not take place in the absence of HHDH (Table 1, entries 6-7). In addition, trace amounts of the by-product diols were formed in the enzymatic and nonenzymatic reactions, which resulted from the spontaneous hydrolysis of epoxides. Considering catalytic enantioselectivity and activity, the best candidate HheC was selected as the biocatalyst for the following investigation on chiral 5-aryl-2-oxazolidinones synthesis.

Table 1. Screening of HHDHs for enantioselective synthesis of **2a** from **1a**.[a)]

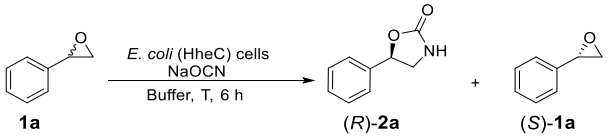


entry	HHDH	activity (U/g cdw)[b)]	yield **2a** (%)[c)]	*ee* **2a** (%)[c)]
1	HheA10	0.4	5	85(*S*)
2	HheA11	0.2	2	84(*R*)
3	HheC	12.0	20	96(*R*)
4	HheE	13.8	31	<5(*S*)
5	HheE5	7.7	20	7(*S*)
6[d)]	-	ND	NR	ND
7[e)]	-	ND	NR	ND

[a)] Reaction conditions: 5 mL PB buffer (KH_2PO_4-Na_2HPO_4, 50 mM, pH 7.0), **1a** (10 mM), NaOCN (15 mM), *E. coli* (HHDH) cells (10 g cdw/L), 30 °C and 6 h. [b)] Determined over the first 1 h. The unit of specific activity was $\mu mol \cdot min^{-1} \cdot g\ cdw^{-1}$. [c)] Determined by chiral HPLC after 6 h. Absolute configurations were judged according to the literature.[9] [d)] Reaction was performed in the absence of *E. coli* cells. [e)] Reaction was performed using host cells *E. coli* BL21 (DE3) in the absence of HHDH enzyme. ND = not detected. NR = no reaction.

Condition optimization of the reaction was then carried out on whole-cell catalysis of recombinant *E. coli* (HheC). We first evaluated the reaction in several buffers, and found the highest yield was obtained in Tris-H_2SO_4 buffer, pH 7.0 (Table 2, entry 4). Subsequent investigation of reaction temperature in a range from 25 to 50 °C revealed that 32% yield was obtained at the optimal temperature of 45 °C (Table 2, entry 8). Additionally, increasing equivalence ratio of cyanate led to increase in yield. The yield was improved to 40% at the ratio of 3:1 (Table 2, entry 12), while further enhancing cyanate concentration did not result in apparent increase in yield (Table 2, entry 13). Examination of cell density indicated that increasing cell density to a concentration of 15 g cdw/L generated the highest yield (45%) without the expense of enantioselectivity (Table 2, entry 15).

Table 2. Screening of reaction conditions for the synthesis of (*R*)-**2a** from **1a**.[a)]



entry	buffer	T (°C)	NaOCN:**1a**	cell density (g cdw/L)	yield **2a** (%)	ee (*R*)-**2a** (%)
1	6.0(PB)	30	1.5:1	10	16	96
2	7.0(PB)	30	1.5:1	10	18	96
3	8.0(PBS)	30	1.5:1	10	12	93
4	7.0(Tris-H_2SO_4)	30	1.5:1	10	21	96

5	8.0(Tris-H_2SO_4)	30	1.5:1	10	11	95
6	8.5(Tris-H_2SO_4)	30	1.5:1	10	7	95
6	7.0(Tris-H_2SO_4)	25	1.5:1	10	19	96
7	7.0(Tris-H_2SO_4)	35	1.5:1	10	25	95
8	7.0(Tris-H_2SO_4)	45	1.5:1	10	32	93
9	7.0(Tris-H_2SO_4)	50	1.5:1	10	18	94
10	7.0(Tris-H_2SO_4)	45	0.5:1	10	18	96
11	7.0(Tris-H_2SO_4)	45	1:1	10	25	95
12	7.0(Tris-H_2SO_4)	45	3:1	10	40	92
13	7.0(Tris-H_2SO_4)	45	4:1	10	41	94
14	7.0(Tris-H_2SO_4)	45	3:1	5	32	93
15	7.0(Tris-H_2SO_4)	45	3:1	15	45	92
16	7.0(Tris-H_2SO_4)	45	3:1	20	44	91

[a] The reactions were carried out in 5 mL buffer solution (50 mM) containing 10 mM **1a**, *E. coli* (HheC) cells and NaOCN. The ee and yields of **2a** at each condition were determined by chiral HPLC after reaction for 6 h.

With the optimized reaction conditions in hand (Table 2, entry 15), substrate concentrations from 5 to 50 mM were investigated. As shown in Figure 1, it could be found that all reactions were almost finished in 12 h. Since the maximum theoretical yield for the kinetic resolution process was 50%, good yields (>35%) of **2a** were obtained at the substrate concentrations of 5-30 mM. In the case of 30 mM **1a**, the reaction generated 10.8 mM **2a** with 36% yield. Further increasing substrate concentration to 50 mM led to the formation of 12 mM **2a** with a moderate yield (24% yield, 12 h). Extending reaction time did not result in noticeable increase in yields, which might be caused by the inactivation of enzyme after 12 h. Additionally, it was noteworthy that increase of substrate concentration did not expend the ee of (*R*)-**2a**, which demonstrated the good enantioselectivity of the HheC in this reaction.

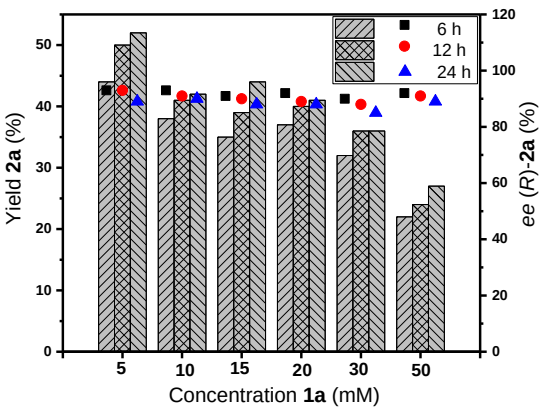
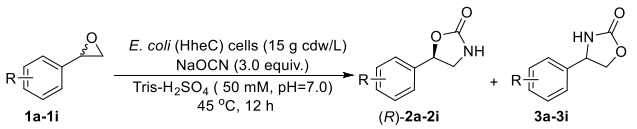


Figure 1. Investigation of substrate concentrations. Reaction conditions: Tris-H_2SO_4 buffer (50 mM, pH 7.0, 5 mL); *E. coli* (HheC) cells (15 g cdw/L), **1a** (5-50 mM), NaOCN (15-150 mM), 45 °C. The yield (column) and ee (scatter) were determined over the formed product at 6, 12 and 24 h by chiral HPLC.

Subsequently, the scope and generality of the biocatalytic reaction were systematically investigated using various styrene oxides as substrates. Reactions were carried out under the optimized conditions (Table 2, entry 15) with an epoxide concentration of 30 mM. To gain isolated yields of the desired products, all the reactions were scaled up to 30 mL. As shown in Table 3, regardless of the electronic nature of the substituents, all substrates could be smoothly transformed into the corresponding chiral 5-aryl-2-oxazolidinones (*R*)-**2a-2i** in moderate to good ee (74-90%), as well as moderate to excellent yields (32-47%). Noteworthy, enantiopure *para*-F substituted 5-aryl-2-oxazolidinones **2f** is an important skeleton structure for the discovery of Δ-5 desaturase inhibitors.[10] Additionally, the regioselectivities of the reactions were also determined via analysis of the ratio of 5-aryl-2-oxazolidinones **2** (C_β-attack) to 4-aryl-2-oxazolidinones **3** (C_α-attack) by ^{1}H NMR. The results revealed that the HheC exhibited a poor to good C_β-position regioselectivity toward these aromatic epoxides (Table 3). In the case of *meta*-Br substituted styrene oxide **1d**, a good regioselectivity of 87:13 (C_β-attack : C_α-attack) was found (Table 3, entry 4), while the regioselectivity almost lost for the *m*-methyl substituted styrene oxide **1e** (Table 3, entry 5). It is noteworthy that, despite the fact that the regioselectivity of ring-opening of these aromatic epoxides was plagued by conflicting steric and electronic factors, the yields of the desired products **2** were not severely influenced. Although previous study indicated that the HheC didn't catalyze the reaction between *para*-nitrostyrene oxide and cyanate by spectrophotometric assay,[11] low conversion of the epoxide substrate was actually observed herein. We speculated that increasing the ratio of nucleophile cyanate accelerated this reaction.

Table 3. Scope of the reaction for synthesis of chiral 5-aryl-2-oxazolidinones **2** from styrene oxides **1**.[a]



entry	epoxide	R	ratio **2**:**3**[b]	yield **2** (%)[c]	*ee* (*R*)-**2** (%)[d]

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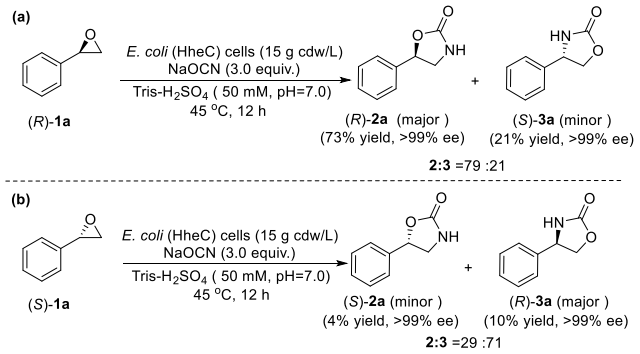
1	**1a**	H	66:34	39	88
2	**1b**	*m*-F	70:30	36	74
3	**1c**	*m*-Cl	71:29	37	81
4	**1d**	*m*-Br	87:13	32	88
5	**1e**	*m*-CH_3	57:43	38	85
6	**1f**	*p*-F	66:34	36	90
7	**1g**	*p*-Cl	71:29	39	84
8	**1h**	*p*-Br	74:26	34	86
9	**1i**	*p*-CH_3	75:25	47	90

[a] Reaction conditions: Tris-H_2SO_4 buffer (50 mM, pH 7.0, 30 mL), *E. coli* (HheC) cells (15 g cdw/L), **1a-1i** (30 mM), NaOCN (90 mM), 45 °C and 12 h. [b] Determined by ^{1}H NMR. [c] Isolated yield. [d] Determined by chiral HPLC.

To gain an understanding of the enantio- and regioselectivity of the HheC-catalyzed cyanate-mediated epoxide ring-opening reaction, both enantiomers of **1a** were individually subjected to bioconversion (Scheme 2). A comparison of the total yields of **2a** and **3a** generated from (*R*)-**1a** (94%) and (*S*)-**1a** (14%) revealed the HheC showed a higher catalytic activity toward (*R*)-**1a**, which corresponded to that in the azide-mediated ring-opening reactions of aromatic epoxides.[12] Interestingly, the ring-opening regioselectivity toward the two enantiomers was quite different. In the case of (*R*)-**1a**, a regioselectivity of 79:21 (C_β-attack : C_α-attack) was found to give major product (*R*)-**2a** in 73% yield (Scheme 2a); however, the regioselectivity was 29:71 (C_β-attack : C_α-attack) for (*S*)-**1a**, generating major product (*R*)-**3a** in 10% yield (Scheme 2b). These results indicated the HheC preferred C_β-position for ring-opening of (*R*)-**1a** while C_α-position for ring-opening of (*S*)-**1a**. Consequently, in the case of (*R,S*)-**1a**, the influence on the ee of (*R*)-**2a** caused by the ring-opening of (*S*)-**1a** could be decreased by the high C_α-attack regioselectivity toward (*S*)-**1a**. Additionally, whether the yield of **2a** or **3a** generated from (*R*)-**1a** was higher than that obtained from (*S*)-**1a**, which further confirmed the *R* enantioselectivity of HheC.



Scheme 2. Investigation of bioconversions of (*R*)-**1a** and (*S*)-**1a** catalyzed by HheC. Reaction conditions: Tris-H_2SO_4 buffer (pH 7.0, 50 mM, 30 mL), *E. coli* (HheC) cells (15 g cdw/L), (*R*)-**1a** or (*S*)-**1a** (30 mM), NaOCN (90 mM), 45 °C and 12 h. The yields of **2a** were isolated by column chromatography; the yields of **3a** were calculated from the yield of **2a** by ^{1}H NMR.

In an attempt to understand the origin of enantio- and regioselectivity, the interactions between HheC and both enantiomers of **1a** were then analyzed. Dijkstra and coworkers have resolved the crystal structure (PDB ID: 1PWZ) of the HheC complexed with (*R*)-**1a** and chloride in previous study.[13] Here, molecular docking of (*S*)-**1a** to the X-ray structure of HheC was performed using AutoDock.[14] The conformations of HheC/(*R*)-**1a** (crystal result) and HheC/(*S*)-**1a** (docking result) were then analyzed in PyMOL to give some insight into the binding of the substrates in the enzyme active site.[15] As showed in Figure 2, both enantiomers bind with their aromatic side chains in a very similar conformation in the active site, and a slight difference that the oxygen atom of the epoxide ring was found. Hydrogen bonds formed between the oxygen atom of the epoxide ring and Ser132/Tyr145 were similar for the two enantiomers. The spontaneous formation of **2a** was not observed in the absence of HHDH (Table 1, entries 6-7), and both enantiomers of **1a** could react with cyanate in the presence of HheC (Scheme 2). These results demonstrated the formation of (*R*)-**2a** and (*S*)-**2a** respectively from (*R*)-**1a** and (*S*)-**1a** was contributed by enzymatic conversion. On the basis of the docking and bioconversion results, we could conclude that both enantiomers of **1a** could be accepted by HheC to form a productive complex.

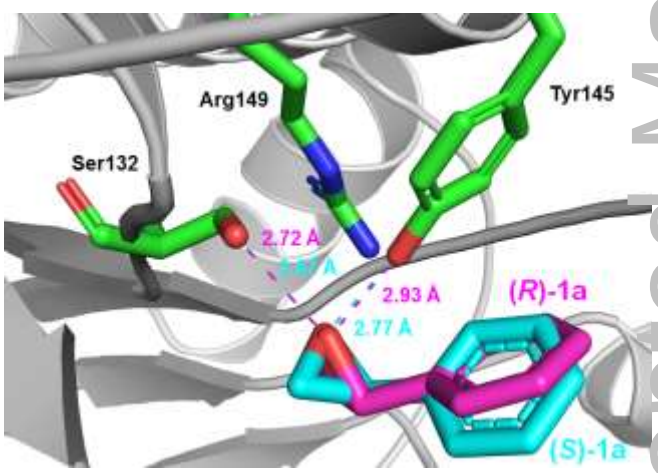


Figure 2. Comparation of (*R*)-**1a** (pink sticks) and (*S*)-**1a** (cyan sticks) binding to active site of the HheC. The catalytic triad Ser132-Tyr145-Arg149 was showed as sticks. Hydrogen bonds (dashed lines) and distances of the Ser132/Tyr145 toward (*R*)-**1a** and (*S*)-**1a** were determined and highlighted in pink and cyan respectively.

In the crystal structure of HheC/(*R*)-**1a**, the halide-binding site was occupied by a chloride which also served as a nucleophile in the reverse reaction.[13] In other ring-opening reactions, nucleophiles (N_3^-, CN^-, OCN^- etc.) would also bound at this region for epoxides ring-opening attack to produce β-substituted alcohols. Therefore we could assume the chloride as the nucleophile cyanate to analyze the possible interactions between cyanate and (*R*)-**1a**/(*S*)-**1a**. The

distances of the Nu^- (blue sphere, represented cyanate) from C_α atom and C_β atom of (*R*)-**1a**/(*S*)-**1a** were measured and displayed in Figure 3. In the case of (*R*)-**1a**, the Nu^- is positioned at approximately 3.46 Å and 3.23 Å from the C_α atom and C_β of the epoxide ring, respectively. However, the corresponding respective distances were 3.51 Å (C_α) and 3.75 Å (C_β) in the case of (*S*)-**1a**. Accordingly, ring-opening of (*R*)-**1a** would take place in favor of C_β atom (3.23 < 3.46 Å), while the C_α atom would be easier to be attacked by Nu^- for (*S*)-**1a** (3.51 < 3.75 Å). Additionally, a comparation between the distances of the C_α atoms to Nu^- of the different enantiomers (3.46 < 3.51 Å) would give a reasonable explanation to that higher yield of (*S*)-**3a** obtained from (*R*)-**1a** than that of (*R*)-**3a** generated from (*S*)-**1a** (Scheme 2). To sum up from these results, we proposed that the interrelations between epoxide **1a** and nucleophile cyanate decided the formation rates of (*R*)-**2a**, (*S*)-**3a**, (*R*)-**3a** and (*S*)-**2a**. This might offer a plausible explanation for the enantioselectivity and regioselectivity of the HheC-catalyzed ring-opening of **1a** with cyanate.

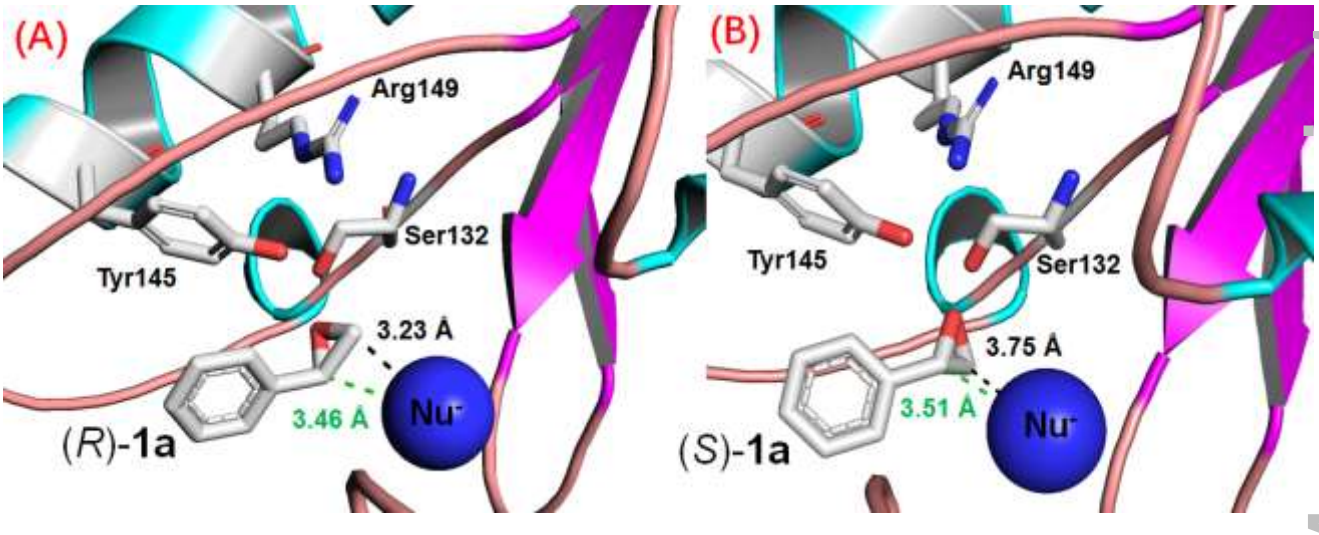


Figure 3. Analysis of the complexes of HheC/(*R*)-**1a**/Nu^- (A) and HheC/(*S*)-**1a**/Nu^- (B). Catalytic triad Ser132-Tyr145-Arg149, (*R*)-**1a** and (*S*)-**1a** were showed as sticks. Nu^- represented nucleophile cyanate (OCN^-) and was showed as sphere. The distances (dashed lines) of the Nu^- from C_α atom and C_β atom of (*R*)-**1a**/(*S*)-**1a** were determined and highlighted in green and black respectively.

Nitrogen containing compounds are of great importance because of their interesting and diverse biological activities. The construction of the C–N bond is of significant importance as it opens avenues for the introduction of nitrogen into organic molecules.[16] Ring-opening of epoxides using nitrogen-containing nucleophile such as azide and amines affords a convenient methodology for C-N bond formation.[17] Chemical ring-opening of epoxides with these nucleophiles has been widely studied, while the work on the reaction with inorganic cyanate is very rare.[18] Herein the synthesis of chiral 5-aryl-2-oxazolidinones via enantio- and regioselective ring-opening of styrene oxides was developed, which showed some greener advantages than previous method.[9] Recently, we have developed a biocatalytic route to 4-aryl-2-oxazolidinones via cyanate-mediated ring-opening of aromatic epoxides using a highly C_α-position regioselective HHDH.[19] Hence this study also provided an biocatalytic approach for regiocomplementary preparation of aryl-substituted-2-oxazolidinones from aromatic epoxides.

In summary, we have developed an efficient biocatalytic approach for the synthesis of chiral 5-aryl-2-oxazolidinones in good yields and ee starting from styrene oxides, which further expanded biotechnology applications of HHDH in organic synthesis. We also tried to uncover the origin of enantioselectivity and regioselectivity of the enzymatic process by single enantiomer bioconversion and molecular docking experiments. We expect that findings gained from our present study will be helpful for preparation and discovery of chiral oxazolidinone drugs.

Experimental Section

General procedure for enantioselective synthesis of chiral 5-aryl-2-oxazolidinones 2a-2i: To a 30 mL suspension of 15 g cdw/L *E. coli* (HheC) cells in Tris-H_2SO_4 buffer (50 mM, pH 7.0) was added solid NaOCN to a final concentration of 90 mM. Epoxide **1a** was then added to a final concentration of 30 mM using 300 μL DMSO as co-solvent. The reaction mixture was shaken at 250 rpm and 45 °C for 12 h. Then the mixture was extracted using ethyl acetate (2 × 30 mL). After centrifugation, the organic phases were separated, combined, dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel

(petroleum ether/ethyl acetate = 1:1) to afford the desired product (*R*)-5-phenyloxazolidin-2-one **2a**.

Acknowledgements

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