RESEARCH ARTICLE

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Synthesis and HHDH-Catalyzed Kinetic Resolution of Propargylic Epoxides

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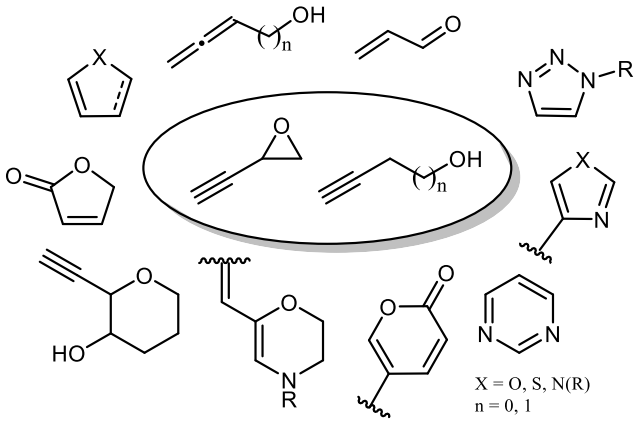
Abstract. The versatile reactivity of propargylic epoxides and alcohols, due to the presence of a triple bond, is used in the synthesis of various organic compounds and building blocks. However, there are not many known methods for the preparation of optically pure propargylic epoxides and alcohols, and the existing ones often require specific reagents. Halohydrin dehalogenases (HHDHs) can be used to obtain enantiomerically pure compounds from racemic epoxides. These important biocatalysts facilitate epoxide ring-opening reactions with unnatural nucleophiles such as azides. Here we report the biocatalytic transformation of propargylic epoxides using HHDHs. Six propargylic epoxides with different substituents were synthesized. Kinetic resolution reactions catalyzed by HHDHs in the presence of azide were performed. Two enzymes with opposite stereoselectivities, HheC and HheA2-N178A were used and yielded azido alcohols (98 - >99% *ee*, *E*-value >200) and epoxides (29 - 88% *ee*). The best performing *p*-tolyl propargylic epoxide derivative was used in a sequence of two enzymatic reactions to obtain both enantiomers of the β-azido alcohol and the (*R*)-enantiomer of the α-azido alcohol, each in >99% *ee*, through complete conversion of the starting epoxide. The obtained azido alcohols were used in further transformations. The click reactions with terminal acetylenes gave triazolyl propargylic alcohols (>99% *ee*, 90 - 98% yield). In the case of the α-azido alcohol, the click reaction was followed by intramolecular cyclization to form the dihydrofuranyl triazole motif that is found in biologically active compounds.

Keywords: biocatalysis; halohydrin dehalogenases; kinetic resolution; propargylic epoxides; propargylic alcohols

Introduction

Owing to the presence of a carbon-carbon triple bond, propargylic epoxides and alcohols undergo various inter- and intramolecular reactions. In addition to the usual epoxide reactions,[1] this reactivity allows for transformation into various heterocyclic compounds, such as furane, pyrrole, and triazole derivatives, as well as allenic compounds (Scheme 1).[2] Thus, it is not surprising that these compounds are used as intermediates in the synthesis of organic compounds, including biologically active substances, natural products, and pharmaceuticals.[3] Although optically pure building blocks are important in such syntheses, known methods for the stereoselective preparation of propargylic epoxides are scarce.[4] Those described in the literature to this date require specific reagents, such as organotellurium ylides, organogallium bases, or chiral dioxiranes.[5] In this work we report the kinetic resolution of propargylic epoxides catalyzed by halohydrin dehalogenases as an alternative method of obtaining optically pure propargylic compounds.

Halohydrin dehalogenases (HHDHs) are a group of enzymes that facilitate the conversion between halohydrins and epoxides in both directions.[6] These lyases were discovered in 1968 as a part of the bacterial metabolism of halogenated organic compounds through cyclization of vicinal halohydrins.[7] Their extensive research began after Nakamura reported the ability to catalyze the reverse process, the opening of the epoxide ring with the cyanide anion.[8] Studies by Janssen *et al.* expanded the range of unnatural nucleophiles (N_3^-, CN^-, CNO^-, SCN^-, NO_2^- and $HCOO^-$), giving access to β-substituted



Scheme 1. Synthetic versatility of propargylic epoxides and alcohols.

alcohols and oxazolidinones.[9] These nucleophiles give different kinetic parameters, with azide showing the highest activity.[6] HHDHs are categorized in seven groups (A – G) that differ in the shape and size of the active site,[10] which dictates their regio- and enantioselectivity, as well as structural characteristics of accepted substrates.[6] The most of HHDHs work well with variously substituted terminal epoxides (including spiroepoxides),[11] both aromatic and aliphatic. Those with a more spacious active site, for example HheD and HheG,[12] accept non-terminal compounds, 2,3-disubstituted (including bicyclic), and polysubstituted epoxides.

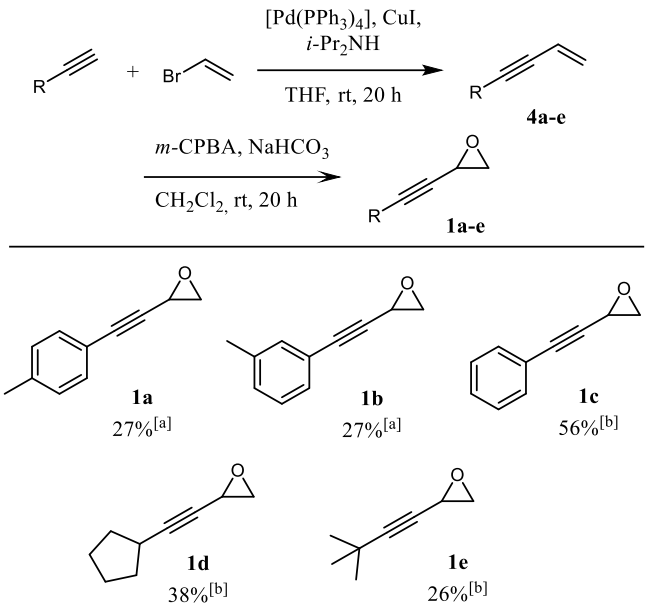
Since the carbon-carbon triple bond is of linear geometry and has the shortest bond length in the hybridization series, its use as a substituent should not be sterically demanding, therefore we assumed that propargylic epoxides could be used as substrates for HHDHs. For this study we chose two enantiocomplementary HHDHs, (*R*)-selective HheC[6] and (*S*)-selective variant HheA2-N178A.[11c] Both enzymes were evaluated as catalysts for the resolution of a series of noncommercial propargylic epoxides. In the presence of azide ions, optically pure propargylic azido alcohols are obtained. A combination of three functional groups in the molecule, alkyne, azide and hydroxide, delivers versatile synthetic building blocks and intermediates.

Results and Discussion

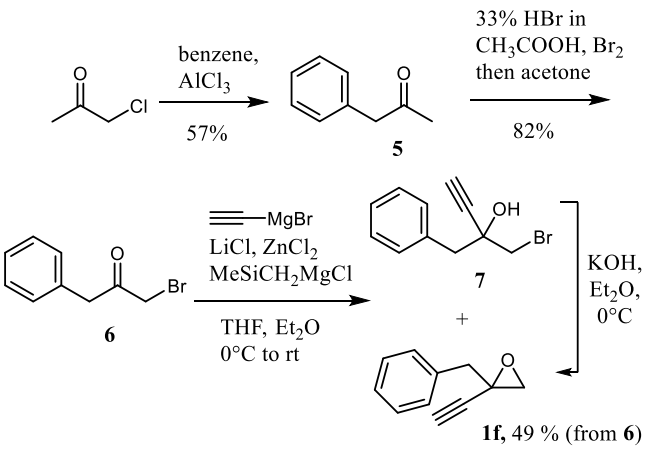
Synthesis of Substrates

A series of racemic propargylic epoxides **1a-f** were prepared. Epoxides **1a-e** were prepared using Sonogashira coupling of the corresponding alkynes and vinyl bromide, followed by epoxidation of enynes **4a-e** with *m*-CPBA (Scheme 2).[13,14] The synthesis of 2,2-disubstituted epoxide **1f** started with the preparation of phenylacetone **5** from chloroacetone and benzene in a Friedel-Crafts reaction (Scheme 3).[15] Compound **5** was then selectively brominated at the methyl position by the action of Br_2 and HBr in acetic acid, yielding benzyl bromomethyl ketone **6**.[16] Next, acetylenic Grignard reagent modified by addition of LiCl and catalytic amounts of $ZnCl_2$ and Me_3SiCH_2MgCl was used for addition to haloketone **6**.[17] The reaction yielded a mixture of tertiary propargylic bromohydrin **7** and the corresponding epoxide **1f**. Treating the crude reaction mixture with KOH converted the remaining bromohydrin **7** to epoxide **1f** in 49% over two steps starting from **6**.

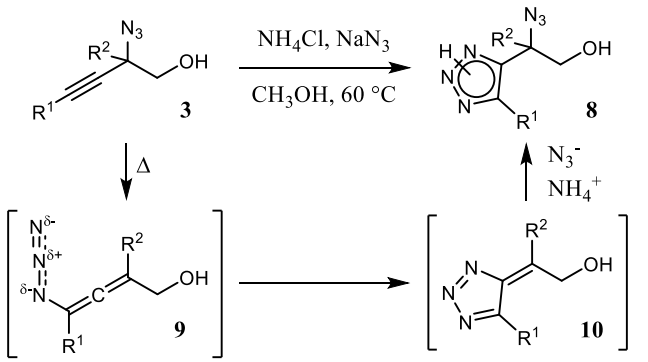
The racemic azido alcohols **2a-f** and **3a-f** used for monitoring enzymatic reactions were synthesized by heating the epoxides **1a-f** in methanol with NaN_3 and NH_4Cl for 3 hours. During the product isolation an unknown byproduct was noticed. Performing an azidolysis reaction of **1a** for a prolonged time of 27 hours resulted in a higher amount of this byproduct.



Scheme 2. Synthesis of monosubstituted propargylic epoxides **1a-1e**. [a] Isolated yield over three steps; [b] Isolated yield over two steps.



Scheme 3. Synthesis of 2,2-disubstituted propargylic epoxide **1f**.



Scheme 4. Formation of triazole **8** from propargylic α-azido alcohol **3** in the azidolysis of propargylic epoxides (**8a**: R^1 = *p*-tolyl, R^2 = H)

Further characterization by NMR, MS and IR identified the unknown compound as triazole **8a** (Scheme 4). The formation of triazoles such as compound **8a** from propargylic azides under these reaction conditions is known in literature, through nominal azide [1,3]-shift leading to propargyl-allenyl isomerization product **9**, followed by the intramolecular cycloaddition of azide and allenic π-bond, and a nucleophilic attack by azide ion on the formed triazafulvene **10** (Scheme 4).[18] Similar transformations through intermolecular reactions leading to polymeric triazoles occur in both neat azido alcohols, and solutions of azido alcohols in different solvents. Therefore, propargylic azido alcohols, especially α-azido alcohols cannot be stored over a prolonged period and should be checked prior to use.

Biocatalytic Reactions

For preliminary studies, the screening of epoxides **1a-f** in the azide mediated ring-opening reactions catalyzed by two stereocomplementary HHDHs, (*R*)-selective HheC and (*S*)-selective HheA2-N178A was performed. The screening reactions were carried out on an analytical scale at a 2 mM concentration of epoxide, and the progress of the reactions was monitored by GC.

Kinetic resolution in the presence of HheC yielded the corresponding β-azido alcohols **2a-e** in high enantiomeric excess, indicating high enzyme enantioselectivity and high β-regioselectivity (Table 1). In addition, the enzyme showed good activity towards **1a** and **1c**, reaching full conversion in 2 – 3 hours (Table 1, entries 1 and 3). On the other hand, the enzyme showed low activity toward compounds **1b**, **1d** and **1e** as seen from lower conversions, even with the double amount of enzyme used for **1e** (Table 1, entries 2, 4 and 5). It can be assumed that **1b** does not fit well in the active site of HheC, as *m*-tolyl is bulkier than phenyl or even *p*-tolyl. The low enzymatic conversions of **1d** and **1e** were observed, as well as significant consumption of substrate in non-enzymatic reactions, namely chemical azidolysis and hydrolysis (Table S2). The degree of chemical azidolysis, which proceeds with high regioselectivity at the α-position, yielding the α-azido alcohol, can be observed from conversions in blank test results: 14% in 3 hours for **1d** and 29% in 4 hours for **1e** (Table S4). In addition, these compounds have proven susceptible to hydrolysis, with the 15% and 25% consumption within 4 hours, respectively. Epoxides **1c** and **1f** were stable towards hydrolysis (Figure S1).

Reactions carried out in the presence of HheA2-N178A yielded alcohols **2a-e** in high enantiomeric excess but with lower regioselectivity (Table 2), which is consistent with the properties of HheA2-N178A.[11c] The enzyme showed good activity towards aryl monosubstituted epoxides **1a-c** (Table 2, entries 1 – 3), but produced mixtures of β-azido alcohol (**2a-c**, >99% *ee*) and α-azido alcohol (**3a-c**, ~80% *ee*). The reaction of **1b** catalyzed by N178A had conversion comparable to that of **1a** and **1c**. Alkyl monosubstituted compounds **1d** and **1e** had poor enzymatic conversions (Table S3), and significant consumption in non-enzymatic reactions: a noticeable degree of chemical azidolysis in blank tests (leading to α-azido alcohols with high regioselectivity, Table S4), and the hydrolytic instability (Figure S1).

Epoxide **1f** was not a substrate for the selected enzymes, probably due to its bulkiness and the inability to fit into the active site of HheC or HheA2-N178A.

Encouraged by these results, the best performing compound **1a** was selected and the reactions catalyzed by both enzymes on the preparative scale were carried out. The upscale test reaction at 50 mM concentration of epoxide **1a** in the presence of cell-free extract containing HheC showed unsatisfactory activity but maintained the showcased enantioselectivity (Table S4). As an alternative, reactions carried out in the presence of bacterial whole cells containing overexpressed enzymes have proven very effective in terms of enzyme stabilization and protection, as well as keeping the substrates and biocatalysts in proximity, often leading to improved results. Therefore, we opted for this approach.[19] The upscale test reaction of **1a** at the same concentration in the presence of cell-free extract containing HheA2-N178A performed well, showing good activity and enantioselectivity (Table S5).

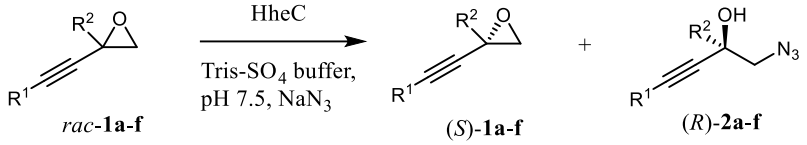
Combining these insights with the principle of good atom economy, a two-pot sequence of two enzymatic reactions starting from **1a**, employing both enzymes to make the most use of the starting material was performed (Scheme 5). In the first step, the reaction of racemic **1a** on a scale of 3 mmol in the presence of *E. coli* MC1061 cells containing HheC, after separation by column chromatography, gave optically pure propargylic β-azido alcohol (*R*)-**2a** in 45% yield and >99% *ee*, and propargylic epoxide (*S*)-**1a** in 42% yield and 80% *ee*. In the second reaction, the previously isolated, enantiomerically enriched (*S*)-**1a** was transformed by the action of HheA2-N178A to a mixture of (*S*)-**2a** and (*R*)-**3a** which were separated by column chromatography to obtain β-azido alcohol (*S*)-**2a** in 32% yield, >99% *ee*, and α-azido alcohol (*R*)-**3a** in 48%, >99% *ee*. Thus, by employing the two separate enzymatic reactions catalyzed by two stereocomplementary HHDHs, three synthetically valuable optically pure propargylic azido alcohols were prepared and isolated, including both enantiomers of the β-azido alcohol and the (*R*)-enantiomer of the α-azido alcohol, through the complete conversion of a single racemic substrate (79% total yield starting from *rac*-**1a**).

Post-modification Reactions

To further illustrate the applicability of the developed method, post-modification reactions of the obtained optically pure propargylic azido alcohols were performed. Click reactions of the β-azido alcohols (*R*) and (*S*)-**2a** with selected terminal acetylenes in the presence of $CuSO_4$ and sodium L-ascorbate gave the

corresponding optically pure triazolyl propargylic alcohols **11** in 98% yield (Scheme 6). The terminal acetylenes substituted with phenyl, ethyl ester, and cyclopropyl groups, which allow for further functionalization, were chosen.

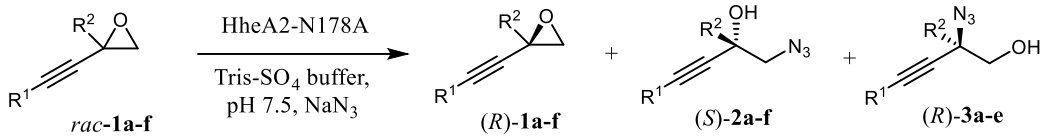
Table 1. Kinetic resolution of propargylic epoxides using HheC[a].



Entry	Epoxide	R^1, R^2	t (h)	Conversion (%)[b]	*ee* (*S*)-**1** (%)[c]	*ee* (*R*)-**2** (%)[c]	*E*[d]
1	**1a**	*p*-tolyl, H	2	47	88	>99	>200
2	**1b**	*m*-tolyl, H	3	23	29	>99	>200
3	**1c**	phenyl, H	3	45	80	98	>200
4	**1d**	cyclopentyl, H	3	32	47	>99	>200
5	**1e**[e]	*t*-Bu, H	4	10	11	>99	>200
6	**1f**	H, Bn	4	0	-	-	-

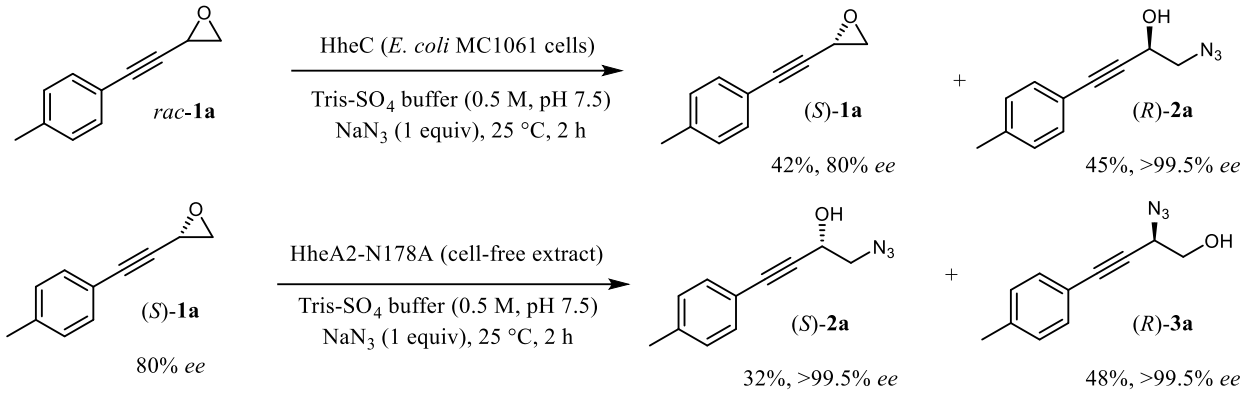
[a] *Reaction conditions*: 2 mM epoxide (0.5 mL, 40 mM, DMSO), 8.8 mL Tris-SO_4 (pH 7.5, 50 mM), 3 mM NaN_3 (0.5 mL, 60 mM, H_2O), 200 µL enzyme (cell-free extract, protein concentration 5.6 mg/mL); final volume 10 mL
[b] Data given for conversion were calculated from *ee* **1** and *ee* **2** according to formula $c=ee_s/(ee_s+ee_p)$
[c] Determined by GC
[d] *E* values were calculated from *ee* **1** and *ee* **2** according to formula $E = \ln[(1-ee_s)/(1+ee_s/ee_p)]/\ln[(1+ee_s)/(1+ee_s/ee_p)]$
[e] Double amount of the enzyme

Table 2. Kinetic resolution of propargylic epoxides using HheA2-N178A[a].

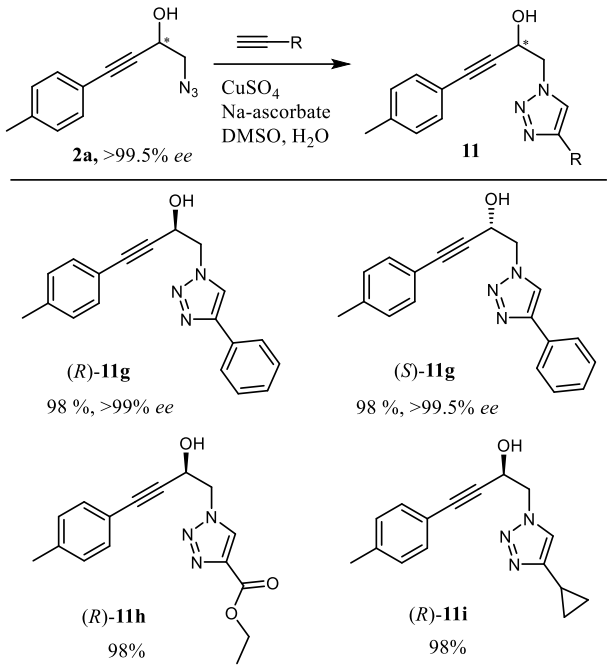


Entry	Epoxide	R^1, R^2	t (h)	Conversion (%)[b]	*ee* (*R*)-**1** (%)[c]	*ee* (*S*)-**2** (%)[c]	*ee* (*R*)-**3** (%)[c]	**2** / **3**[c]	*E*[d]
1	**1a**	*p*-tolyl, H	2	47	88	>99	82	54/46	>200
2	**1b**	*m*-tolyl, H	3	44	78	>99	80	71/29	>200
3	**1c**	phenyl, H	4	44	79	>99	80	66/34	>200
4	**1d**	cyclopentyl, H	3	7	7	>99	-	70/30	>200
5	**1e**[e]	*t*-Bu, H	4	5	5	>99	-	90/10	>200
6	**1f**	H, Bn	4	0	-	-	-	-	-

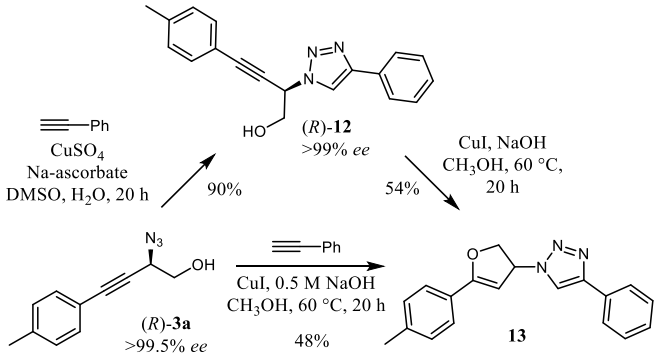
[a] *Reaction conditions*: 2 mM epoxide (0.5 mL, 40 mM, DMSO), 8.8 mL Tris-SO_4 (pH 7.5, 50 mM), 3 mM NaN_3 (0.5 mL, 60 mM, H_2O), 200 µL enzyme (cell-free extract, protein concentration 2.8 mg/mL), final volume 10 mL
[b] Data given for conversion were calculated from *ee* **1** and *ee* **2** according to formula $c=ee_s/(ee_s+ee_p)$
[c] Determined by GC or HPLC
[d] *E* values were calculated from *ee* **1** and *ee* **2** according to formula $E = \ln[(1-ee_s)/(1+ee_s/ee_p)]/\ln[(1+ee_s)/(1+ee_s/ee_p)]$
[e] Double amount of the enzyme



Scheme 5. Sequence of enzymatic reactions on a 3 mmol scale (50 mM) of *rac*-**1a** epoxide. Isolated yields after column chromatography are reported



Scheme 6. Click reactions of optically pure propargylic β-azido alcohols (*R*)- and (*S*)-**2a.**



Scheme 7. Click reaction of (*R*)-**3a** followed by 5-*endo-dig* cyclization.

Depending on the reaction conditions, the click reaction of the α-azido alcohol (*R*)-**3a** with phenylacetylene resulted either in the click product (*R*)-**12** or in product **13**, where the click reaction was followed by 5-*endo-dig* cyclization (Scheme 7). The click reaction catalyzed by $CuSO_4$ and sodium L-ascorbate led to (*R*)-**12** in 90% yield with retention of enantiomeric purity. However, the subsequent 5-*endo-dig* cyclization of (*R*)-**12** proceeds through an allene intermediate; therefore, the formation of the final product **13** occurred with almost complete racemization (12% *ee*). A two-step, one-pot reaction with phenyl acetylene, CuI, and NaOH in methanol yielded product **13** in 48% yield with the same extent of racemization. The obtained compound **13** contains the dihydrofuranyl triazole moiety, which is found in naphthoquinoidal triazoles, compounds known to have biological activity such as antiparasitic, antibacterial, and antitumor activity.[20]

Conclusion

In summary, six propargylic epoxides were synthesized and used for the development of a chemoenzymatic method for the preparation of chiral propargylic compounds through the kinetic resolution of epoxides in the presence of azide ions. Two stereocomplementary HHDHs, (*R*)-selective HheC and (*S*)-selective HheA2-N178A were used as biocatalysts in ring-opening reactions which yielded optically pure azido alcohols (98 – >99% *ee*), and enantiomerically enriched epoxides (29 – 88% *ee*). To our knowledge, propargylic epoxides have not been studied as substrates for HHDHs to this date.

The best performing substrate, the *p*-tolyl substituted propargylic epoxide **1a** was used in a two-pot sequence of two enzymatic reactions employing both enzymes (Scheme 5). First, the kinetic resolution of racemic **1a** in the presence of *E. coli* MC1061 cells containing HheC was performed, followed by product separation using column chromatography. In the second reaction, isolated enantiomerically enriched (*S*)-**1a** was again opened with azide, but this time in

the presence of cell-free extract containing HheA2-N178A, followed by product separation using column chromatography. In this way, both the (*R*) and (*S*)-enantiomers of the corresponding β-azido alcohol **2a**, as well as the (*R*)-enantiomer of the α-azido alcohol **3a** were obtained through almost complete conversion of the starting material. Besides the very high enantioselectivity of HHDHs and the ability to access both enantiomers, there are some limitations that challenge upscaling. HHDH-enzymes are prone to substrate and/or product inhibition, often already at 20 mM concentration.[21] This limits the substrate loading to lower concentrations (up to 50 mM). To speed up the reaction and to suppress the formation of side products, often requires high catalyst loading. We believe that the high value of the obtained enantiomerically pure compounds justifies the use of a larger amount of enzymes, even on commercial scale, since the HHDH enzymes are easily prepared in large quantities, and therefore not costly. This especially concerns the use of whole-cell biocatalyst, which can easily be reused.

The obtained optically pure propargylic β-azido alcohols **2a** were used in a series of copper-catalyzed click reactions with selected terminal acetylenes to obtain the corresponding optically pure triazolyl propargylic alcohols 90-98% yield. Finally, the two step click reaction followed by *endo*-cyclization was performed starting from optically pure α-azido alcohol **3a** to obtain compound **13**, which contains the dihydrofuranyl triazole moiety that is found in biologically active compounds.

The obtained azido alcohols and their post-modification products are valuable synthons in stereoselective synthesis, as they contain functional groups that allow for further modifications, which emphasizes the applicability of the chemoenzymatic method developed in the course of this work.

Experimental Section

Kinetic Resolution Experiments – General Procedure

To 8.8 mL of Tris-SO_4 buffer (50 mM, pH 7.5) at room temperature, 0.5 mL of NaN_3 stock solution in water (0.03 mmol, final concentration 3 mM) and 200 μL of cell-free extract in TEMG buffer were added. The reaction was started by the addition of 0.5 mL of epoxide stock solution in DMSO (0.02 mmol, final concentration 2 mM). In parallel, a blank test without enzyme (spontaneous reaction of azidolysis) was performed by adding stock solutions of NaN_3 (0.5 mL, 0.03 mmol) and then epoxide (0.50 mL, 0.02 mmol, final concentration 2 mM) in Tris-SO_4 buffer (9.0 mL). The progress of the reaction was followed by periodically taking samples (0.5 mL) from the reaction mixture. Samples were extracted with MTBE (1.0 mL, containing mesitylene or chlorobenzene as internal standard), dried over anhydrous Na_2SO_4, and analyzed by GC to determine the conversion and regioisomeric ratio. In parallel, chiral GC or HPLC analyses were performed to determine enantiomeric purity of the product and remaining substrate.

Sequential Two-Pot Reactions with Epoxide 1a on a 3.0 mmol Scale

Lyophilized cells of *E. coli* MC1061 that contained overexpressed HheC (300 mg) were rehydrated in a Tris-SO_4 buffer (57 mL, 0.5 M, pH 7.5). *Rac*-**1a** (3.0 mmol, 510 mg, 93% purity, 50 mM final concentration) dissolved in DMSO (3 mL) was added, followed by NaN_3 (3.0 mmol, 195 mg). The reaction mixture was stirred at 25 °C and 1000 rpm for 2 h (conversion around 45%). The mixture was extracted with EtOAc (4 x 60 mL). Combined organic phases were dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. The crude product was purified by chromatography (*n*-hexane/EtOAc = 9:1) to obtain (*S*)-**1a** (198 mg, 42%, 80% *ee*) and (*R*)-**2a** (270 mg, 45%, >99.5% *ee*, $[\alpha]^{25}_D$ = -72.4 (c 0.98, $CHCl_3$)).
The enantiomerically enriched epoxide (*S*)-**1a** (1.25 mmol, 198 mg, 80% *ee*, 50 mM final concentration) obtained in the previous step, was dissolved in DMSO (1.25 mL). Tris-SO_4 buffer (17.5 mL, 0.5 M, pH 7.5) was added together with HheA2-N178A (6 mL cell-free extract, 2.8 mg/mL) and NaN_3 (1.25 mmol, 82 mg). After 30 min, another portion of HheA2-N178A (6 mL) was added. The reaction mixture was stirred at 25 °C and 1000 rpm for 2 h. The mixture was extracted with EtOAc (4 x 40 mL). Combined organic phases were dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 9:1) to obtain (*S*)-**2a** (80 mg, 32%, >99.5% *ee*, $[\alpha]^{25}_D$ +72.2 (c 0.83, $CHCl_3$)) and (*R*)-**3a** (121 mg, 48 %, >99.5% *ee*, $[\alpha]^{25}_D$ = -166.1 (c 1.15, $CHCl_3$)).

General Procedure for Click Reactions

To a solution of optically pure **1a** (1 equiv., 0.15 mmol, > 99.5% *ee*) in DMSO (0.4 mL) and H_2O (1.1 mL) was added aqueous solution of $CuSO_4$ (0.1 M, 0.08 mL, 0.008 mmol, 5 mol%), followed by aqueous solution of sodium L-(+)-ascorbate (0.1 M, 0.37 mL, 0.037 mmol, 25 mol%) and neat acetylene (0.31 mmol, 2 equiv.). The reaction mixture was stirred at rt for 20 h. Water (10 mL) was added, and the mixture extracted with EtOAc (3 × 10 mL). Combined organic phases were dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. The products were purified using silica gel column chromatography (*n*-hexane/EtOAc = 3:2).

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