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Dual Catalytic Functions of Human Carbonic Anhydrase II in the Tandem Synthesis of Chiral Halohydrins and Epoxides from α-Haloketones

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Human carbonic anhydrase II (hCA II) is a zinc-dependent metalloenzyme best known for catalyzing the reversible hydration of carbon dioxide. Beyond its physiological role, hCA II can display catalytic promiscuity in hydride-transfer reactions from silanes to carbonyl compounds, providing a useful platform for stereoselective biotransformations under mild conditions. In this work, we report a single-enzyme cascade approach for the conversion of α-haloketones into chiral halohydrins and the corresponding epoxides using hCA II and phenylsilane as reducing agent.

The transformation proceeds through the enzyme-mediated reduction of the carbonyl group, affording enantioenriched halohydrins as key intermediates. These compounds are valuable bifunctional building blocks, as they contain both a stereodefined alcohol center and a reactive carbon-halogen bond. Moreover, they can undergo intramolecular dehydrohalogenation to generate epoxides, transferring the stereochemical information established during the reduction step to strained three-membered heterocycles with high synthetic utility.

The method was investigated using purified hCA II and whole-cell biocatalysts, as well as mutant variants generated to modulate catalytic performance and stereoselectivity. α-Haloacetophenone derivatives afforded predominantly *R*-configured halohydrins and the corresponding phenyl oxiranes, while chloropropiophenone substrates showed substrate-dependent stereochemical outcomes. The hCA II-mediated reduction of 2-chloropropiophenone preferentially afforded *R*-configured halohydrins, whereas 1-chloropropiophenone favored *S*-configured alcohol products. In both cases, the corresponding epoxides were generated through intramolecular ring closure of these stereodefined halohydrin intermediates.

The configuration of the newly formed alcohol center, together with that of the adjacent halogen-bearing carbon, defines the diastereomeric distribution of the intermediates and governs the stereochemical course of subsequent ring closure. Notably, for para-substituted derivatives bearing 4-Br, 4-Cl, and 4-F groups, the V121A mutant induced an inversion of epoxide configuration, affording the *S*-epoxide while the halohydrin intermediate retained the *R* configuration. These results highlight the potential of hCA II as an engineered biocatalyst for stereodivergent access to chiral halohydrins and epoxides from readily available α-haloketones.

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