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Styrene Oxide Isomerase-Catalyzed Meinwald Rearrangement and its Applications in Enantioselective Cascade Biotransformations

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PURPOSE OF THE ABSTRACT

The Meinwald rearrangement of epoxides is a synthetically useful reaction to produce aldehydes and ketones, but typically requires harsh conditions and toxic reagents, while also lacking regioselectivity and stereo-control. Styrene oxide isomerase (SOI) catalyzes the Meinwald rearrangement of aryl epoxides to carbonyl compounds with high selectivity under mild conditions, offering an effective biocatalytic alternative to chemical Meinwald rearrangement. Herein, we describe our recent applications of SOI-catalyzed epoxide isomerization as a key step in enantioselective cascade biotransformations.

We report the discovery of a new type of SOI-catalyzed Meinwald rearrangement, which involves the isomerization of internal epoxides via a 1,2-methyl shift without 1,2-H shift to produce the corresponding aldehydes or cyclic ketone. SOI-catalyzed isomerization was determined to proceed via a 1,2-trans-shift in a stereospecific manner, thereby retaining the substrate's enantio-configuration. The synthetic utility of this unique enzymatic Meinwald rearrangement involving a stereospecific 1,2-methyl shift was demonstrated by its incorporation into enantioselective cascades, to convert trans-methyl styrenes into (R)-configured 2-arylpropanols, 2-arylpropionic acids, or 2-arylpropyl amines with high enantioselectivity and yield.

In addition, new types of one-pot enzymatic cascades involving SOI-catalyzed Meinwald rearrangement and dynamic kinetic resolution were developed to convert readily available racemic epoxides into valuable chiral products. SOI-catalyzed isomerization of racemic trans-methyl epoxides (via 1,2-methyl shift) or alpha-methyl epoxides (via 1,2-H shift) generated 2-arylpropanal in situ, which was followed by spontaneous racemization and enantioselective alcohol dehydrogenase-catalyzed oxidation or transaminase-catalyzed amination, producing a wide range of pharmaceutically relevant (S)-2-arylpropionic acids, (R)- and (S)-2-arylpropyl amines with high enantioselectivity and yield. The cascade reactions were performed with isolated enzymes or whole-cell biocatalysts, and the use of SOI to generate the aldehyde intermediate in situ effectively minimized side reactions related to aldehyde instability.

Finally, chemoenzymatic cascades involving SOI-catalyzed Meinwald rearrangement were also developed. The combination of enantioselective whole-cell cascade biotransformation and metal-catalyzed coupling reactions successfully produced several examples of drug-related molecules.

FIGURES

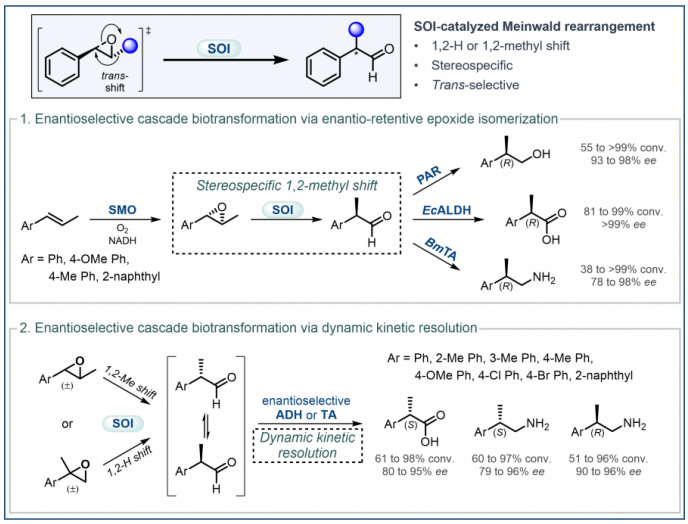

FIGURE 1

SOI-catalyzed Meinwald rearrangement and its applications in enantioselective cascade biotransformations

Part 1. Discovery and application of SOI-catalyzed stereospecific epoxide isomerization via 1,2-methyl shift

Part 2. Development of enantioselective cascades involving SOI-catalyzed epoxide isomerization and dynamic kinetic resolution

FIGURE 2

KEYWORDS

Styrene oxide isomerase | Biocatalytic cascade reactions | Enantioselective synthesis | Dynamic kinetic resolution

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