

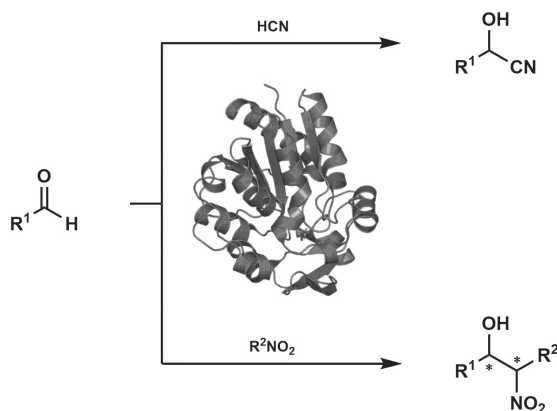
Abstracts

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2.1.1 Cyanohydrin Formation/Henry Reaction

K. Steiner, A. Glieder, and M. Gruber-Khadjawi

Enantiopure cyanohydrins and β -nitro alcohols serve as versatile building blocks for a broad range of chemical and enzymatic reactions, resulting in highly valuable products for many applications. Hydroxynitrile lyases comprise a diverse group of enzymes that catalyze the reversible cleavage of cyanohydrins to carbonyl compounds and hydrogen cyanide. The enzymes have been studied broadly concerning their substrate scope, specificity, structure, and reaction mechanism, and many have been successfully applied and engineered for the synthesis of cyanohydrins from laboratory to industrial scale. Both *R*- and *S*-cyanohydrins are accessible from a broad variety of substrates and, in most cases, high yields and enantiopurities can be obtained after enzyme and reaction engineering. Recent progress in the development and optimization of heterologous expression systems make recombinant hydroxynitrile lyases available in the quantities needed for industrial production. The procedures for safe handling of cyanides are also well-defined and established. In addition, some hydroxynitrile lyases are able to catalyze the nonnatural asymmetric Henry reaction. Although the enzyme activities are rather low, the enzymatic synthesis of enantiopure β -nitro alcohols shows promising results.



Keywords: hydroxynitrile lyase · cyanohydrin · nitroaldol · β -nitro alcohol · Henry reaction · enantioselectivity · enzyme engineering

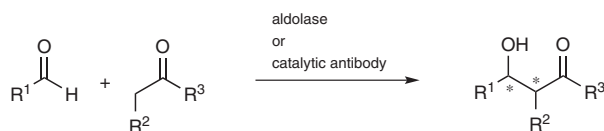
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2.1.2 Aldol Reactions

P. Clapés

The asymmetric aldol addition reaction is a cornerstone transformation in organic chemistry and one of the most useful methods for C—C bond formation. Aldolases and catalytic antibodies catalyze aldol and retroaldol reactions with high stereoselectivity and catalytic efficiency. Therefore, they constitute very useful tools in chemical research and the production of complex, multifunctional chiral compounds, such as carbohydrates and amino acids, as well as their derivatives and analogues. In addition, carbolygating enzymes and antibodies offer a unique tool to perform asymmetric C—C bond formation in a sustainable, environmentally benign fashion. This review describes the different methodologies

and procedures used for enzymatic C—C bond formation by aldol reaction. These include the asymmetric catalytic aldol additions of dihydroxyacetone phosphate (DHAP), 1-hydroxyalkan-2-ones (i.e., dihydroxyacetone, hydroxyacetone, and 1-hydroxybutan-2-one), pyruvate, glycine, acetaldehyde, and glycolaldehyde as the nucleophilic components to a variety of electrophilic aldehyde structures.



R^1 = diverse; R^2 = H, OH, NH_2 , F, Me, Et, SMe; R^3 = H, OH, Me, Et, CO_2^- , CH_2OH , $\text{CH}_2\text{OPO}_3^{2-}$

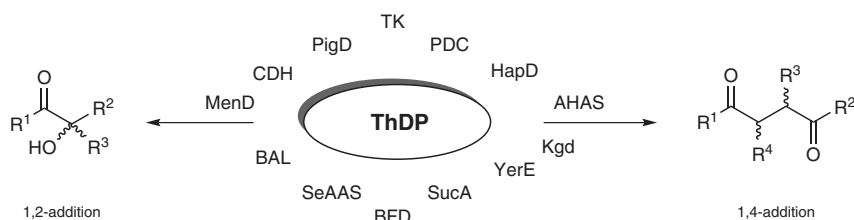
Keywords: asymmetric C—C bond formation • aldol additions • DHAP dependent aldolases • D-fructose 6-phosphate aldolase • DHAP mimics • transketolases • pyruvate aldolases • glycine aldolases • catalytic antibodies • self- and cross-aldol additions • 2-deoxy-D-ribose 5-phosphate aldolase • dihydroxyacetone phosphate (DHAP) • dihydroxyacetone • hydroxyacetone • 1-hydroxybutan-2-one • pyruvate • glycine • glycolaldehyde • alkylaldehydes • hydroxyaldehydes • aminoaldehydes

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2.1.3 Acyloin, Benzoin, and Related Reactions

M. Pohl, C. Wechsler, and M. Müller

This chapter gives a broad overview of different thiamine diphosphate (ThDP) dependent enzymes and their applicability in organic synthesis as a practical alternative to traditional cross-coupling reactions. Complementary to known nonenzymatic umpolung reactions, enzymatic versions of the benzoin condensation, the asymmetric cross-benzoin condensation, the resolution of racemic 2-hydroxy ketones via C—C bond cleavage, the synthesis of bis(α -hydroxy ketones), the homocoupling of aliphatic aldehydes, the Stetter reaction, and aldehyde–ketone cross-benzoin reactions have been developed. The broad diversity of the products from enzymatic transformations is nicely complemented by the possible subsequent diversity-oriented chemistry. Starting from simple, commercially available aldehydes, many different chiral building blocks can be selectively obtained in a few steps, thus mimicking the diversity-oriented biosynthesis of natural biosynthetic pathways.



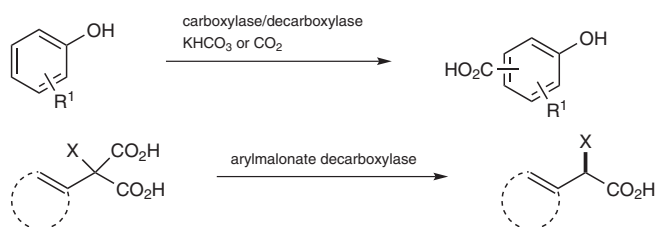
Keywords: regioselectivity • enantioselectivity • enzyme catalysis • C—C bond formation • asymmetric Stetter reaction • asymmetric benzoin condensation • asymmetric enzyme catalysis • thiamine diphosphate • stereocontrol • benzoin • acyloins • chiral resolution • kinetic resolution

2.1.4 Enzymatic Carboxylation and Decarboxylation

R. Lewin, M. L. Thompson, and J. Micklefield

Carboxylation reactions utilizing whole cells or purified carboxylase/decarboxylase enzymes enable the regioselective formation of new C—C bonds under more benign conditions than are typically used in nonenzymatic transformations such as the Kolbe–Schmitt reaction. A wide variety of substrates have been used in enzymatic carboxylation reactions including phenols, styrenes, pyrroles, and indoles.

Enzymatic decarboxylation can be used to transform simple achiral carboxylic acid substrates into more valuable homochiral building blocks through stereoselective C—H or C—C bond formation. For example, arylmalonate decarboxylases catalyze the enantioselective decarboxylative protonation of α -aryl- and α -alkenylmalonic acids under mild conditions and with excellent enantioselectivity. In addition, thiamine diphosphate dependent decarboxylases catalyze C—C bond formation with a broad range of α -keto acid and aldehyde substrates to produce homochiral α -hydroxy ketones.

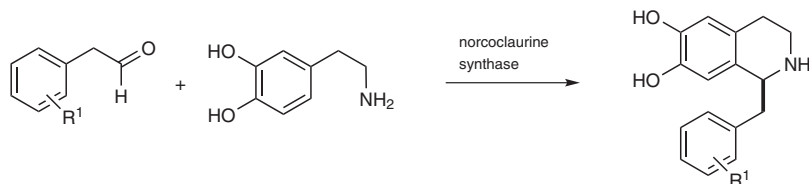


Keywords: carboxylation • Kolbe–Schmitt reaction • regioselectivity • whole-cell reaction • C—C bond formation • enantioselectivity • decarboxylation • arylmalonate decarboxylase • malonic acids • stereoselectivity • enantioselective decarboxylative protonation

2.1.5 Addition to C=N Bonds

A. Ilari, A. Bonamore, and A. Boffi

The Pictet–Spengler reaction consists of a Mannich-type cyclization in which an electron-rich aromatic carbon attacks a C=N bond, in the form of an electrophilic iminium ion, thus yielding a heterocyclic scaffold and generating a new asymmetric center. In this chapter, the substrate scope and limitations of the best-known Pictet–Spenglerase enzymes are discussed in order to pave the way for development of a general biocatalytic strategy for the stereoselective addition to the C=N bond.



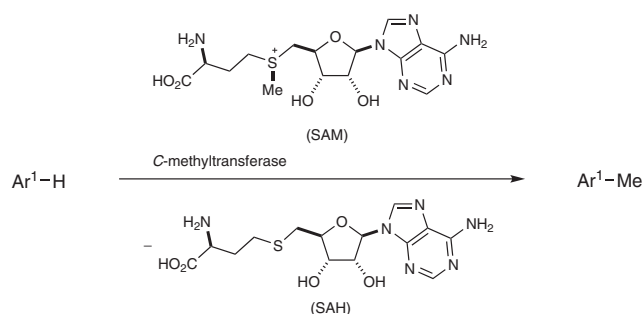
Keywords: Pictet–Spengler reaction • tetrahydroisoquinolines • indole alkaloids • strictosidine synthase • norcoclaurine synthase • β -carboline • azaindoles

2.2 Enzymatic C-Alkylation of Aromatic Compounds

L. A. Wessjohann, H. F. Schreckenbach, and G. N. Kaluđerović

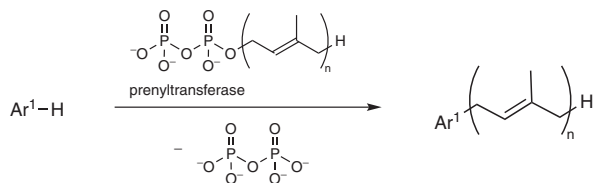
C-Alkylation of aromatic groups, as in Friedel–Crafts chemistry, is an energetically difficult process with significant chemo- and regioselectivity problems, especially if other nucleophiles, such as hydroxy groups or nitrogen atoms, are present in the substrate. Nature provides alkylating enzymes that selectively transfer a methyl, prenyl, or glycosyl group to carbon atoms of aromatic moieties under mild conditions, at room temperature, and mostly with excellent chemo- and regioselectivity. In this review, current enzymatic processes are highlighted and the increasing availability of cosubstrates, cofactors, and suitable enzymes is discussed as a prerequisite for scaling up such processes.

methyltransferases (MTases)

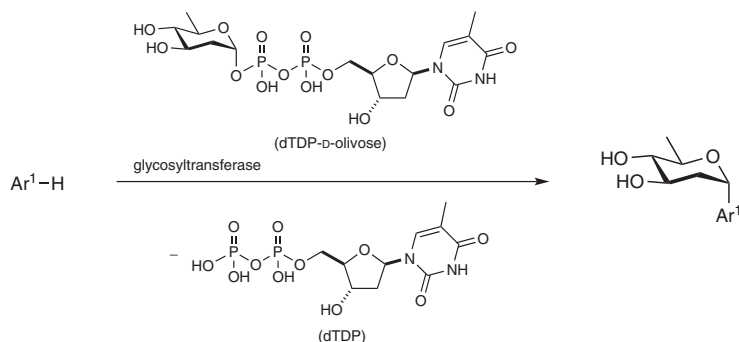


SAM = S-adenosyl-L-methionine; SAH = S-adenosyl-L-homocysteine

prenyltransferases (PTases)



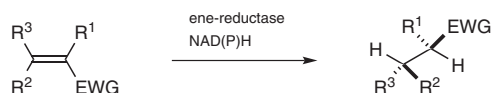
glycosyltransferases (GTases)



Keywords: transferases • alkylation • methylation • prenylation • glycosylation • phenolic compounds • C–C bond formation • natural products • Friedel–Crafts-like reactions • electrophilic aromatic substitution

2.3.1 Addition of Hydrogen to C=C Bonds: Alkene Reduction*K. Faber and M. Hall*

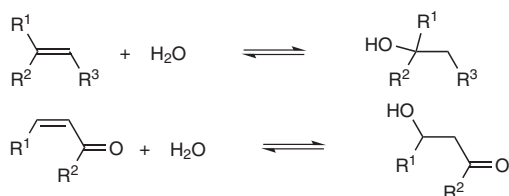
Ene-reductases are flavoproteins which catalyze the asymmetric reduction of activated alkenes at the expense of a nicotinamide cofactor. The substrate scope is broad and includes α,β -unsaturated carbonyl compounds, carboxylic acid derivatives, and nitro compounds, which upon reduction yield the corresponding saturated products in high enantioselectivity.



Keywords: asymmetric catalysis • ene reaction • enzyme catalysis • reduction • stereoselective synthesis

2.3.2 Addition of Water to C=C Bonds*V. Resch and U. Hanefeld*

While chemists struggle to find efficient methods to perform the asymmetric addition of water, nature employs countless enzymes (called hydratases or hydro-lyases) to perform this reaction using substrates with both activated and nonactivated double bonds. However, compared to the vast number of hydratases involved in metabolic pathways in nature, only a few are described for their use in organic synthesis. Nevertheless, their potential in asymmetric catalysis has been recognized and some hydratases are used on a large scale in industrial processes. Since hydratases perform the addition of water, water is used as both a solvent and a reagent, opening up a very efficient and green route to both secondary and tertiary alcohols. This chapter focuses on hydratases that catalyze interesting reactions and are tested beyond their biochemical characterization.

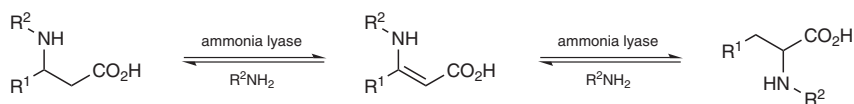


Keywords: acetylene hydratase • aconitase • carotenoid hydratases • citraconase • fumarase • hydratase • hydratase–tautomerase bifunctionality • hydro-lyase • kievitone hydratase • limonene hydratase • linalool dehydrogenase–isomerase • malease • oleate hydratase • phaseollidin hydratase • urocanase • water addition

2.3.3 Addition of Ammonia and Amines to C=C Bonds*S. Bartsch and A. Vogel*

Ammonia lyases and aminomutases catalyze the reversible, nonreductive, asymmetric amination of α,β -unsaturated carboxylic acids. They utilize ammonia and, to a lesser extent, substituted amines as substrates. The most common acceptors are fumarate and aromatic α,β -unsaturated carboxylic acids. Typical products are optically pure α -amino acids, but production of β -amino acids is also described. No cofactor recycling is required and, by using high concentrations of ammonia, conversion up to 100% can be reached

with excellent enantioselectivity. Ammonia lyases comprise a very heterogeneous group of enzymes from plants and microbes, showing diverse substrate selectivities and reaction mechanisms. The most commonly used members are the aspartate and phenylalanine ammonia lyases.



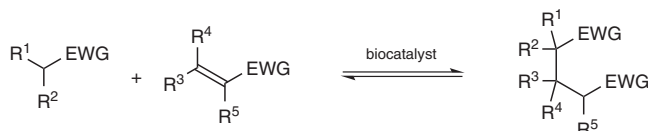
Keywords: ammonia lyase • aminomutase • nonreductive amination • α,β -unsaturated carboxylic acids • aspartase • 3-methylaspartate ammonia lyase • adenylosuccinate lyase • argininosuccinate lyase • α -amino acids • β -amino acids

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2.3.4 Enzymatic Carbon–Carbon Bond-Forming Michael-Type Additions

E. M. Geertsema and G. J. Poelarends

This chapter gives an overview of practical biocatalytic procedures for C–C bond-forming Michael(-type) additions suitable for organic synthesis purposes. Reported product yields, workup and isolation methods, stereoselectivity, and availability of the applied enzymes are assessed. All methodologies involve promiscuous enzyme activities, since natural enzyme-catalyzed C–C bond-forming Michael additions are extremely rare.



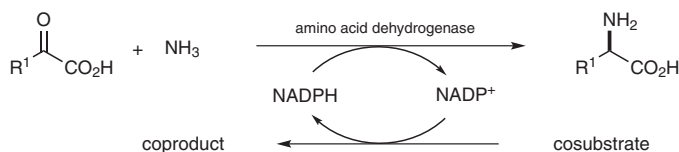
Keywords: enzyme catalysis • Michael addition • C–C bond formation • stereoselective catalysis • enantioselectivity • diastereoselectivity • enzyme promiscuity • lipase • acylase • proteinase • tautomerase

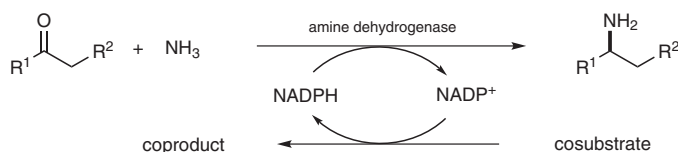
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2.4.1 Amino Acid and Amine Dehydrogenases

A. S. Bommarius and S. K. Au

α -Keto acids can be reductively aminated to α -amino acids via amino acid dehydrogenase catalysis, with NAD(P)H as cofactor. Regeneration of the oxidized cofactor NAD(P)⁺ back to NAD(P)H is required for synthesis and is commonly achieved via formate dehydrogenase catalyzed oxidation of formate to carbon dioxide or glucose dehydrogenase catalyzed oxidation of glucose to gluconic acid. Recently, amine dehydrogenases, which reductively aminate ketones to amines, have been developed via protein engineering. Both amino acid and amine dehydrogenases are exquisitely enantioselective, leading to (*S*)- or (*R*)-amino acids or (*R*)-amines.





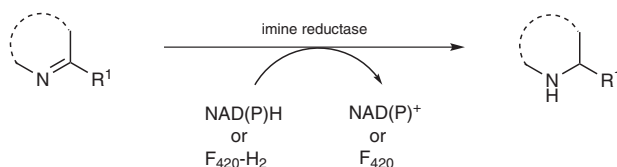
Keywords: enantioselectivity • reductive amination • keto acids • α -amino acids • ketones • amines

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2.4.2 Imine Reductases

F. Leipold, S. Hussain, S. P. France, and N. J. Turner

Imine reductases catalyze the asymmetric reduction of imines to the corresponding chiral amines. The excellent enantioselectivities achieved in these conversions make this biocatalyst an attractive addition to the toolbox for chiral amine synthesis. This chapter details recent developments in the application of different classes of imine reductases in the synthesis of chiral amines as well as amino acids.



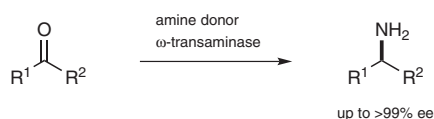
Keywords: amines • α -amino acids • imine reduction • reductive amination • tetrahydro- β -carbolines • tetrahydroisoquinolines • piperidines • pyrrolidines

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2.4.3 α -Transaminases

R. C. Simon, E. Busto, E.-M. Fischereder, C. S. Fuchs, D. Pressnitz, N. Richter, and W. Kroutil

Optically pure amines are prepared from the corresponding prochiral ketones via asymmetric amination employing ω -transaminases and selected amine donors.



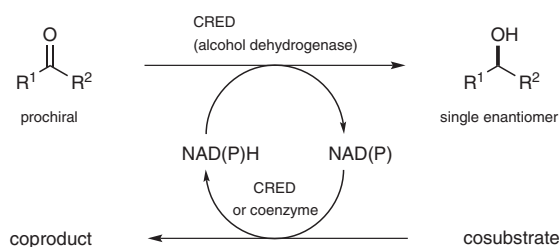
Keywords: amination • aldehydes • amines • asymmetric catalysis • ketones • ω -transaminases

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2.5.1 Ketone and Aldehyde Reduction

T. S. Moody, S. Mix, G. Brown, and D. Beecher

The modern organic chemist increasingly uses biotransformations to solve synthetic problems. In particular, stereoselective reduction of prochiral ketones using enzymes has moved from an academic curiosity to a commercial success. Bioreduction using both whole-cell microbial and recombinant systems has proven to be a robust and reliable alternative to other asymmetric chemical methods, resulting in green, economic, and scalable processes for the chemical industry. This review highlights bioreduction applications available to the modern practical chemist.



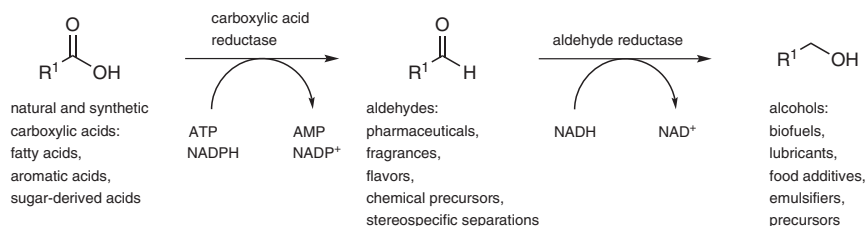
Keywords: asymmetric catalysis • alcohols • chiral compounds • green chemistry • reduction

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2.5.2 Carboxylic Acid Reductase

A. S. Lamm, P. Venkitasubramanian, and J. P. N. Rosazza

This chapter highlights the versatility of carboxylic acid reductase and its ability to efficiently catalyze the bioconversion of a wide range of natural and synthetic carboxylic acids into their corresponding aldehydes and alcohols.



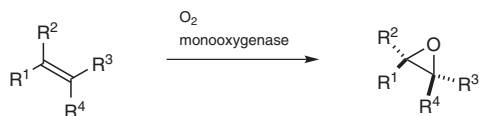
Keywords: alcohols • arylaldehyde oxidoreductase • biofuels • carboxylate reductase • carboxylic acid reductase • enzymatic reduction • fatty acids • oxidoreductase • racemate resolution

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2.6.1 Asymmetric Synthesis of Enantiopure Epoxides Using Monooxygenases

A. T. Li and Z. Li

Monooxygenases catalyze the asymmetric epoxidation of different types of alkenes, providing a green and useful method to synthesize the corresponding epoxides in high enantiomeric excess and good yield. The epoxidations catalyzed by styrene monooxygenase, xylene monooxygenase, alkane monooxygenase, alkene monooxygenase, and cytochrome P450 monooxygenase are reviewed in this chapter.

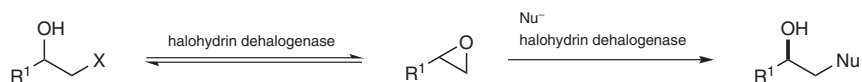


Keywords: asymmetric epoxidation • asymmetric synthesis • enzyme catalysis • monooxygenase • chiral epoxides • green oxidation

2.6.2 Reactions Catalyzed by Halohydrin Dehalogenases

M. Majerić Elenkov, W. Szymański, and D. B. Janssen

In some bacteria, halohydrin dehalogenases catalyze the conversion of vicinal halo alcohols, such as 1,3-dichloropropane or 3-chloropropane-1,2-diol, into epoxides, and thereby play a role in the biodegradation of halogenated organic compounds. In the reverse reaction, i.e. epoxide ring opening, various small anions can replace the halide, allowing the synthesis of β -substituted alcohols, including β -hydroxynitriles and β -azido alcohols. These remarkable catalytic properties have been modified by structure-based protein engineering, making the enzymes suitable for diverse applications.

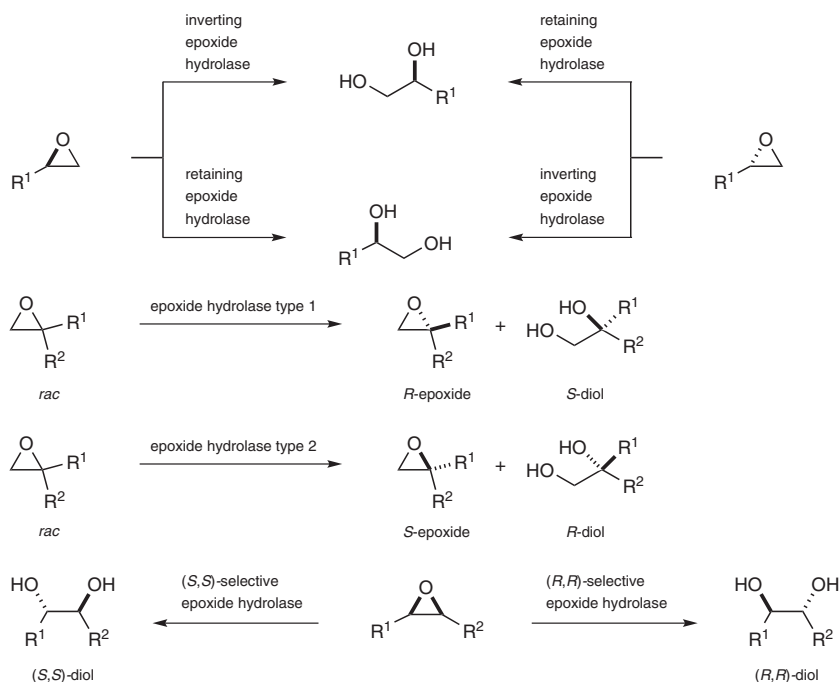


Keywords: epoxides • hydroxynitriles • microorganisms • alcohols • cyanides

2.6.3 Epoxide Hydrolysis

R. Wohlgemuth

This chapter focuses on the selective biocatalytic ring opening of epoxides by water, leading to vicinal diols or other reaction products. This strategy is also used by nature to prepare a range of important metabolites and natural products by epoxide hydrolase catalyzed ring-opening reactions. The hydrolysis of easily accessible racemic epoxides to enantiomerically pure epoxides or vicinal diols has become of increasing interest as a method for preparing a great variety of chiral intermediates for the synthesis of pharmacologically active compounds, agrochemicals, flavors and fragrances, and metabolites.



Keywords: epoxy compounds • oxiranes • epoxide hydrolase • diols • hydrolysis • resolution • ring opening