Synthesis of 1,2-Difunctionalized Fine Chemicals through Catalytic, Enantioselective Ring-Opening Reactions of Epoxides

Christoph Schneider*
Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
Fax +49(341)9736599; E-mail: schneider@chemie.uni-leipzig.de
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Dedicated to Professor Lutz F. Tietze on the occasion of his 65th birthday

Abstract: This review summarizes the development of metal- and enzyme-catalyzed, enantioselective ring-opening reactions of meso-epoxides and racemic epoxides with various hetero and carbon nucleophiles towards the synthesis of highly enantiomerically enriched 1,2-difunctionalized fine chemicals.

1 Introduction

Epoxides are among the most important classes of compounds in organic chemistry on the basis of their facile nucleophilic ring opening which takes place in an $S_N2$-pathway with inversion of configuration at the reacting carbon atom. The origin of this reactivity is the inherent ring-strain of approximately 27 kcal/mol associated with the three-membered heterocycle which provides sufficient driving force for the ring-opening event. Thus, a broad range of 1,2-difunctionalized organic compounds with two contiguous chiral centers are easily available in one step with full control of stereoselectivity.

It therefore comes as no surprise that much effort has been devoted to the enantioselective preparation of the starting epoxides and that this has furnished a number of highly useful procedures. Starting from the requisite alkenes, a diverse set of differently substituted epoxides is now synthetically available with exceptional levels of enantioselectivity in one step. Alternatively, vicinal 1,2-diol sulfates readily accessible via the Sharpless asymmetric dihydroxylation of alkenes may be employed as epoxide surrogates.

There are, however, limitations to this approach. Some alkene classes, e. g. 1-mono-substituted alkenes, still give rise to only moderate enantioselectivity with any of the currently available epoxidation procedures. Additionally, some of the most interesting chiral ring-opened products, for example with trans-cycloalkane or trans-stilbene backbones, are derived from symmetrical and hence achiral meso-epoxides to which the above-mentioned protocols do not apply. Therefore, a conceptually different approach has been developed for the synthesis of enantiomerically pure ring-opened products used as precious fine chemicals which does not rely on enantioselective epoxidation but rather on enantioselective ring-opening of either an achiral or a racemic epoxide.

Scheme 1 Enantioselective ring-opening of a meso-epoxide (A) and a racemic epoxide (B)

In the former scenario, a suitable chiral catalyst, typically a chiral Lewis acid which coordinates to the oxygen and thereby activates the epoxide towards nucleophilic attack, must differentiate between the enantiotopic carbon atoms of the meso-epoxide and direct the attack of the nucleophile selectively to one of the epoxide termini (Scheme 1). In this process of desymmetrization, a chiral product forms with two new contiguous stereogenic centers in principally up to 100% yield and typically high enantioselectivity from a cheap bulk chemical.
In the latter case, the chiral catalyst has to differentiate between two enantiomers and converts ideally just one of them to the ring-opened product and leaves the other one basically untouched. This process is a typical kinetic resolution which yields the unreacted epoxide and the ring-opened product in maximum 50% yield each.

A number of highly efficient and selective metal catalysts, as well as enzymes, have been developed for both purposes and for various nucleophiles. This review summarizes recent work in both areas – desymmetrization of meso-epoxides and kinetic resolution of racemic epoxides.\(^6\)

### 2 Desymmetrization of meso-Epoxides

#### 2.1 Azide Additions

The importance of enantioselective azidolysis of epoxides stems from the facile conversion of the 1,2-azido alcohol products into valuable, highly enantiomerically enriched 1,2-amino alcohols in just one step. After first reports from the Yamashita\(^5\) and Oguni\(^6\) groups who employed metal tartrates and titanium Schiff base complexes, respectively, as chiral Lewis acids, the breakthrough in catalytic, enantioselective azide additions to meso-epoxides came in 1992 when Nugent reported that a zirconium(IV) complex generated in situ from Zr(Ot-Bu)\(_4\) and (S,S,S)-trisopropylamine (8 mol%) catalyzed the reaction of various cyclic and acyclic meso-epoxides and trialkylsilyl azides and furnished azido silyl ethers with very good yields (Scheme 2).\(^7\) Larger trialkylsilyl azides performed more selectively than trimethylsilyl azide and the catalyst loading may be lowered to just 1–2 mol% without detrimental effects on the enantioselectivity of the reaction.

On the basis of detailed structural investigations\(^8\) the authors proposed a dimeric zirconium-trialkanolamine species as the active catalyst which showed a strong positive nonlinear effect. The kinetic analysis revealed a cooperative action of both zirconium centers in the catalytic cycle with one of them activating the epoxide as a Lewis acid and the other one delivering the azide nucleophile. Thus, this reaction constitutes one of the first examples of two-center asymmetric catalysis.

#### Scheme 2 Zirconium-trialkanolamine catalyzed azidolysis of epoxides (DMIPS = dimethylisopropylsilyl)

Jacobsen and co-workers have developed a family of chiral metal(salen) complexes for various important transformations such as epoxidation,\(^9\) Strecker,\(^10\) and 1,4-conjugate addition reactions.\(^11\) The chiral salen ligand is easily synthesized by condensation of aromatic aldehydes and trans-cyclohexane-1,2-diamine. Specifically, a chromium(III)(salen) complex \(2\) (2 mol%) was shown to catalyze the azidolysis of meso-epoxides very selectively with up to 98% ee (Scheme 3).\(^12\) Five-membered cyclic epoxides performed particularly well and the entire process may even be run without solvent. This proved to be especially advantageous for reactions in which the catalyst was reused in multiple cycles (up to 10 times). In this way, the azido silyl ether product was simply distilled off the catalyst after the reaction had reached completion, before additional epoxide and trialkylsilyl azide were added to the reaction vessel to start a new reaction cycle.

Initial production of trace amounts of chlorohydrins indicated early on that the chromium(III)(salen) chloride complex \(2\) served only as a precatalyst which was converted into the active chromium(III)(salen) azide complex \(3\) after the first catalytic cycle. The structure of complex \(3\) was later proven by spectroscopic and crystallographic means. Subsequent kinetic investigations revealed a second-order dependence of the reaction rate on the chromium(III)(salen) azide complex, suggesting again that it fulfilled a double role: activation of the epoxide as a Lewis acid, and nucleophilic delivery of the azide.

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**Biographical Sketch**

**Christoph Schneider** studied chemistry at the University of Göttingen (1984–1989) and obtained his doctoral degree in organic chemistry in the group of Prof. Tietze (1992). After postdoctoral studies in the group of Prof. David Evans (Harvard University) he returned to Göttingen and completed his habilitation from 1994 until 1998. He was visiting professor at the Universities of Szeged (Hungary), Toronto (Canada), and Saarbrücken (Germany). Since 2003 he has been full professor at the University of Leipzig. His main research activities are in the areas of stereoselective reaction development, natural product synthesis, and asymmetric catalysis.
Interestingly, it was shown that trimethylsilyl azide did not take part in the actual catalytic cycle but served only as a source for HN₃ which could be employed with comparable success in these reactions.

The finding of a dual activation mode suggested the synthesis and application of a dimeric catalyst which was expected to activate both the epoxide and the azide simultaneously. Indeed, the carefully designed dimeric catalyst 4 gave rise to a dramatic rate enhancement in the azidolysis of epoxides while comparable levels of enantioselectivity were observed (Scheme 3). Other dimeric catalysts with shorter and longer tethers between the salen ligands were also evaluated and gave rise to identical enantioselectivity but reduced rate enhancement. Significantly, whereas the monomeric chromium(III)(salen) complex displayed a positive nonlinear effect, the dimeric catalyst revealed a strict linear relationship between the ee of the catalyst and that of the product, pointing to a strictly intramolecular mode of Lewis acid and nucleophilic catalysis.

This methodology was successfully applied by the Jacobsen group to the catalytic asymmetric synthesis of a bal-
anol 515 and a prostaglandin precursor 616 as well as direct precursors 7–8 of some clinically important carbocyclic nucleoside analogues (Figure 1).17

![Synthesis of ring-opened products](image)

Some heterogenous versions of the Jacobsen asymmetric epoxide opening have been developed recently in order to devise an even more practical procedure with a simpler work-up and easier separation of reagents and reaction products. Thus, Garcia and co-workers bound various chiral chromium(salen) complexes through 3-aminopropyl tethers to functionalized silicates.18 In the model reaction of cyclohexene oxide and trimethylsilyl azide, they observed quantitative conversion to the product, which was isolated with 70% ee. Almost half of the catalyst amount, however, had leached during the reaction and was dissolved in the solvent.

Moberg and Adolfsson reported a catalyst system prepared in situ from Zr(Ot-Bu)4 and bispicolinic amides (10 mol% each) which catalyzed the azidolysis of cyclohexene oxide with trimethylsilyl azide in 60% yield and up to 71% ee (Scheme 5).19 Small amounts of diethyl amine helped to form the metal–ligand complex and increased the enantioselectivity of the reaction. The authors proposed a purely Lewis acid catalyzed mechanism and nucleophilic addition of free azide towards a Lewis acid complexed epoxide.

![Scheme 5](image)

2.2 Amine Additions

The addition of amines to meso-epoxides typically suffers from compatibility problems of the Lewis basic amine and the Lewis acid employed as chiral catalyst, which tend to coordinate irreversibly. Careful adjustment of the Lewis basic properties of the amine and the Lewis acidity of the chiral catalyst, however, furnished some highly active and enantioselective catalysts for the aminolysis of meso-epoxides.

Thus, Hou et al. developed a Yb(OTf)3–(R)-BINOL-catalyst which, in combination with a tertiary amine, catalyzed the addition of aniline to cyclohexene oxide in excellent yield and 80% ee (Scheme 6).20 The addition of the tertiary amine was crucial for the effective formation of the chiral ytterbium complex, in analogy to observations by Kobayashi in Diels–Alder reactions.21 Whereas some other anilines could be readily employed in this reaction with comparable success, the substrate scope on the epoxide part proved to be very narrow. Thus, cyclopentene oxide, cis-2-butene oxide, and cis-stilbene oxide all gave rise to low enantioselectivity in the reaction with aniline.

![Scheme 6](image)

Inaba and co-workers prepared a 2-amino-1,3,4-butanetriol building block through aminolysis of the seven-membered cyclic epoxide 9 that contained a ketal moiety. With just 1 mol% of a catalyst made from equimolar amounts of Ti(Oi-Pr)4 and (S)-BINOL, the addition of benzyl amine to this epoxide proceeded in excellent yield and enantioselectivity (Scheme 7).22 When structurally similar epoxides such as cycloheptene oxide were submitted to the same reaction conditions, the reaction did not proceed at all, again indicating a very narrow substrate scope for this procedure.

![Scheme 7](image)

In a formal total synthesis of 4-demethoxy daunomycin, Shibasaki and co-workers employed a Pr(Oi-Pr)3([R]-BINOL) complex (10 mol%) for the catalytic enantioselective addition of p-anisidine to cyclic epoxide 10 and
obtained the ring-opened amino alcohol 11 in 75% yield and 50% ee.\textsuperscript{23} The use of 30 mol% Ph$_3$P=O increased the enantioselectivity further to 65% ee; this was attributed to stabilization of the monomeric active catalyst (Scheme 8). This protocol was further applied to other more common epoxides and furnished ring-opened products in up to 53% ee.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme_8}
\caption{Pr(Oi-Pr)$_3$–(R)-BINOL-catalyzed aminolysis of epoxides\textsuperscript{23}}
\end{scheme}

The first highly enantioselective aminolysis of meso-epoxides was reported by Schneider et al. in 2004.\textsuperscript{24} They utilized a chiral scandium–bipyridine complex (10 mol%) generated in situ from equimolar amounts of scandium(III) trifluoromethanesulfonate and the chiral 2,2'-bipyridine 12 first introduced by Bolm et al.\textsuperscript{25} Aromatic meso-epoxides underwent ring-opening with anilines and O-benzylxoy amines in good yields and with 82–97% ee (Scheme 9). The catalyst loading may be lowered to 5 mol% with only marginal effects on yield and enantioselectivity. Aliphatic meso-epoxides gave rise to varying levels of enantioselectivity ranging from 54% ee to 74% ee.

A crystal structure of the related ScBr$_3$–bipyridine complex\textsuperscript{26} reveals a pentagonal-bipyramidal coordination geometry around the scandium center, with the two bipyridine nitrogen atoms and the two hydroxyl oxygen atoms bound to the central ion in the ligand plane and two bromine atoms in apical positions. The hydroxyl protons appear to be essential for obtaining high enantioselectivity, as the related scandium complex with the bis-O-methyl bipyridine ligand 13 does not give rise to any enantioselectivity in the epoxide ring-opening reaction.\textsuperscript{24}

Subsequently Kobayashi and co-workers established that just 1 mol% of a scandium–bipyridine complex with dodecyl sulfate counterions was sufficient for the aminolysis of epoxides in water, and comparable levels of enantioselectivity (up to 96% ee) were obtained as reported for the reaction run in dichloromethane (Scheme 10).\textsuperscript{27} Hydrophobic interactions were proposed to account for the extraordinarily efficient catalysis.

Very high enantioselectivities of greater than 90% ee were reported by Collin and co-workers for the aminolysis of cyclic meso-epoxides with 10 mol% of the Sm(III)(io- do)[(S)-BINOL] complex (Scheme 11).\textsuperscript{28} o-Anisidine proved to be the amine of choice and the optimal reaction temperature was –40 °C in dichloromethane, with diminished selectivity in either direction. This behavior was explained by a reaction pathway with two different enantioselectivity-determining steps and at least two different catalytic species exhibiting different enantioselectivity.
Kureshy et al.\textsuperscript{29} reported the titanium BINOLate catalyzed aminolysis of meso-epoxides with anilines furnishing the corresponding 1,2-amino alcohols in good yields and moderate enantioselectivities ranging from 39–78% ee. Only two different epoxides, cis-stilbene oxide and cyclohexene oxide, were, however, employed in this study.

### 2.3 Alcohol and Acid Additions

The first report on the catalytic, enantioselective addition of an oxygen nucelophile to a meso-epoxide came from the Jacobsen group in 1997. A cobalt(III)(salen) complex (5 mol%) catalyzed the addition of benzoic acid to a range of epoxides and furnished 1,2-diol monoesters in excellent yields and with 55–93% ee (Scheme 12).\textsuperscript{30} The addition of an equimolar amount of a tertiary amine, preferably Hünig’s base, relative to the acid had a beneficial effect on conversion and selectivity. The corresponding cobalt(II)(salen) complex \textsuperscript{14} may be conveniently used as precatalyst and is believed to be oxidized to the active cobalt(III) catalyst in situ. Only aromatic meso-epoxides, such as cis-stilbene oxide and cyclic aliphatic epoxides were ring-opened with 55–77% ee. The crystallinity of the benzoate esters, however, allowed easy enhancement of their optical purity by recrystallization. For example, cyclohexanediol monobenzoate (\textsuperscript{15}), generated in 98% yield and 77% ee, was obtained in 75% overall yield and 98% ee after a single recrystallization.

An intramolecular cyclization utilizing the same chiral catalyst was realized shortly thereafter on some meso-epoxy diols.\textsuperscript{31} In particular, cyclopentene oxide structures could be successfully ring-opened with tethered alcohol linkages to furnish various interesting bicyclic structures in excellent enantioselectivities of up to 99% ee (Scheme 13).

Shibasaki and co-workers devised a heterobimetallic chiral catalyst for the enantioselective addition of phenols to meso-epoxides.\textsuperscript{32} The lithium–gallium(BINOL) \textsuperscript{2} complex \textsuperscript{16} (20 mol%) catalyzed the addition of \( p \)-methoxyphenol to various cyclic epoxides in moderate yields and good enantioselectivities, requiring, however, very long reaction times of 72–96 hours at elevated temperatures (Scheme 14). A further refinement of ligand architecture led to the novel linked-BINOL ligand \textsuperscript{17}, which, as a mixed lithium–gallium complex, gave substantially improved rates and selectivities in the phenol addition at elevated temperatures of 60–75 °C. Thus, a broad range of cyclic epoxides were now opened with \( p \)-methoxyphenol and just 10 mol% of the modified chiral catalyst in high yields and enantioselectivities.\textsuperscript{32} Mechanistically, the reaction was proposed to proceed by dual activation of both the epoxide, through the Lewis acidic gallium, and the phenol, by deprotonation through the Brønsted base lithium binaphtholate in a tightly bound transition state.

The first catalytic, enantioselective addition of aliphatic alcohols to meso-epoxides was reported by Schneider et al. (Scheme 15).\textsuperscript{24} They employed the same scandium-bipyridine complex generated from scandium(II) trifluoromethanesulfonate and 2,2’-bipyridine \textsuperscript{12} which had...
already been successful in the aminolysis of epoxides. Thus, 1,2-diol monoethers 18 were obtained in good yields and very high enantioselectivities of up to 97% ee with a broad range of aliphatic alcohols. Although the reported results were obtained with 10 mol% of the chiral catalyst, the catalyst loading may be lowered to 2–5 mol% without significant effects on yield or enantioselectivity. The same trend as in the aminolysis of epoxides was observed here: aromatic meso-epoxides performed more selectively than aliphatic meso-epoxides which gave rise to only moderate enantioselectivity.

2.4 Thiol Additions

The first highly enantioselective addition of thiol to meso-epoxides was realized in the Shibasaki group, who employed the lithium–gallium(BINOL)_2 complex 16 (10 mol%) to open a variety of mostly cyclic epoxides with tert-butyl hydrosulfide in good yields and high enantioselectivities of up to 98% ee (Scheme 16).33 The use of bulky tert-butyl thiol was necessary to prevent undesired ligand exchange on the metal catalyst with subsequent erosion of enantioselectivity. Other thiols, such as benzyl thiol, gave significantly reduced ee values. The use of molecular sieves was advantageous to enhance the reaction rate.

The working model proposed again involves dual activation of both the epoxide and the thiol through the Lewis acidic gallium and the Brønstedt basic lithium binaphtholate, respectively, in the same catalyst molecule. In order to prove that hypothesis, the Ga(BINOL)_2 monomethyl ether complex, lacking the Brønsted base, was prepared and submitted to the epoxide-opening reaction. No significant enantioselectivity was detected in this reaction, indicating the importance of additional Brønsted base activation and close orientation of epoxide and the nucleophile.

Jacobsen and co-workers applied their chromium(salen) complex for the addition of benzyl thiol to cyclic epoxides which gave, however, only moderate levels of enantioselectivity.34 Substantial improvement was realized when dithiol 18 was employed: this underwent a double addition...
tion to two epoxide molecules, furnishing a diastereomeric mixture of $C_2$-symmetric and meso-compounds (2–3:1) from which the $C_2$-symmetric product 19 could be isolated in high enantioselectivity (Scheme 17). Subsequently, the 1,2-mercapto alcohol was revealed through reductive cleavage of the benzyl group with sodium/ammonia.

**Scheme 17**  
Cr(salen)-catalyzed thiolysis of epoxides

On the basis of precedence established by Sharpless and co-workers on the Ti(Oi-Pr)$_4$-catalyzed addition of thiols to epoxides, Hou and co-workers developed a chiral titanium(salen) complex, which on a 5 mol% level converted a limited number of meso-epoxides into the corresponding $\beta$-hydroxy sulfides in good yields and moderate enantioselectivity (Scheme 18). Dithiophosphorous acids may be employed in place of thiols. Thus, reaction of cyclohexene oxide with diethyl dithiophosphate furnished the ring-opened product 20 in 94% yield and 73% ee.

**Scheme 18**  
Ti(salen)-catalyzed thiolysis of epoxides

2.5 Selenol Additions

Zhu and co-workers reported the first catalytic, highly enantioselective addition of aryl selenols to meso-epoxides using a heterobimetallic titanium–gallium(salen) complex (Scheme 19). A broad range of aromatic, aliphatic, and cyclic epoxides were readily ring-opened with phenylselenol in typically very good yields and 72–97% ee.

**Scheme 19**  
Ti–Ga(salen)-catalyzed selenolysis of epoxides

The gallium atom was proposed to coordinate as a soft Lewis acid to the selenium atom, whereas the titanium ion, as a hard Lewis acid, would activate the epoxide. Control experiments with homobimetallic complexes, that gave rise to substantially reduced enantioselectivity, corroborated the assumption of a synergistic interplay of dual activation of substrate and reagent.

2.6 Halogen Additions

In continuation of studies on the azidolysis of epoxides (see above) Nugent developed a protocol for the bromination of epoxides which utilized the same chiral Zr(trialkanolamine) complex as catalyst and a reagent combination comprising trimethylsilyl azide (1 equiv) and allyl bromide (20 equiv). On the basis of the mechanistic model discussed above, it was proposed that the intermediate zirconium azide would react with excess allyl bromide to form a zirconium bromide which eventually transferred the bromine atom to the epoxide. The excess of allyl bromide was intended to suppress the undesired formation of the azido silyl ether product resulting from direct reaction of trimethylsilyl azide with the epoxide. Indeed, a broad range of mostly cyclic meso-epoxides were ring-opened efficiently, and the 1,2-bromohydrins were formed in good yields and enantioselectivities ranging from 84–95% ee (Scheme 20).
Instead of using a chiral Lewis acid, Denmark et al. established that chiral Lewis bases such as the phosphoramidate 21 (10 mol%) catalyzed the reaction of silicon(IV) chloride and epoxides to furnish 1,2-chlorohydrins in good yields and varying enantioselectivity (Scheme 21). The Lewis base most likely ionized silicon(IV) chloride to form a highly reactive, positively charged chiral silicon species and a nucleophilic chloride counterion which attacked the silicon-coordinated epoxide. Whereas cis-stilbene oxide gave rise to product with 87% ee in high yield, other meso-epoxides were ring-opened much less selectively.

Fu and co-workers utilized the same concept and applied planar-chiral pyridine-\(N\)-oxides 22 as Lewis bases to catalyze the addition of silicon(IV) chloride to meso-epoxides. Just 5 mol% of the chiral catalyst was sufficient for quantitative conversion, indicating powerful electron-donation from the \(N\)-oxide. Excellent enantioselectivities were obtained for aromatic epoxides, whereas aliphatic epoxides gave rise to only moderate enantioselectivity (Scheme 21).

Nakajima et al. applied chiral bisquinoline-\(N\)-oxides 23a (10 mol%) for this very reaction and obtained the 1,2-chlorohydrins in high yields and 70–90% ee. Interestingly, cyclohexene oxide gave rise to a completely unselective reaction. Subsequently, the same group employed BINAPO (23b) as chiral catalyst (10 mol%) for the addition of silicon(IV) chloride to various meso-epoxides; this improved the enantioselectivity especially for cyclic epoxides such as cyclohexene oxide (Scheme 21). Even the notoriously unreactive cyclooctene oxide could now be ring-opened in 81% yield and 50% ee after an extended period of reaction time.

Enantioselective fluorination of epoxides was achieved with chromium(III)(salen) complex 2 and KHF\(_2\)/18-crown-6 as source of fluoride. Cyclohexene oxide was converted to (R,R)-2-fluorocyclohexanol in good yield and 55% ee with stoichiometric amounts of the chiral catalyst. Better yields and enantioselectivities for a small selection of meso-epoxides were obtained with silver fluoride in refluxing acetonitrile at 50 °C which, however, again required the use of 50–100 mol% of the chiral catalyst (Scheme 22). Following this protocol, the formation of the corresponding 1,2-chlorohydrins as byproducts could be completely suppressed.

### 2.7 Cyanide Additions

The cyanide ion is an attractive carbon nucleophile due to its pronounced nucleophilicity and documented compati-
bility with a Lewis acid. The typical cyanide source employed in these reactions is either trimethylsilyl cyanide or hydrogen cyanide itself, which may, however, also be generated in situ from the former through hydrolysis.

Based upon precedence established by Oguni and co-workers about the viability of titanium Schiff base complexes as chiral catalysts, Snapper, Hoveyda, and co-workers discovered that titanium dipeptide Schiff base complexes (20 mol%) optimized in a combinatorial ligand screen furnished β-cyanohydrins in good yields and 46–86% ee (Scheme 23). The chiral ligands were easily assembled from two amino acids, a salicylaldehyde and a glycine linker on a solid support which allowed for rapid screening of a broad number of ligands. Interestingly, the chiral ligand responded very selectively to small structural variations in the epoxide. Thus, the most selective chiral ligand for the ring-opening of cyclohexene oxide was the tert-leucine–threonine-derived dipeptide ligand 24, whereas the tert-leucine–phenylalanine-based dipeptide ligand 25 gave rise to higher enantioselectivity in the ring-opening of cyclopentene oxide.

In a subsequent study, the chiral Schiff base ligands were further optimized and it was shown that the tert-leucine–threonine–glycine tripeptide 26, rather than the previously employed dipeptide Schiff bases 24 or 25, was the optimal backbone for a common chiral Schiff base ligand. Optimization for each epoxide was then achieved by small variations in the salicylaldehyde component. A set of four different meso-epoxides was then successfully ring-opened with 20 mol% of the respective titanium complex and trimethylsilyl cyanide, affording the corresponding silylated β-cyanohydrins in good yields and enantioselectivities (Scheme 24).

Jacobsen and co-workers developed a set of different YbCl3/(pybox) catalysts (10 mol%) for the reaction of meso-epoxides and trimethylsilyl cyanide that furnished the corresponding silylated β-cyanohydrins in 83–92% ee (Scheme 25). Whereas five-membered epoxides were ring-opened most selectively with the YbCl3/(t-Bu-pybox, 27) complex, other cyclic and acyclic epoxides gave best results with the YbCl3/(Ph-pybox, 28) complex. Interestingly, the absolute configuration of the products obtained with these two chiral catalysts were opposite, although the absolute configuration of the ligands was identical; this was indicative of a different coordination geometry of the two ytterbium complexes.

The ambident nature of the cyanide ion also allows, in principle, nucleophilic addition of the nitrogen terminus leading to isonitriles, though this has been only rarely observed. Zhu et al. discovered that gallium(III)(monobenzyl-BINOL) and indium(I)(monobenzyl-BINOL) complexes catalyzed the formation of β-isocyanohydrins.
from meso-epoxides and trimethylsilyl cyanide with up to 95% ee when the most selective catalyst, 29, was employed (Scheme 26). The soft Lewis acid character of the gallium(III) and indium(III) ions was put forth to rationalize the regioisomeric outcome of the reaction.

2.8 Alkylations and Reductions

The nucleophilic alkylation of epoxides with hard organometal compounds such as organolithium reagents can be accomplished under Lewis acid activation, whereas soft organometals such as organocopper reagents cleanly open epoxides without any additive.

In the context of enantioselective synthesis, Tomioka and co-workers discovered that a combination of phenyl lithium with chiral ether 30 and BF3·OBu2 provided sufficient activation to initiate the ring-opening of cyclohexene oxide (Scheme 27). The product was obtained in quantitative yield and with 47% ee. The main drawback of this approach was the necessity to use superstoichiometric amounts (>2 equiv) of the chiral ligand.

Alexakis et al. have pursued a similar concept and took advantage of the known enantiodifferentiating ability of (−)-sparteine. Thus, mixing 2 equivalents each of various aryllithiums and (−)-sparteine (31) with various cyclic meso-epoxides, and 1.5 equivalents BF3·OEt2 to activate the epoxide, furnished trans-2-arylcycloalkanols in good yields and with up to 62% ee (Scheme 27). Even the notoriously unreactive cyclooctene oxide was ring-opened in moderate yield.

The first catalytic, enantioselective phenyl addition to meso-epoxides was realized by Oguni et al. (Scheme 27). They employed 5 mol% of the chiral Schiff base 32, derived from tert-leucinol, to catalyze the addition of phenyllithium to cyclohexene oxide in 92% yield and 86% ee. Cyclopentene oxide and cis-butene oxide were ring-opened with phenyllithium according to this protocol with 78% ee and 76% ee, respectively. Other alkylolithium compounds were much less reactive and gave the products in low yields and enantioselectivities.

Zhu et al. achieved the first gallium(III)(salen)-catalyzed alkynylation of meso-epoxides with lithium alkynylides (Scheme 28). Three different cyclic epoxides were ring-opened in moderate yields and 41–55% ee; no assignment
of absolute product configuration was, however, undertaken. A novel chiral 1,4-diamine was developed as a backbone for salen ligand 33 and proved to be superior compared to the standard trans-cyclohexane-1,2-diamine.

More reactive allylic meso-epoxides were readily ring-opened with dialkyl zinc reagents when catalyzed with chiral copper complexes. Inspired by the highly enantioselective 1,4-conjugate addition of dialkyl zinc compound to enones developed by Feringa’s group, Pineschi and co-workers reported that a copper catalyst made from copper(II) trifluoromethanesulfonate and chiral phosphoramidite 33 catalyzed the ring-opening of divinyl epoxides with diethyl zinc in very good yields, high regioselectivity in favor of the SN2¢ type products and up to 97% ee (Scheme 29). Mechanistically, this reaction resembles a conjugate addition event. When a meso-vinyl diepoxide was employed, the desymmetrization reaction was not so successful and furnished the two double bond isomers in almost equal amounts and moderate enantiomeric excess.

Cyclooctatetraene monoepoxide underwent conjugate Cu(II)(phosphoramidite)-catalyzed ring-opening with dialkyl zinc reagents in good yields and enantioselectivities, furnishing interesting cyclooctatrienols 34. Oxepin, being in equilibrium with benzene oxide, was converted into a mixture of α-adduct 35 (S02) and γ-adduct 36 (S02') in good yields and 93% and 64% ee, respectively (Scheme 29).

A conceptually different approach was developed by Ganäsuer et al. based upon precedence established by Nugent et al. They ring-opened meso-epoxides through single-electron transfer from an in situ generated chiral titanium(III) reagent 37 to form an intermediate radical anion which was trapped either with a hydrogen donor or with an alkene. As precatalysts, they employed titanoocene(IV) complexes with chiral 8-phenylmenthyl residues on the cyclopentadienyl rings which were reduced in the catalytic cycle through metallic zinc to the active [Cp2TiCl] catalysts. In order to effect turnover, they added 2,4,6-collidinium hydrochloride which protonated the titanium alkoxide formed and regenerated the active catalyst. Thus, 1,4-dioxy-2,3-epoxybutane (38) was reductively ring-opened with 1,4-cyclohexadiene as hydrogen donor to furnish 2-hydroxy-1,4-dioxybutane (39) in good yield and high enantioselectivity (Scheme 30).

Net alkylation of the epoxide was achieved with acrylates added to the reaction mixture which trapped the radicals formed in a fast carbon–carbon bond-forming reaction. A small selection of cyclic meso-epoxides was thus converted into the 2-alkylated cycloalkanols 40 in good to very good overall yields and well above 80% ee. In contrast to other stereospecific ring-opening reactions of epoxides, the trans-diastereomers were not formed exclusively here, but varying amounts of the cis-diastereomers were generated as well owing to the intermediacy of the radical anion.
2.9 Rearrangements

Upon treatment with strong, non-nucleophilic lithium amide bases which abstract a proton in the β-position, epoxides may undergo rearrangement to chiral allylic alcohols.61 After suitable chiral bases had been discovered, this powerful transformation was employed in a number of synthetic applications, most importantly in the synthesis of prostaglandin precursors.62 Typically, stoichiometric amounts of a chiral base are required for this transformation and only recently have catalytic versions been developed. The greatest challenge has been to identify a suitable combination of a very strong, catalytic, chiral base, together with a stoichiometric base that is sufficiently basic to regenerate the chiral base without competing effectively for the substrate.

Asami et al. were among the first to investigate the catalytic reaction and introduced a combination of either proline-based or octahydroindol-based chiral bases (41 and 42, respectively) in 20 mol% with 1.8 equivalents of lithium diisopropylamide to regenerate the chiral base. The choice of lithium diisopropylamide as achiral, stoichiometric base proved to be essential, as other lithium dialkylamides gave rise to lower enantiomeric excesses. Thus, a small selection of meso-epoxides were ring-opened and converted into allylic alcohols in good yields and moderate to very high enantioselectivities (Scheme 31).63 Whereas in the case of 41 the additive DBU was required to achieve good enantioselectivity, 42 proved to be highly enantioselectively on its own and further additives even deteriorated the enantioselectivity.

The key to the success was the additional tertiary nitrogen atom, which upon chelation to the lithium apparently enhanced the basicity sufficiently that lithium diisopropylamide did not interfere in spite of its higher concentration. Sticking to the same general structure, an even better system was subsequently reported by Andersson and co-workers who employed the azanorbornane-derived chiral base 43 on just a 5 mol% level with lithium diisopropylamide as stoichiometric base (2 equiv) in a THF–DBU solvent system (Scheme 32).64 The beneficial effect of DBU was believed to affect the aggregation properties of the catalyst. Cyclohexene oxide was thus ring-opened to 2-cyclohexen-1-ol in 91% yield and 96% ee, which was almost the same enantioselectivity as for the stoichiometric reaction (97% ee). Other cyclic meso-epoxides were converted to the corresponding allylic alcohols in good to excellent enantioselectivity, whereas acyclic meso-epoxides gave rise to reduced ee values.

Andersson and co-workers further improved this procedure by developing the modified chiral base 44. Sticking to the azanorbornane backbone, they added an element of C₂-symmetry to the pyrrolidine appendage by using the (R,R)-2,5-dimethylpyrrolidine heterocycle instead.65 According to a transition-state model put forth by Asami et al.
al., the chirality in the pyrrolidine component enhanced the enantioselectivity exerted by the chiral azanorbornane backbone in that one of the additional methyl groups blocked the frontside in TS 45 for epoxide approach (matched combination). In the mismatched pair with the (S,S)-configured heterocycle, unfavorable steric interaction between the methyl group and the epoxide emerges. Truly spectacular levels of enantioselectivity were observed for a range of acyclic and cyclic meso-epoxides employing just 5 mol% of 44 together with 1.5 equivalents of lithium diisopropylamide and 5 equivalents of DBU in tetrahydrofuran (Scheme 32).

In the presence of organolithium compounds, the deprotonation of epoxides typically occurs at the α-position furnishing α-lithio epoxides such as 46 which can undergo various subsequent reactions. Hodgson et al. reported enantioselective α-deprotonation–transannular cyclizations of cyclooctene oxide with isopropyllithium (2.4 equiv) and (-)-sparteine (2.5 equiv) to furnish, via 46, bicyclic alcohol 47 in 86% yield and 84% ee (Scheme 33). This reaction was rendered catalytic in the chiral diamine with identical results when (-)-isopartiene (20 mol%) was employed in place of (-)-sparteine. Enantiomerically enriched bicyclic alcohols containing rings of different sizes were thus available in just one step. Functionalized cyclooctene oxides gave rise to interesting, more highly substituted bicyclic alcohols in 50–72% yield and 83–89% ee.67

When epoxides with a suitable heteroatom in the β-position were treated with RLi/(-)-sparteine combinations the α-lithio epoxides formed in situ underwent a double alkylative ring-opening to furnish unsaturated chiral diols or amino alcohols. Aza- and oxabicyclic epoxides such as 48 (X = O) or 49 (X = NBoc) proved to be particularly well suited for this kind of transformation and yielded chiral six- and seven-membered unsaturated diols and amino alcohols, respectively, in moderate to good yields and up to 87% ee (Scheme 34).68
2.10  Enzymatic Hydrolysis

Microsomal epoxide hydrolases (mEH’s) of mammalian origin have been successfully employed in hydrolyses of meso-epoxides. Belluci et al. obtained high enantioselectivities in the hydrolysis of cyclohexene oxide and cyclopentene oxide with mEH’s from rabbit liver. Various cis-stilbene oxides were also converted into the corresponding 1,2-diols with good levels of enantiocontrol. Weijers employed EH’s from the yeast Rhodotorula glutinis for the highly enantioselective hydrolysis of some cyclic and acyclic meso-epoxides, giving rise to the 1,2-diols in up to 98% ee (Scheme 35).

A breakthrough in the hydrolytic desymmetrization of meso-epoxides catalyzed by enzymes was realized in 2004 when scientists at Diversa discovered over fifty novel microbial epoxide hydrolases (EH’s) using sequence-based and activity-based high-throughput assays (Scheme 35). Although the sequence identity of the various active EH’s was low, they all shared the central aspartate residue which has been postulated as the active-site nucleophile in the initial step of the catalytic cycle.

For every given epoxide, multiple enzymes were found to catalyze the formation of the R,R-diols. Whereas cyclic meso-epoxides (five examples) were ring-opened in 81–96% ee, the hydrolysis of cis-stilbene oxides proved to be extraordinarily enantioselective, with up to 99.5% ee and turnover frequencies of up to 16.5 (TOF: mol product per mol catalyst per second). Interestingly, a number of S,S-selective EH’s was also found in the library, furnishing the corresponding diols with opposite stereochemistry in 56–99% ee. The activity of those enzymes, however, proved to be significantly lower.

In a select example, Jacobsen and Ready reported on the enantioselective hydrolysis of cyclohexene oxide catalyzed by a cyclic oligomeric cobalt(III)(salen) complex (1.5 mol%) which furnished cyclohexane-trans-1,2-diol in 98% yield and 94% ee (Scheme 36). In terms of both rate and enantioselectivity, this catalyst proved to be superior than its monomeric counterpart.

3  Kinetic Resolution of Racemic Epoxides

As mentioned in the introduction, the direct enantioselective preparation of optically highly enriched terminal epoxides remains an unsolved challenge today. Since racemic terminal epoxides are available in large quantity at low cost, an efficient kinetic resolution with a readily available chiral catalyst is an attractive alternative to the enantioselective preparation. Such a process would not only give rise to the epoxide itself, but also to a second 1,2-difunctionalized fine chemical which might be important in its own right. With vinyl epoxides being excellent
substrates for a palladium-catalyzed dynamic resolution, both enantiomers of the substrate may be ideally converted into a single enantiomeric product.

3.1 With Azides

Jacobsen and co-workers disclosed the first report on a kinetic resolution of terminal epoxides with 0.5 equivalent of trimethylsilyl azide catalyzed by typically just 2 mol% of a chromium(III)(salen) azide complex furnishing the ring-opened 1-azido-2-silyl ethers in close to the theoretical maximum of 50% yield and 89–98% ee (Scheme 37). A particularly striking example was the reaction of propylene oxide and trimethylsilyl azide, which gave rise to 49% yield and 97% ee in the product from which a selectivity factor of at least 230 was calculated. Other straight-chain epoxides proved to be excellent substrates as well, with s-values typically exceeding 100. A broad range of functional groups in the backbone of the epoxide, such as halogens, ethers, nitriles, acetals, and alkenes, was readily tolerated and gave rise to slightly diminished selectivity factors. A solvent-free protocol was developed and facilitated product isolation such that it simply required evaporation of the unreacted epoxide and vacuum distillation of the ring-opened product. The utility of this procedure was illustrated through a synthesis of the antihypertensive agent (Scheme 38). A particularly striking example was the reaction of propylene oxide and trimethylsilyl azide, which gave rise to a single enantiomeric product.

This protocol was later extended to the kinetic resolution of 2,2-disubstituted epoxides, and high selectivity factors were observed when the 2-substituents had distinctly different steric properties (Scheme 37). Here, in situ formed HN₃ (from trimethylsilyl azide and propan-2-ol) was employed instead of trimethylsilyl azide, and the corresponding 1,2-azido alcohols, as well as the recovered epoxides, were formed in close to 50% yield and exceptional enantioselectivity. This methodology was successfully applied to the enantioselective preparation of enantiopure epoxide, a key intermediate in a synthesis of taurosporin A.

3.2 With Amines, Carbamates, and Imides

Bartoli et al. employed a structurally related chromium(III)(salen) chloride complex as chiral catalyst (10 mol%) for the aminolysis of trans-stilbene oxide and related aromatic epoxides with anilines, giving rise to synthetically useful 1,2-anti-amino alcohols such as in 83–99% ee and complete regioselectivity (Scheme 38). A suitable nitrogen protecting group, such as para-methoxyphenyl, may be readily cleaved off oxidatively without affecting the stereogenic center nearby. Since the amount of the nucleophile was limited to 0.4 equivalent, the reaction was only run to maximum 40% conversion, which was beneficial to the product ee but detrimental to that of the epoxide.

The same group utilized a cobalt(III)(salen) complex previously developed by the Jacobsen group for the hydrolytic kinetic resolution of epoxides (see below) to open terminal epoxides with carbamates furnishing Boc-protected 1,2-amino alcohols in good yields and with exceptionally high enantioselectivity of >99% ee (Scheme 39). Selectivity factors were calculated to be >500 for all examples examined. This protocol was later extended to the enantioselective preparation of 5-substituted oxazolidinones, which have been shown to be valuable structural motifs of medicinally active drugs. Trost et al. discovered a palladium-catalyzed dynamic kinetic resolution of 1,3-butadiene monoepoxide with phthalimide as nucleophile (Scheme 40). The chiral palladium complex based on chiral ligand exhibited the best enantioselectivity by furnishing the unsaturated 1,2-amino alcohol in 99% yield and 98% ee in favor of the internal regioisomer. It was suggested that the alkoxide anion formed upon ring-opening of the epoxide facilitated the formation of the internal regioisomer through a hydrogen bond to the incoming nucleophile. The rapid racemization required for a dynamic process occurs via a π→σ→π isomerization of the intermediate π-allyl complexes. Using this methodology, the authors developed a practical synthesis of vinlylglycerol, vigabatrin, and ethambutol.
3.3 With Alcohols

Jacobsen and co-workers employed a cobalt(III)(salen) perfluoro tert-butoxide complex 57 for the kinetic resolution of terminal epoxides with phenols (Scheme 41). The typical catalyst loading was 2–4 mol% and the resulting α-aryloxy alcohols 58 were obtained in high yields and excellent enantioselectivities. Like in the azidolysis of epoxides, the functional group tolerance was quite high with halogen, ketone, ether, and ester moieties readily tolerated in the epoxide component. Quite interestingly, a dynamic kinetic resolution of epibromohydrin was realized with this protocol on the basis of the facile racemization of the starting epoxide. Thus, 1,2-bromohydrin 59 was obtained in 74% yield and with >99% ee.

A polymer-supported chiral cobalt(III)(salen) catalyst was subsequently developed for the purpose of an automated parallel synthesis of small libraries of 1-aryloxy-2-alcohols. When starting from epibromohydrin, the corresponding ring-opened products were further converted into pharmalogically interesting 1,2-amino alcohols and 1,2-diol monoethers.
The cooperative mode of catalysis frequently observed in metal(salen)-catalyzed ring-opening reactions of epoxides further suggested the use of cyclic oligomeric cobalt(III)(salen) complexes which contain multiple metal centers in appropriate vicinity. Accordingly, a mixture of cyclic oligomers 60 containing two to six metal centers was prepared and employed in the addition of alcohols to terminal epoxides, furnishing α-alkoxy alcohols in high enantioselectivities and yields close to 50% (Scheme 42).

With vinyl epoxides as substrates, a palladium-catalyzed dynamic kinetic resolution process via a π-allyl–palladium complex became feasible. In a total synthesis of the protease inhibitor tipranavir, Trost et al. employed a chiral palladium complex for the reaction of vinyl epoxide 61 and p-methoxybenzyl alcohol. Again, the internal regioisomer carrying a quaternary stereogenic center was obtained, in 69% yield and 98% ee (Scheme 43).

### 3.4 With Water (Hydrolytic Kinetic Resolution, HKR)

#### 3.4.1 With Chemical Catalysts

In continuation of their efforts in the area of asymmetric epoxide-opening reactions, Jacobsen and co-workers discovered that the cobalt(III)(salen) acetate complex 62 was capable of catalyzing a highly enantioselective and efficient hydrolysis of epoxides to furnish valuable enantiomerically pure terminal epoxides and 1,2-diols in yields approaching 50% each. To access the epoxides, the procedure simply involves mixing the racemic epoxide with 0.55 equivalent of water and typically 0.2–0.8 mol% of the catalyst with no other solvent required (Scheme 44). For more functionalized epoxides, tetrahydrofuran was added as cosolvent [1:1 (v/v) with respect to the epoxide]. Subsequently, it was discovered that the corresponding cobalt(III)(salen) tosylate complex 63 was even more reactive, giving rise to similar results at significantly lower catalyst loadings of down to 0.05 mol%. A broad range of sterically and electronically different epoxides can thus be resolved in >99% ee and yields of typically 40–45% making this process the method of choice.
for the preparation of enantiomerically pure terminal epoxides as may be judged from a number of applications in complex natural product syntheses. Selectivity factors were measured at 20% conversion and were generally above 50, and in select examples even higher than 200. The reaction follows a second-order dependence on the cobalt catalyst, suggesting a cooperative bimetallic mechanism with the catalyst serving as both nucleophilic and Lewis acidic components, as has been observed in other metal(salen)-catalyzed processes (see above).

The operational simplicity is indeed noteworthy: stirring the reactants and the catalyst for a certain period of time at room temperature and successive distillation of first the volatile epoxide and then the 1,2-diol yields the desired products and leaves the reduced cobalt(II)(salen) complex as a residue which can be recycled by oxidation with air and acetic acid. Following this procedure, up to six cycles have been performed with yields and ee values for the product being identical to the results with fresh catalysts.

Enantioselective preparation of 1,2-diols via the HKR of terminal epoxides

If enantiopure 1,2-diols are the products of interest, the amount of water used in this HKR is reduced to 0.45 mol% level which gave rise to the enantiopure epoxide (>98% ee) at 50% conversion (Scheme 45). The control experiment with the monomeric cobalt(III)(salen) complex did not give rise to any conversion, documenting the catalytic efficiency of the dendrimeric catalyst.

A number of other reports have appeared recently which deal with modifications of the original procedure in order to devise even more practical or enantioselective processes.

3.4.2 With Enzymes

A variety of different enzymes have been discovered that are capable of catalyzing an enantioselective hydrolysis of racemic epoxides. Such epoxide hydrolases (EH’s) are obtained from various sources such as bacteria, yeast, fungi, plants, insects and mammals. These cofactor-independent enzymes, which are catalytically active even in the presence of organic solvents, are typically not isolated and purified, but used in culture medium, as whole cells or lyophilized whole cells. EH’s from microbial sources are more easily accessible in large quantities using conventional fermentation techniques, as opposed to mammalian enzymes; this makes microbial EH’s the enzymes of choice, especially for large-scale applications.

The rationale for how these enzymes actually work is based on crystallographic data for an EH from Agrobacterium radiobacter AD1, and appears to be similar in mammalian and fungal EH’s (Scheme 46). In the active site of this enzyme, the epoxide is positioned in close proximity to two tyrosine hydroxyl groups (Tyr152 and Tyr215) and two aspartate (Asp107 and Asp246) and one histidine (His275) residue. The tyrosine hydroxyl groups are believed to act as proton donors for the activation of the epoxide that is attacked by nucleophilic Asp107 to form the α-hydroxy ester intermediate 65. In a second step, this intermediate is hydrolyzed by one molecule of water which is, itself, directed and activated by the histidine residue to release the 1,2-diol product and restore the active site of the enzyme.

Faber and co-workers discovered that bacterial EH’s from Rhodococcus sp. proved to be particularly well suited for the kinetic resolution of 1,1-disubstituted epoxides with selectivity factors well above 100, furnishing differentially substituted enantiopure epoxides in good yields (Scheme 47). The substrate scope was quite narrow as only methyl-alkyl epoxides were resolved efficiently whereas ethyl-alkyl and higher analogues failed to give high selectivity factors.

EH’s from Nocardia sp. also efficiently resolve 1,1-disubstituted epoxides (Scheme 47). This process was successfully applied to the large-scale and enantioconvergent preparation of the (S)-2-methyl-3-phenyl-1,2-propanediol which was further converted into (R)-mevalonolactone (68) (Scheme 48). The enzymatic hydrolysis that took place at the terminal site and proceeded under retention of configuration was succeeded by an acidic hydrolysis at
the internal site with inversion of configuration. Thus, diol 67 was obtained in 94% yield and 94% ee from a racemic mixture. A similar phenomenon of enantioconvergence was observed in the Nocardia EH1-catalyzed hydrolysis of rac-cis-2,3-epoxyheptane (69a,b), furnishing diol 70 in 79% isolated yield and 91% ee. Careful kinetic analysis of the reaction with isotope-labeled water revealed that 69b was the fast-reacting enantiomer and that the enzyme-catalyzed hydrolysis preferentially occurred at the S-configured carbon atom in both cases (C-3 in 69a and C-2 in 69b).94

Recombinant EH’s from Agrobacterium radiobacter AD1, which have been overexpressed in E. coli, performed very well for styrene oxides and phenyl glycidyl ether, with selectivity factors exceeding 100.95 Thus, a selection of styrene oxides were synthetically available in >99% ee and moderate to good yields (Figure 3).

Scheme 45  Dendrimeric Co(III)(salen) complex 64 for hydrolytic kinetic resolution87

Figure 3  Enzymatic hydrolysis of epoxides with recombinant EH’s95

The most important classes of EH’s have been collected from fungal and yeast origins. Furstoss et al. identified the fungus Aspergillus niger as a particularly good source of epoxide hydrolases which readily resolve a number of terminal epoxides such as styrene oxides, heteroaromatic ep-
oxides, and functionalized 1,2-epoxy alkanes with moderate to good selectivity factors approaching or sometimes exceeding 100. They typically used lyophilized enzyme preparations which have been obtained after concentration and desalting. Figure 4 compiles some terminal epoxides and 1,2-diols resolved by this method.96–98 Some of these procedures have been applied in syntheses of biologically active compounds such as the anti-inflammatory agent (S)-ibuprofen (71)97 and the neuroprotective agent (R)-eliprodil (72) (Scheme 49). Interestingly, in the latter example a sequential use of two EH’s from Aspergillus niger and from Solanum tuberosum afforded the R-diol 73, in a total yield of 93% with 96% ee, which was further converted into (R)-eliprodil. Here, the A. niger EH-catalyzed reaction occurred at the terminal position of the R-epoxide with retention of configuration, whereas S. tuberosum selectively hydrolyzed the S-epoxide via attack at the internal site with inversion of configuration. A similar case of opposite regio- and enantioselectivity was reported for EH’s from Aspergillus niger and Beauveria sulfurescens. A simultaneous application of these two EH’s was shown to convert rac-styrene oxide, within two hours, to R-diol 74 in 92% yield and 89% ee (Scheme 49).99

Reetz et al. have developed two strategies to improve the enantioselectivity of EH from Aspergillus niger. Directed evolution through error-prone polymerase chain reactions furnished enzyme mutants with slightly higher selectivity factors than the wild-type enzyme (s = 10.8 vs. 4.6) and mutation sites far away from the binding pocket of the enzyme.100 Much more successful, however, was another approach. Based on the exact three-dimensional structure of the enzyme, various amino acids in the vicinity of the active site were randomized simultaneously to furnish small, but focussed, libraries of mutants around the binding pocket in a process called combinatorial active site saturation test (CAST). Using just five rounds of CASTing improved the selectivity factor of Aspergillus niger

Scheme 46 Schematic model for EH-catalyzed hydrolysis of epoxides91

Scheme 47 Rhodococcus sp. EH-catalyzed hydrolytic kinetic resolution of 1,1-disubstituted epoxides92

Scheme 48 Enantioconvergent epoxide hydrolyses93,94
EH in the HKR of glycidyl ether 75 from s = 4.6 to s = 115 (Scheme 50).101

EH’s from the yeast Rhodotorula glutinis have been investigated by Weijers et al. and were shown to exhibit moderate to excellent enantioselectivity towards various terminal and 1,2-trans-disubstituted epoxides (Figure 5). As a selected example for trisubstituted epoxides, limonene oxide was successfully resolved in excellent yield and enantioselectivity.71,102

Scheme 49 Enantioconvergent HKR of styrene oxides with two different EH’s98,99

![Scheme 49](Image)

Scheme 50 Aspergillus niger EH-mutant-catalyzed HKR of glycidyl ether100,101

### 3.5 Enzyme-Catalyzed Addition of Halides and Pseudohalides to Epoxides

Haloalcohol dehalogenases (also called halohydrin dehalogenases) catalyze the reversible dehalogenation of 1,2-halohydrins to form epoxides. From the standpoint of an organic chemist, however, the reverse reaction, the enantioselective ring-opening of an epoxide with a halide or pseudo halide anion such as azide, cyanide, or nitrite, is much more intriguing and constitutes an excellent method to furnish enantiopure 1,2-halohydrins, 1,2-azido alcohols, 1,2-cyano alcohols, and 1,2-nitro alcohols, respectively, from racemic epoxides through a kinetic resolution process.103

Janssen and co-workers have pursued this strategy for the highly enantioselective conversion of styrene oxides into the corresponding 1,2-azido alcohols catalyzed with a recombinant haloalcohol dehalogenase from Agrobacterium radiobacter AD1 (Hhe C) and additional NaN₃.104 Racemic para-nitrostyrene oxide (75) was highly regio- and enantioselectively resolved and gave rise to 1,2-azido alcohol 76 in 96% ee and the epoxide in >99% ee, from which a selectivity factor of s > 200 was calculated.
Catalytic, Enantioselective Ring-Opening Reactions of Epoxides

3.6 With Carbon Nucleophiles

Pineschi, Feringa, and co-workers investigated the copper phosphoramidite catalyzed reaction of cyclic vinyl epoxides 77 with dialkyl zinc reagents (0.50 equiv). The product cycloalkenols 78 were obtained mainly through an \( \text{anti-SN}2' \) mechanism in 12–38% yield with 50–96% ee (Scheme 52). The enantioselectivity strongly depended upon the ring-size with six- and seven-membered rings, giving rise to higher ee values than did the five-membered rings. In a subsequent study, the authors showed that alkynyl epoxides were also good substrates for the ring-opening with dialkyl zinc reagents. \( \text{anti-\( \alpha \)-Allenic alcohols} 79 \) were obtained in good yields as single diastereomers and with up to 38% ee.

\( \text{Scheme 52} \) Copper phosphoramidite catalyzed reaction of unsaturated epoxides with dialkylzinc reagents

When the same catalyst was applied to the ring-opening of racemic exo-methylene cyclohexene oxide 80 with dialkyl zinc reagents, complete conversion was observed and two regioisomers, 81 and 82, were formed in roughly equal amounts, each with excellent enantioselectivity (Scheme 52). Apparently, the regioisomers were derived from opposite enantiomers, indicating that the chiral catalyst had induced a highly enantioselective and regiodivergent reaction.

\( \text{Scheme 51} \) Haloalcohol dehydrogenase (Hhe C)-catalyzed ring-opening of epoxides

(Scheme 51). The high \( \beta \)-regioselectivity was remarkable and stands in contrast to most other ring-opening reactions involving styrene oxides.

Other pseudohalides that inhibited the ring-closure reaction were tested in the reaction with 75 and were readily accepted as nucleophiles by the haloalcohol dehalogenase. In reactions with sodium cyanide and sodium nitrite as nucleophiles, (S)-75 was obtained in >90% ee at approximately 50% conversion, whereby good selectivity factors of up to 105 were calculated. Crystallographic structures of the haloalcohol dehydrogenase in complex with a halo alcohol mimic (for the forward reaction) and para-nitrostyrene oxide (75) (for the reverse reaction) have been obtained, and shed light on the enzyme mechanism involving a Ser132-Tyr145-Arg149 catalytic triad and on the origin of the enantioselectivity.

Janssen and co-workers were recently able to extend the Hhe C-catalyzed cyanide addition to a broad range of 1-monalkyl- and 1,1-dialkyl-substituted epoxides (Scheme 51). Two more haloalcohol dehydrogenases, which they obtained from \( \text{Arthrobacter AD2 (Hhe A)} \) and \( \text{Mycobacterium GP1 (Hhe B)} \), displayed only low enantioselectivity, while Hhe C efficiently resolved various terminal epoxides with high enantioselectivity.
2-Methylindole (82) has been successfully employed as carbon nucleophile in a kinetic resolution of various racemic cis- and trans-epoxides with chromium(III)(salen) complexes as catalysts (5 mol%). When the ring-opened compounds were to be obtained in high enantioselectivity, three equivalents of the starting epoxides were employed in order to keep the conversion well below 50%. On the other hand, the starting epoxides were isolated in >99% ee with 0.60 equivalent or more of 2-methylindole (Scheme 53)\textsuperscript{111}

![Scheme 53](image)

### 4 Conclusion

The catalytic, enantioselective ring-opening of epoxides with carbon and heteronucleophiles has been developed into a highly useful method for the synthesis of enantiomerically highly enriched, valuable 1,2-difunctionalized fine chemicals such as 1,2-amino alcohols, 1,2-diols, 1,2-mercapto alcohols, and 1,2-haloethyls. Both chemical and biological catalysts are employed with great success, either in the desymmetrization of meso-epoxides or in the kinetic resolution of racemic epoxides. The amount of chiral catalyst required is frequently in the 2–5 mol% range and the products are obtained in >95% ee in many cases. There is, however, much room for improvement, as many processes described in this review have either specific substrate scope or still require unacceptably high catalyst loadings. The near future will certainly see further advances in the field of asymmetric ring-opening of epoxides.

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### References
