

Oxidations

8.1 Introduction and scope

Some of the most effective and commonly used techniques in asymmetric synthesis utilize oxidation reactions, especially epoxidation and (increasingly) dihydroxylation reactions. The reasons for this begin with the general utility of the products in organic synthesis. Because of ring strain, epoxides are excellent partners for substitution reactions by a very wide variety of nucleophiles. Epoxides can also be readily converted to allylic alcohols by elimination or ketones by rearrangement. Although less important historically, the chemistry of 1,2-diols (as obtained by hydration of epoxides or directly by dihydroxylation) has received more and more attention, largely driven by the increasing availability of simple enantioselective methods for their synthesis.

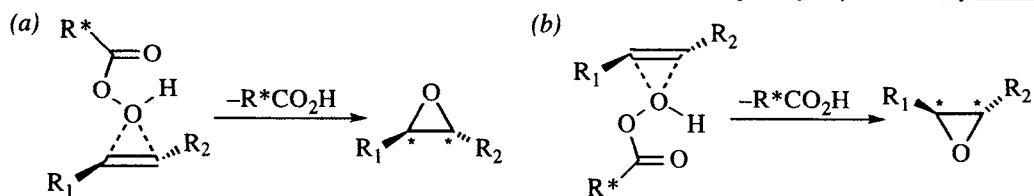
Some of the most pertinent virtues of asymmetric epoxidations and dihydroxylations were already present in their classical versions. Both reactions are highly chemo-selective and can be carried out in the presence of many other functional groups. More important with respect to stereochemistry, each reaction is stereospecific in that the product faithfully reflects the *E* or *Z* configuration of the starting olefin (the nucleophilic epoxidation of α,β -unsaturated carbonyl compounds is an important exception). And one should not underestimate the importance of experimental simplicity: in most cases, one can carry out these reactions by simply adding the often commercially available reagents to a substrate in solvent, without extravagant precautions to avoid moisture or air.

This chapter summarizes several types of asymmetric oxidation reactions. Since most of these reactions have been thoroughly reviewed, coverage is selective. Once again, the emphasis is on utility and rationales of stereoselectivity.

8.2 Epoxidations and related reactions

8.2.1 Early approaches and relevant issues of diastereoselectivity

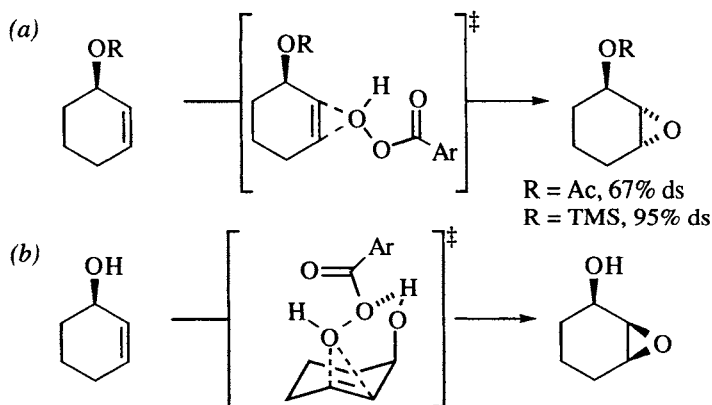
Most early approaches to the incorporation of enantioselectivity into oxidation chemistry utilized straightforward chiral variants of the peracids so popular in standard epoxidation reactions; the essential aspects of this work have been summarized [1]. The main difficulties arose from the nature of the transition state in peracid-mediated epoxidations, as illustrated for a simple *trans* alkene (Scheme 8.1). Regardless of the size differential of the ligands in a chiral peracid $R^*-\text{CO}_3\text{H}$, the stereogenic center(s) on R^* are too far away from the developing stereogenic centers in the epoxide to exert much influence between the two possible transition structures shown in Scheme 8.1. This is true whether the transition structure has the peracid functional group and the developing epoxide in a plane (the butterfly arrangement, shown) or within planes perpendicular to each other (the spiro arrangement). Clearly,



Scheme 8.1. Generalized illustration of epoxidation of a *trans*-alkene using a chiral peracid; R^* = a generic chiral substituent (in early work, monoperoxycamphoric acid was often used).

a transition state in which the chirality in the reagent is closer to the reacting olefin is required.

An important clue as to how this could be done came from work done by Henbest and coworkers [2]. This group compared the diastereoselectivity of peracid oxidation reactions of 3-hydroxy and 3-acyloxycyclohex-2-enes (Scheme 8.2). When the alcohol was capped by an acetate group, the *trans* addition product predominated. Better selectivity was later obtained by placing a larger trimethylsilyl group on the allylic alcohol [3]. In both cases, the source of the selectivity could be ascribed to the approach of the reagent from the least hindered side of the molecule (*anti* to OR); put another way, the approach from one face was slowed relative to the other (Scheme 8.2a).

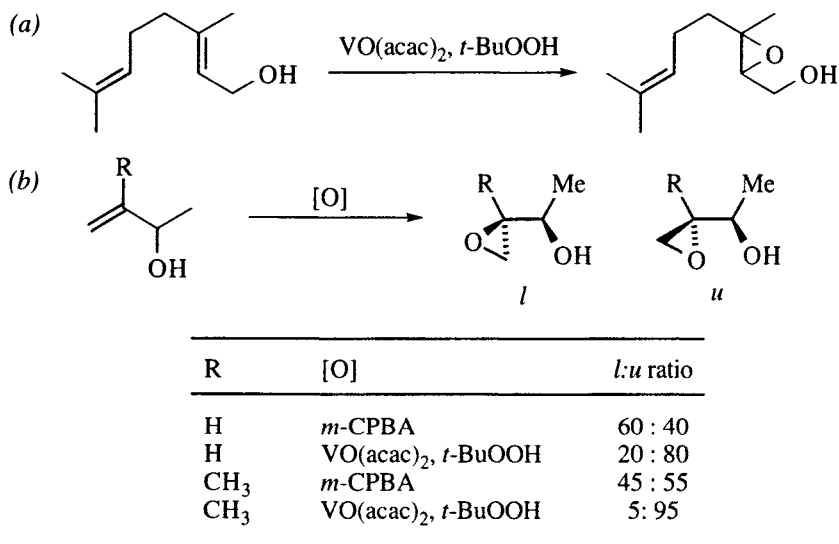


Scheme 8.2. (a) Addition of *m*-CPBA from the face opposite to the allylic acyloxy or trimethylsilyloxy ligand. (b) Proposed delivery of peracid to the β -face of the substrate mediated by the allylic alcohol group. Other modes of hydrogen bonding have been proposed for this type of reagent delivery [4,5].

In contrast, attack was found to occur *syn* to an allylic hydroxy group; obviously, simple steric effects do not account for this result. Instead, it appears that the alcohol is hydrogen bonded to the peracid in the transition state. One possible transition structure for this is shown in Scheme 8.2b; note that the allylic alcohol must occupy a pseudoaxial position to “deliver” the reagent to the olefin. In addition to this stereochemical feature, such an intrasupramolecular delivery of reagent might be expected to lower the activation barrier of the reaction due to favorable entropic considerations. Thus, rather than achieving selectivity by blocking an unfavorable path relative to an achiral model system, one might effect facial selectivity by

enhancing the rate of attack from one face relative to the other. Similar directing effects have been observed in a wide variety of oxidations [6] and other reactions [7].

This idea was later extended by Sharpless and his group to include epoxidation reactions mediated by transition metals, notably those based on vanadium [5]. More than any other system, these diastereoselective epoxidation reactions laid the groundwork for the development of the first truly catalytic asymmetric epoxidation reactions. Thus, soluble metal complexes such as $\text{VO}(\text{acac})_2$ react with simple organic peroxides, such as *tert*-butylhydroperoxide, to form a potent oxidizing system in situ. However, an allylic alcohol is *essential* for the oxidation reaction to proceed: isolated alkenes do not react under similar conditions. Accordingly, a mechanism involving intimate contact between all three components of the reaction around the transition metal was proposed. The various components of the oxidizing system seemed to be close to the reacting olefin in the transition state, as reflected in higher diastereoselectivities relative to peracid oxidations. Some outstanding results were obtained; several chemo- and stereoselective examples are depicted in Scheme 8.3 [5].



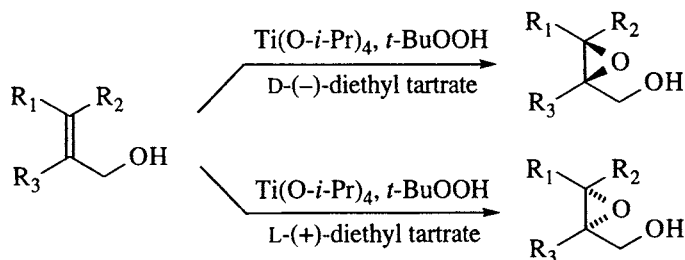
Scheme 8.3. Some examples of V^{+5} -mediated reactions of allylic alcohols with *t*-BuOOH. (a) A chemoselective reaction [8]. (b) Stereoselective reactions of acyclic allylic alcohols, compared to results obtained using *m*-CPBA [9]. Note that better selectivity is usually obtained using the metal-based oxidation system, but not always with the same relative topicity as observed using a peracid.

The requirement for coordination of an allylic alcohol to the metal and the lack of epoxidation by *t*-BuOOH in the absence of metal guaranteed a potent rate acceleration for suitable substrates. In addition, this phenomenon allowed the very useful chemoselective differentiation between allylic alcohols and unsubstituted olefins. These experiments set the stage for the development of an efficient asymmetric epoxidation reaction.

8.2.2 Epoxidations

Katsuki–Sharpless asymmetric epoxidation. Since its introduction in 1980 [10], the Katsuki–Sharpless asymmetric epoxidation (AE) reaction of allylic alcohols has been one of the most popular methods in asymmetric synthesis ([11–14]). In this work, the metal-catalyzed epoxidation of allylic alcohols described in the previous section was rendered asymmetric by switching from vanadium catalysts to titanium ones and by the addition of various tartrate esters as chiral ligands. Although subject to some technical improvements (most notably the addition of molecular sieves, which allowed the use of catalytic amounts of the titanium–tartrate complex), this recipe has persisted to this writing.

In general, the reaction accomplishes the efficient asymmetric synthesis of hydroxymethyl epoxides from allylic alcohols (Scheme 8.4). Operationally, the catalyst is prepared by dissolving titanium isopropoxide, diethyl or diisopropyl tartrate (DET or DIPT, respectively), and molecular sieves in CH_2Cl_2 at $-20\text{ }^\circ\text{C}$, followed by addition of the allylic alcohol or $t\text{-BuOOH}$. After a brief waiting period (presumably to allow the ligand equilibration to occur on titanium), the final component of the reaction is added.

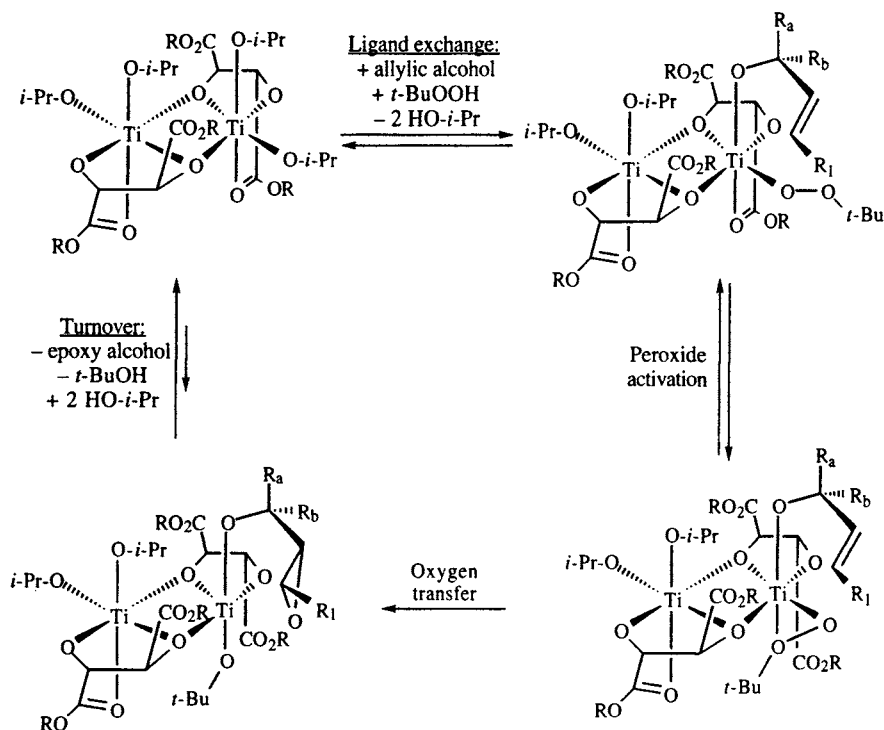


Scheme 8.4. The asymmetric epoxidation reaction of allylic alcohols. As usually carried out in CH_2Cl_2 at $-20\text{ }^\circ\text{C}$, the reaction generally affords the product epoxides in excellent yields (>70%) and enantioselectivities (>95%). In addition, the reaction is predictable with respect to the predominant enantiomer obtained according to the above scheme.

The virtues of the AE are obvious. In each case, the components are commercially available at reasonable cost. The availability of tartrate esters in both enantiomeric forms is especially fortunate, allowing the synthesis of either enantiomer of a desired product. A key feature in this regard is the predictability of the process; no exceptions to the trend shown in Scheme 8.4 have been noted in reactions using achiral substrates. And the simplicity of standard epoxidation reactions has been effectively retained, especially considering that the chiral catalyst system is prepared *in situ*.

A simplified version of the mechanism proposed by Sharpless is given in Scheme 8.5. Early work on the mechanism of this useful and important reaction has been reviewed [11], and references to more recent mechanistic studies have been collected [13]. To date, evidence in support of this mechanism has included extensive kinetic studies, spectroscopy, and molecular weight determinations [15,16].¹

¹ An alternative mechanism involving a monomeric complex has also appeared [17].



Scheme 8.5. Proposed mechanism for the Sharpless asymmetric epoxidation reaction of allylic alcohols, shown here for a simple *trans*-allylic alcohol. For the AE reaction, $R_a = R_b = \text{H}$. When one (or occasionally both) of these substituents are alkyl groups, the Scheme pertains to the kinetic resolution sequence described in the next section.

A very important aspect of this mechanism is not shown in the scheme. This is the formation of the titanium–tartrate species from its commercially available precursors, $\text{Ti}(\text{O-}i\text{-Pr})_4$ and the dialkyl tartrate. The equilibrium in this step lies far toward the formation of the chiral complex formed; this is critical because the enantioselectivity of the process depends on the absence of any active *achiral* catalyst. Note that the complex as drawn (in the upper left of Scheme 8.5) is dimeric and has a C_2 axis of symmetry. This structure has not been isolated in the solid state, but is based in part on an X-ray structure of a related tartramide complex [18]. The situation is undoubtedly complicated by dynamic equilibria between this form and other species in solution.

Without specifying the order of events, two isopropoxide ligands must be replaced by one molecule of peroxide and one molecule of allylic alcohol to give the species shown in the upper right of Scheme 8.5 (recall that, in reality, the peroxide and allylic alcohol are added at different times). The ease of such ligand exchange reactions in these titanium complexes largely accounts for their utility here. The other function of the titanium is to activate the distal oxygen of the peroxide for transfer.

At this point (lower right of Scheme 8.5), the complex is fully loaded and ready for oxygen transfer to the alkene. In this mechanism, the allylic alcohol occupies a position *cis* to the reactive peroxide oxygen. In the AE reaction ($R_a = R_b = \text{H}$), the diastereofacial selectivity of the olefin in the complex results from the avoidance of

the allylic carbon and a carboxylic ester (Figure 8.1b). After oxygen transfer, the final step is the exchange of the reaction products, epoxy alcohol and *t*-BuOH, with other ligands to give either the starting complex or some other species on the way to the loaded catalyst. The importance of turnover must not be underappreciated, for without it one may have a reagent but never a catalyst.

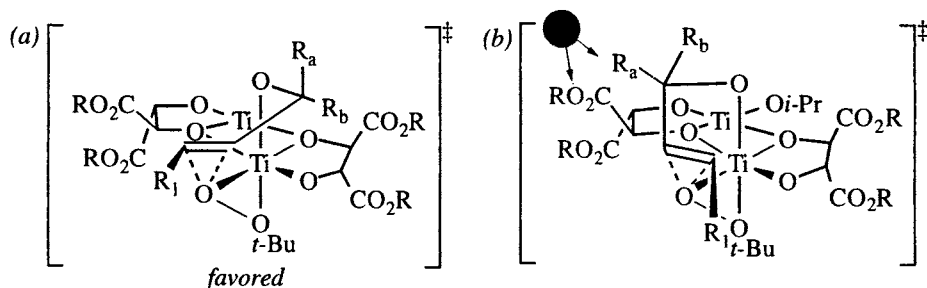


Figure 8.1. Proposed steric interactions leading to enantioselectivity in the Sharpless AE reaction.

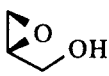
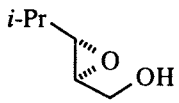
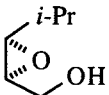
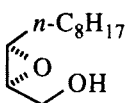
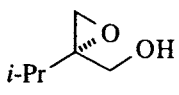
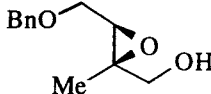
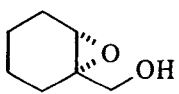
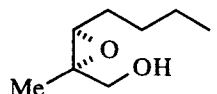
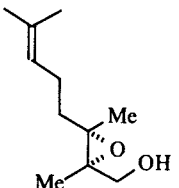
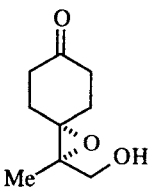
This model is consistent with much that is known about the scope of the Sharpless AE. The most common and best-behaved substrates are simple *trans*-allylic alcohols; their reactions are generally fast and reliably give products with very good enantioselectivity (>95% es). Inspection of the loaded complex in Figure 8.1 might suggest that substrates with an alkyl group *cis* to the hydroxymethyl substituent (*i.e.*, where R₂ ≠ H in Scheme 8.4) may be less stable due to steric interactions with the main portion of the catalyst. Indeed, such compounds are the slowest-reacting and subject to the most variation in enantioselectivity. However, there are examples of excellent results using alkenes of every conceivable type, although some work may need to be invested in optimizing reaction conditions (Table 8.1).

AE reactions of simple olefins. The Sharpless AE reaction has been supplemented by other approaches to asymmetric epoxide synthesis; the most evident goal being to obviate the need for an allylic alcohol. Attempts to carry out asymmetric epoxidation reactions on simple olefins have utilized transition-metal-containing catalysts such as porphyrins as well as stoichiometric chiral reagents (peroxides, dioxiranes, and oxaziridines). These approaches have been summarized [19].

The most promising procedure so far was introduced by Jacobsen and coworkers in 1990 [20] and has been reviewed [19]. The method uses chiral, C₂-symmetric (salen)Mn complexes, such as shown in Scheme 8.6. Such materials are very easily prepared by the condensation of a chiral diamine with a substituted salicylaldehyde, followed by coordination of the metal. The ready availability of both components and the swift synthesis of the target complexes permits easy access to a great many catalyst variations, which facilitates reaction optimization. The starting Mn(III) complex is subjected to *in situ* oxidation with the stoichiometric oxidant, usually NaOCl (bleach!). The use of this inexpensive and relatively safe oxidant is another virtue of this system.

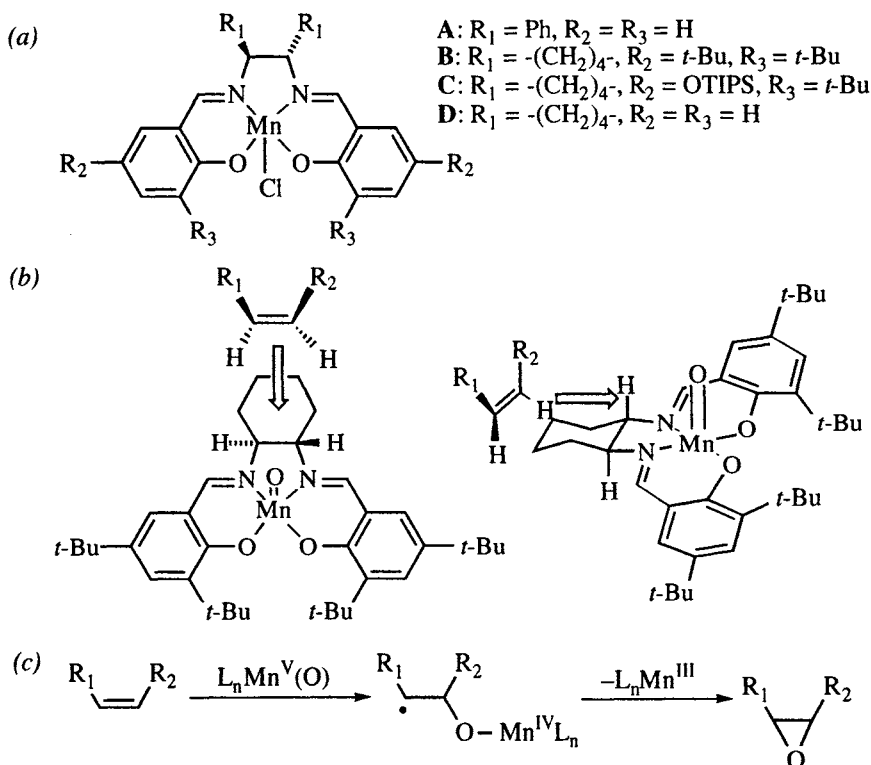
Although some outstanding results have been obtained, there are some limitations to the scope of this process (see examples in Table 8.2). The reaction works best with *cis*-olefins, in contrast to the situation with the Sharpless reaction. This can be accommodated with a side-on approach of reagent to the catalyst system, as depicted

Table 8.1. Examples of Sharpless AE Reactions. These reactions were carried out under catalytic conditions (<10 mol % of $\text{Ti}(\text{OR})_4$ and tartrate), except for entry 8 (done using stoichiometric catalyst).

Entry	Product	Tartrate	% Yield	% es	Ref.
1		(-)-DIPT	50-60	94-96	[21]
2		(+)-DET	85	97	[21]
3		(+)-DET	54	83	[22]
4		(+)-DIPT	63	>90	[21]
5		(+)-DET	88	97	[21]
6		(-)-DIPT	87	95	[23]
7		(+)-DET	77	96	[21]
8		(+)-DET	80	94	[10]
9		(+)-DET	95	95	[21]
10		(+)-DET	<i>not reported</i>	>95	[24]

in Scheme 8.6b. However, differences in catalyst structure can lead to reversal of the sense of selectivity. This observation has been attributed to attack from different sides of the complex [25].

The reaction affords the highest selectivities with conjugated, preferentially cyclic olefins. Acyclic *cis* olefins are subject to various amounts of isomerization, one observation that led to the radical mechanism proposed (Scheme 8.6c). This isomerization can be facilitated by the addition of chiral quaternary ammonium salts, leading to synthetically useful (>10:1 *trans*:*cis*, >80% ee) conversions of *cis* olefins to *trans*-dialkyl epoxides (*cf.* entries 2 and 3 in Table 8.2) [26]. Further improvements have resulted in a substantial broadening of this profile, obtaining some good-to-excellent selectivities from styrene [27] and tri- and tetra-substituted olefins that are not subject to isomerization (either due to symmetry or by constraining the double bond in a ring) [28,29].



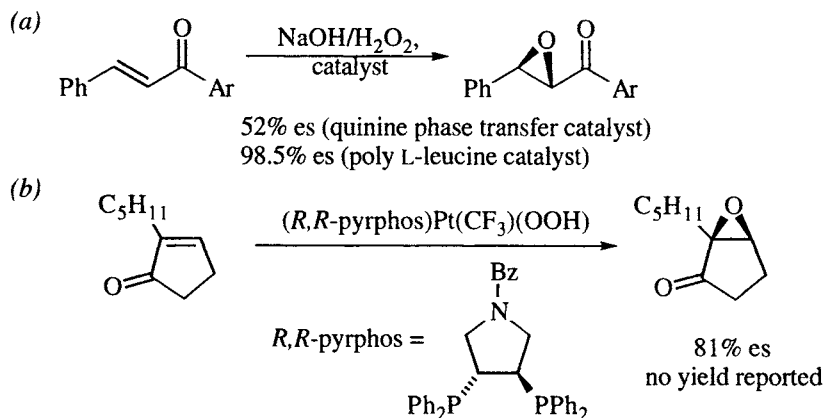
Scheme 8.6. Jacobsen's approach to epoxidation of simple olefins. (a) A few examples of (salen)Mn(III) epoxidation catalysts prior to reaction with NaOCl. (b) Two views of the proposed side-on approach of a generic *cis* olefin to the loaded catalyst. Different approach vectors have been proposed depending on the catalyst structure [25]. (c) Proposed stepwise mechanism of the reaction [26].

In sharp contrast to the oxidation reactions of electron-rich olefins just described, attempts to carry out nucleophilic epoxidation reactions of α,β -unsaturated carbonyl compounds have enjoyed only limited success (Scheme 8.7) [19]. The most successful attempts have been with chalcones, using standard basic peroxidation conditions with additives such as a quinine-derived phase-transfer catalyst first

Table 8.2. Examples of Jacobsen AE Reactions. See Scheme 8.6(a) for catalyst structures.

Entry	Olefin	Catalyst	% Yield (<i>cis/trans</i>)	% es	Ref.
1		A	71 (<i>trans</i> only)	10	[20]
2		B	84 (92:8)	96 (<i>cis</i>) 91.5 (<i>trans</i>)	[19,25]
3		C	not reported (5:95)	90.5 (<i>trans</i>)	[26]
<i>Used a quinine-derived additive</i>					
4		B	96	98.5	[19,25]
5		B	65 (16:84)	82 (<i>cis</i>) 99 (<i>trans</i>)	[30]
6		B	73	82	[31]
7		B	87	94	[28]
8		D	72	90.5	[29]
9		A	12	72	[29]

reported by Wynberg in 1976 [32] or poly-L-leucine [33]. Although seemingly limited to this substrate type, the products have been converted to the corresponding α,β -epoxy esters via a regioselective Baeyer-Villiger oxidation in at least one case [34]. More recently, a glimmer of success in applying organometallic catalysis to this problem has been seen in a platinum-based approach, although the products have yet to be isolated in synthetically useful yields [35].



Scheme 8.7. Nucleophilic epoxidation reactions of enones. (a) Epoxidation of chalcone using phase-transfer [32] or polymeric amino acid [33] catalysis. (b) Platinum-based epoxidation method [35].

8.2.3 Sharpless kinetic resolution

Inspection of the mechanism in Scheme 8.5 suggests that the Sharpless epoxidation should be relatively insensitive to configuration of any stereocenter in an alkene substituent with one very important exception: the allylic carbon bearing the alcohol. Indeed, good diastereoselectivity was often obtained in reactions of various chiral allylic alcohols with achiral epoxidizing agents (Scheme 8.3). Substitution at this particular position is important because of its proximity to the bulk of the catalyst. Thus, one might expect substitution at R_a to be well-tolerated because this group points away from the catalyst, whereas R_b should be much more sterically encumbered (Figure 8.2). Some experimental observations that address this issue and ultimately led to the application of the Katsuki–Sharpless catalyst to kinetic resolution reactions are shown in Scheme 8.8.

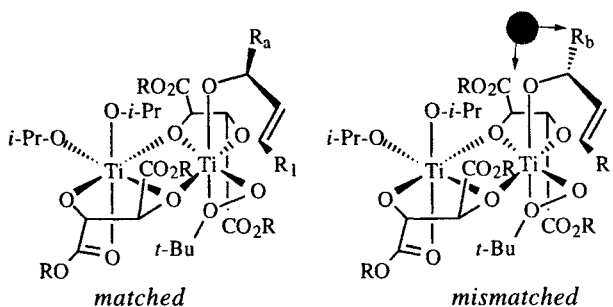


Figure 8.2. Origins of selectivity in the Sharpless kinetic resolution procedure.

(a)



L-(+)-DIPT



enantiomeric purity of the epoxy alcohol, with longer conversions sometimes allowing very high (>99%) enantiomeric purities of allylic alcohols, albeit in reduced yields.² Scheme 8.8c shows an example of what is possible under optimized conditions with a favorable substrate.

The KR procedure is not limited to making simple epoxides bearing an adjacent stereogenic center. Figure 8.3 depicts several interesting classes of molecules that have been resolved using KR procedures. Although results have been spotty, alternative sites of oxidation have included attempts with alkynes, furans, and β -amino alcohols. Of particular interest to stereochemistry buffs are procedures that result in different classes of enantiomerically pure compounds, such as those with axial chirality (cycloalkylidenes or allenes) or planar chirality. And, although not as far along as the now-standard reactions utilizing allylic alcohols, some progress has been made in extending both the AE and KR procedures to homoallylic alcohols [37].

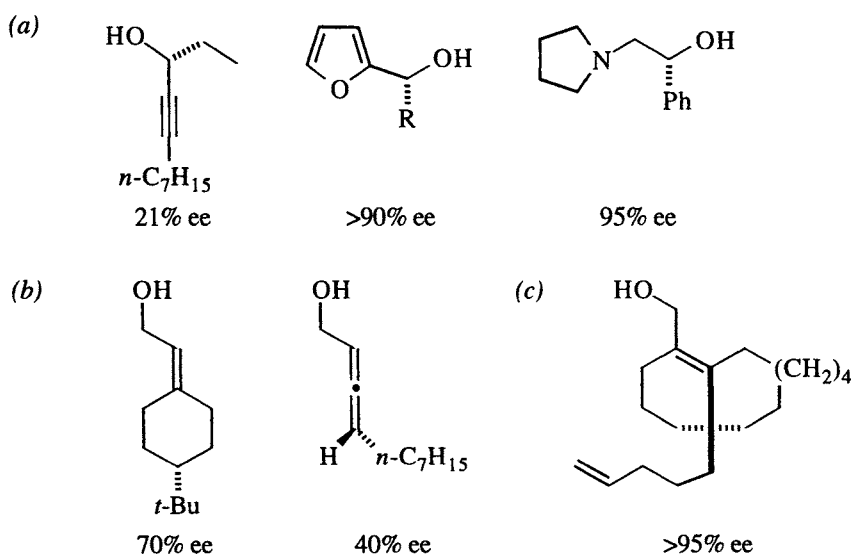


Figure 8.3. Examples of molecules prepared in enantiomerically enriched form using Sharpless KR procedure. (a) Compounds having alternative sites of oxidation: acetylene [38], furan [39], and amine [40]. (b) Compounds bearing axial chirality [38]. (c) An alkene with planar chirality [41].

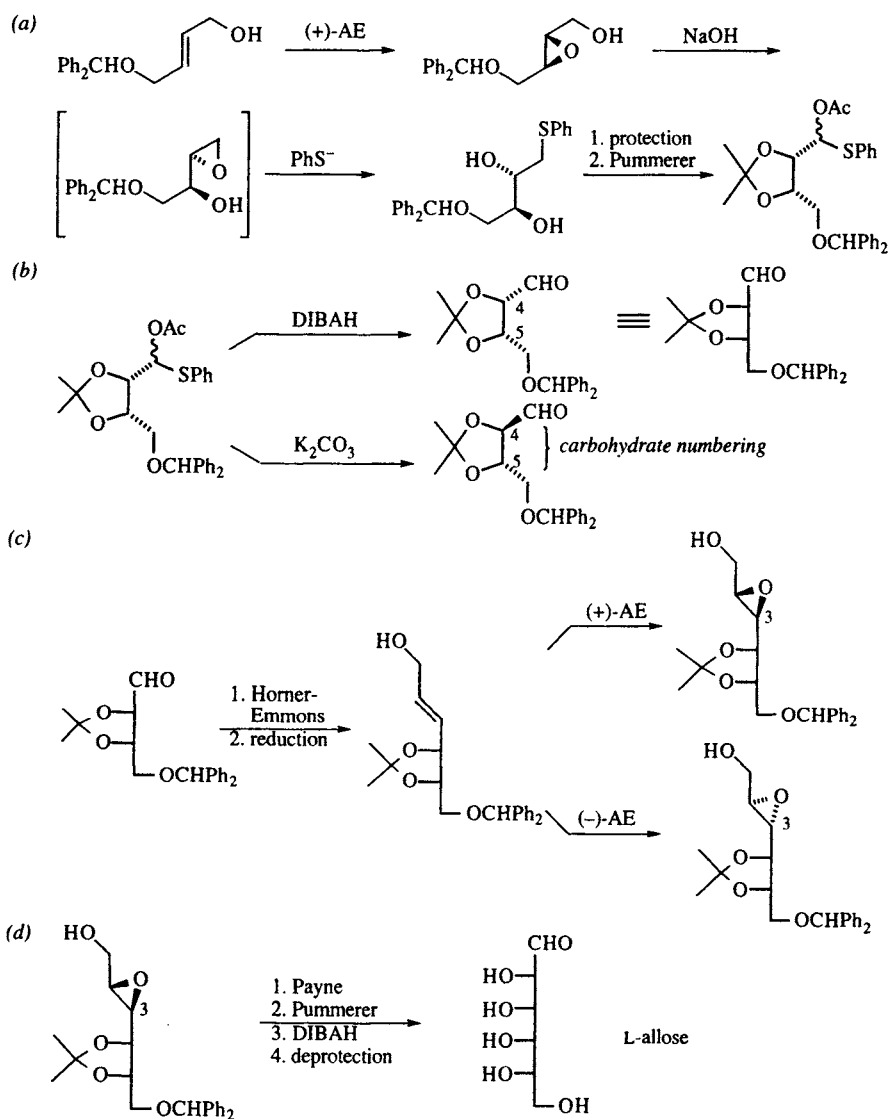
8.2.4 Applications of asymmetric epoxidation and kinetic resolution procedures

The importance of the Sharpless AE and KR procedures is best measured by the speed with which they have become a part of the synthetic chemist's "bag of tricks". Although a measure of their utility can be gleaned from examples given in sections 8.2.2 and 8.2.3, their influence has been far too pervasive to allow even a partial representative listing here. However, a few examples where these reactions have been used to illustrate principles of more general stereochemical interest will be summarized in this section.

Carbohydrate synthesis. Save the all-important hydroxymethyl group that the titanium reagent uses as a handle, the Sharpless AE is remarkably insensitive to

² The reader is directed to the original literature for a quantitative treatment [13,36].

stereogenic centers extant in the substrate. This has led to the wide use of this system for *reagent-based stereocontrol*, wherein the chirality of a new stereocenter is determined simply by pulling the appropriate reagent off of the shelf (as opposed to *substrate control*, in which a new element of chirality is installed under the influence of those already in the reactant; see Section 1.5). This strategy was nicely illustrated by the synthesis of all eight isomeric hexoses in their unnaturally-occurring L-series, summarized for L-allose in Scheme 8.9 [42,43].



Scheme 8.9. Reagent-controlled synthesis of L-allose ((+)-AE = Sharpless AE using L-(+)-DIPT; (-)-AE = Sharpless AE using D-(-)-DIPT). (a) A Sharpless AE followed by Payne rearrangement and oxidation. (b) Stereodifferentiation of the C-4 and C-5 stereocenters. (c) Chain extension followed by reagent-controlled oxidation of the olefin. (d) Completion of the synthesis.

This is an excellent example of an iterative sequence that takes full advantage of the stereochemical versatility of the Sharpless AE reaction. The synthesis prepares the target carbohydrate in the C-6 \rightarrow C-1 direction and starts with a readily prepared *trans*-allylic alcohol. The first AE directly sets the C-5 stereogenic center (carbohydrate numbering), now requiring that the epoxide be opened in a regio- and stereoselective manner and that the primary alcohol be converted to the oxidation state of an aldehyde. Both tasks were accomplished by a Payne rearrangement in base, which isomerizes the epoxy alcohol with strict inversion at the C-4 center. The new epoxide thus formed is monosubstituted and therefore suffers a kinetically favored attack by an external nucleophile, in this case the thiophenolate anion.^{3,4}

Next, the researchers took advantage of the acetonide protecting group to control the relative configuration between C-4 and C-5 (the use of a protecting group for this kind of stereochemical finesse is *ancillary stereocontrol* [46]). A mild, nonbasic unraveling of the aldehyde by reduction at the acetate carbonyl group was accomplished with diisobutyl aluminum hydride, which left the target in its initial *cis* configuration about the five-membered ring. Alternatively, basic deprotection led to epimerization to the *trans* isomer. Two interesting points:

1. Isomerization is only possible because of poor overlap between the enolate leading to epimerization and the C-5 carbon-oxygen bond (which doesn't allow for β -elimination).
2. This maneuver was used instead of making the same compound via a similar sequence using the *cis* allylic alcohol.

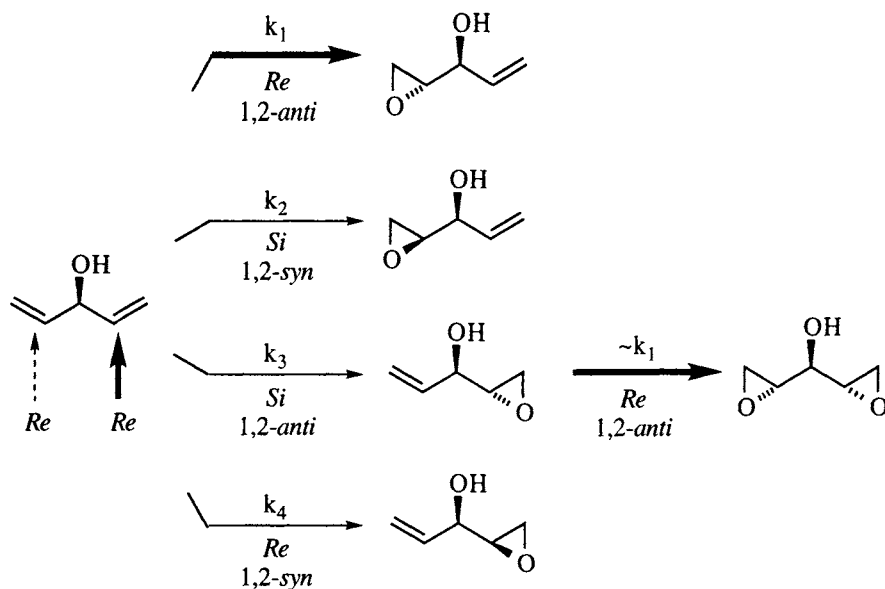
This is a good example of stereochemical divergence from a single precursor and obviates the necessity of preparing and working with the less reactive *cis* olefins. Overall, the conversions indicated in Schemes 8.9a and b constitute a single iteration of the synthesis.

Scheme 8.9c shows how the aldehyde could be homologated to a new allylic alcohol and how simple choice of tartrate ligand afforded the diastereomeric epoxides shown, since the AE process effectively ignores the resident stereocenter in the new substrate. This is the essence of reagent-controlled synthesis: the utilization of a tool for enantioselective elaboration to permit the selective synthesis of diastereomeric compounds. Once prepared, the utilization of the diisobutyl aluminum hydride variant of the iterative sequence followed by final deprotection steps led to the synthesis of L-allose. A useful exercise is to arbitrarily draw an isomer of allose and synthesize it using this technique (on paper, of course), or to imagine a modification that would lead to the corresponding pentoses [47].

Group selective reactions of divinyl carbinols. It is important to remember that the reagent control strategy is inapplicable to situations where the resident chirality is on the allylic position bearing the hydroxyl "handle" for the catalyst. However, the pref-

³ The regiochemistry of ring opening in epoxy alcohols has been more generally examined [44].

⁴ Although known prior to the discovery of the Sharpless AE, this use of the Payne rearrangement is a good example of how the availability of a particular functional array by asymmetric synthesis provoked a reaction's further development [45]. In this case, the product sulfide allows the chemoselective conversion of this carbon to the oxidation state of the aldehyde, in the guise of an acetoxysulfide.

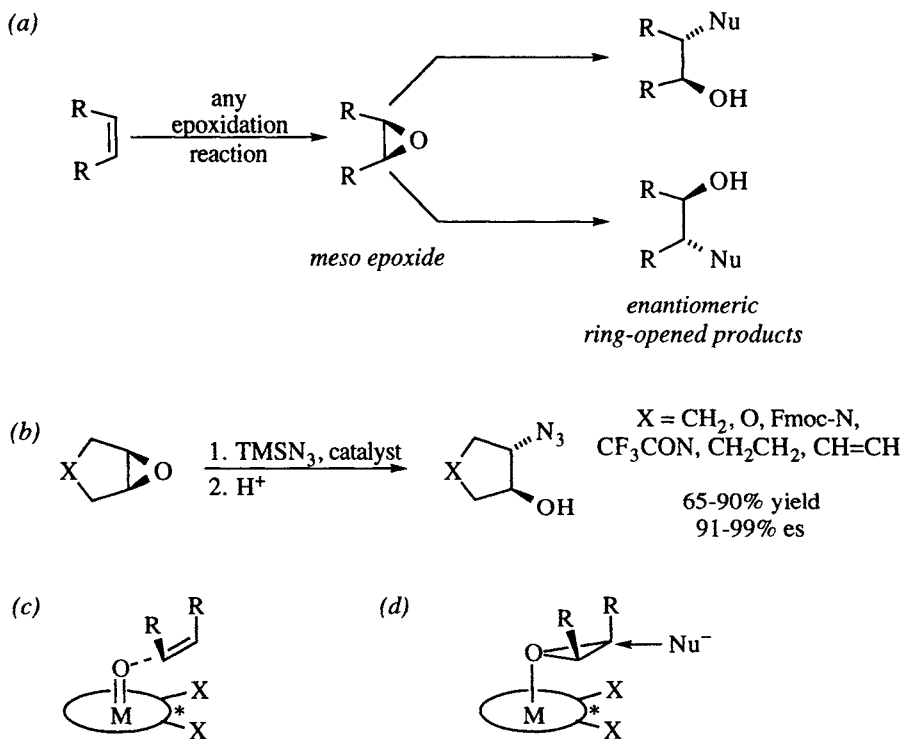


Scheme 8.10. Reaction of divinyl carbinol under (+)-AE conditions as an example of enantiotopic group selectivity in epoxidation chemistry. Matched cases of enantiofacial selectivity are shown with bold arrows. Qualitative rate differences are on the order $k_1 \gg k_2$, $k_3 \gg k_4$ (without specifying an order for k_2 vs. k_3 (however, cf. Scheme 8.8b). Note that the products arising from the pairs k_1/k_3 and k_2/k_4 are enantiomers.

erence for 1,2-*anti* product has been cleverly applied to a problem in diastereotopic group selectivity (Scheme 8.10) [48-52]

under such conditions [51,53]. Provided that one is able to distinguish either end of a developing chain, such reactions have promise in applications involving two-dimension chain elongation strategies [54].

Epoxide-opening reactions. The most common use of epoxides is in S_N2 ring-opening reactions leading to 1,2-difunctionalized compounds. Clearly, the availability of enantiomerically enriched epoxides, when combined with appropriate regiochemical control of their opening, has enhanced the applicability of this approach to the preparation of enantiomerically pure compounds. An alternative approach is to begin with a *meso* epoxide, and then follow this reaction with a sequence able to distinguish between the enantiotopic carbons of the epoxide (Scheme 8.11a).

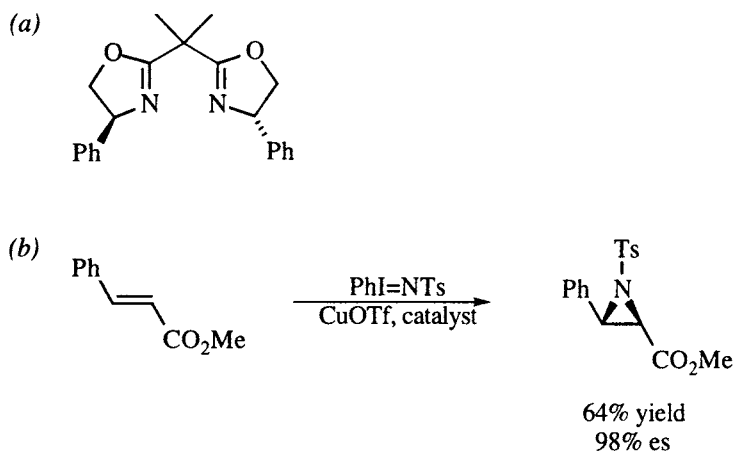


Scheme 8.11. (a) Group-selective ring-opening of *meso* epoxides by nucleophiles leads to enantioselective syntheses of 1,2-difunctionalized compounds. (b) Azido alcohol synthesis from epoxides and trimethylsilyl azide as catalyzed by (salen)CrCl complexes (see Scheme 8.6a for general structures of salen catalysts) [55]. Comparison of proposed ensembles for (c) asymmetric epoxidation and (d) Lewis-acid activation of epoxides for nucleophilic attack.

Several groups have addressed this problem using chiral aminating reagents [56] or, more recently, chiral catalysts [57]. Jacobsen has reported the efficient use of (salen)Cr(III) complexes for such conversions (Scheme 8.11b; cf. Section 8.2.2 and Scheme 8.6) [55]. These authors point out the similarities between transition structures for oxygen transfer in an epoxidation reaction (Scheme 8.11c) and epoxide activation (Scheme 8.11d), suggesting that the nonbonded interactions leading to selectivity ought to be similar in both cases.

8.2.5 Aziridinations

Although less commonly investigated, several catalytic, enantioselective aziridination reactions have also been developed. As an example, copper complexed to a chiral bisoxazoline ligand such as shown in Scheme 8.12a has been shown to catalyze the addition of *N*-(*p*-toluenesulfonylimino)phenyliodinane across a double bond [58]. Some promising results have been obtained (Scheme 8.12b), but work to fully define and optimize the range of olefins susceptible to this process is still ongoing.



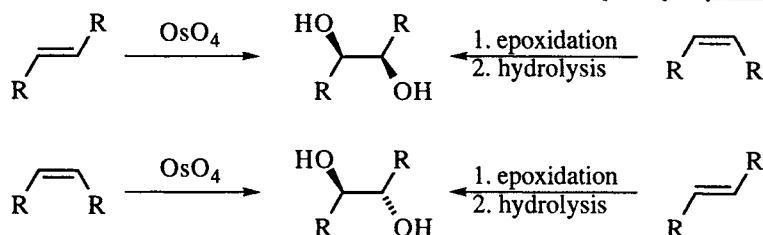
Scheme 8.12. (a) An example of a bidentate catalyst for copper salts used in asymmetric aziridination reactions. (b) An asymmetric aziridination reaction [58].

In addition, chiral salen complexes of Mn [59] and Cu [60] have been found to catalyze similar reactions with moderate enantioselectivities. In contrast to the salen complexes used in Mn-mediated epoxidation reaction, which use tetradentate complexes, the best results were obtained with bidentate ligands. Mechanistic work has implicated a metal-bound nitrene species in the reaction [61].

8.3 Dihydroxylations⁵

The synthesis of vicinal diols from olefins using OsO₄ complements epoxidation/hydrolysis as a route to 1,2-diols (Scheme 8.13 [65]). Both reagents effect *cis* difunctionalization of an olefin, but since the epoxide-opening step involves an inversion of configuration, the two routes afford opposite diastereomers beginning with a single olefin geometry. The development of an efficient asymmetric dihydroxylation process, again pioneered by the Sharpless laboratory, has become the most general single method for the oxygenation of unactivated olefins (*i.e.*, those without an allylic alcohol). The rapid acceptance of the Sharpless asymmetric dihydroxylation (AD) reaction by the organic chemistry community is a lesson in the value of a method able to convert a simple, readily available functional group into another common moiety, particularly when the reaction can be done stereoselectively.

⁵ Reviews: ref. [62-64].



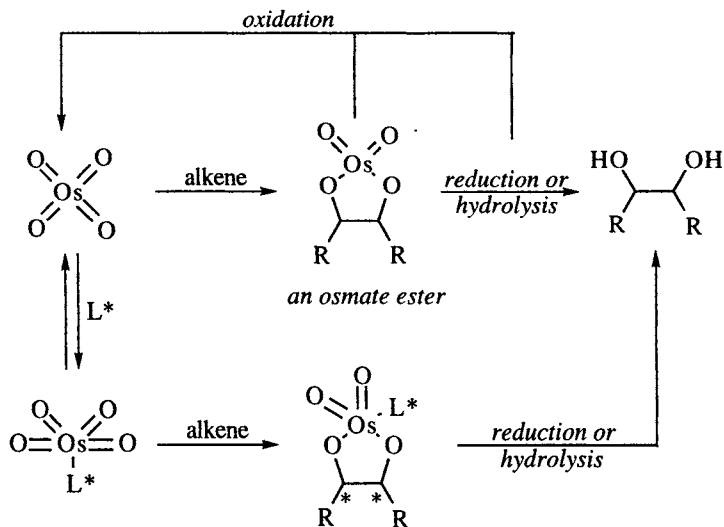
Scheme 8.13. 1,2-Diol synthesis from alkenes via direct osmylation or epoxidation followed by hydrolysis.

8.3.1 Development, scope, and mechanism

Three things were required to realize a useful catalytic, asymmetric dihydroxylation reaction:

1. An efficient osmylation reaction using achiral catalysts.
2. Appropriate chiral ligands to effect face selectivity in the addition of the osmylation reagent to an alkene.
3. Some way to enforce the participation of the chiral osmium catalyst in the reaction to the exclusion of non-stereoselective pathways.

These issues are summarized in the *extremely* simplified mechanism given in Scheme 8.14. All osmylation reactions ultimately afford the osmate ester shown, although the mechanism for this step has been controversial.⁶ Note that the osmium is reduced over the course of the reaction. In efforts to minimize the amount of toxic osmium used in these reactions, catalytic methods using a variety of stoichiometric reoxidants for osmium were introduced, beginning with the introduction of KClO_4 in 1917 by Hofmann [66] and including the convenient Upjohn process, which uses *N*-methylmorpholine-*N*-oxide for this purpose [67].



Scheme 8.14. Simplified mechanism for the dihydroxylation of olefins. A more complete description is available [63].

⁶ Both [3 + 2] concerted mechanisms and schemes involving the formation of a metalloxetane intermediate by [2 + 2] cycloaddition followed by rearrangement have been proposed.

An asymmetric dihydroxylation reaction requires some form of “chiral osmium”. The first evidence that amine ligands could affect the chemistry of this dihydroxylation reaction was published by Criegee, who found that the reaction was accelerated by the addition of pyridine [68]. Sharpless later showed that useful enantioselectivities (up to 97% es) could be realized when chiral amines were added to OsO_4 -mediated oxidation reactions. The ligands used by the Sharpless group were representatives of the cinchona alkaloid family, dihydroquinidine (DHQD) and dihydroquinine (DHQ) (Figures 8.4a and b). Note that although these ligands are nearly enantiomeric with respect to the quinuclidine base and aromatic side chain, their mirror symmetry is spoiled by the placement of the ethyl group on the bicyclic portion of the molecules. The existence of these alkaloids in the chiral pool would prove to be fortuitous indeed, as modifications of the alcohol group would be the key to the development of effective *catalytic* complexes. In addition, other workers have reported a variety of totally synthetic ligands able to effect highly selective stoichiometric dihydroxylation reactions; these ligands very often incorporate C_2 symmetry into their design (e.g., Figures 8.4c and d).

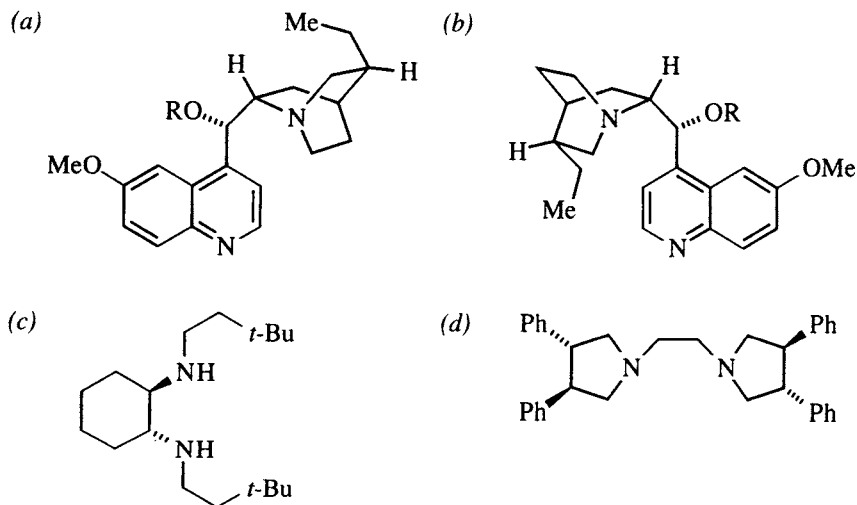
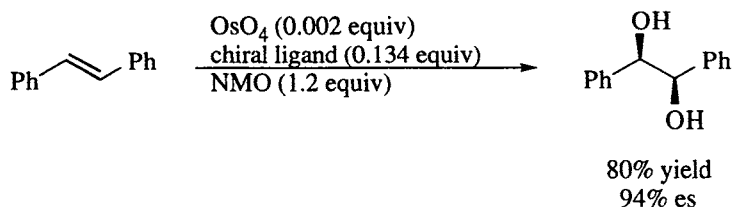


Figure 8.4. Representative ligands used in stoichiometric, asymmetric dihydroxylation reactions. (a) Dihydroquinidine (DHQD) and (b) dihydroquinine (DHQ) are used for stoichiometric osmylation reactions when $R = H$; effective dihydroxylation catalysts result from appropriate modifications at this position (e.g., see Figure 8.5 below). Also, (c) [69] and (d) [70] are examples of C_2 symmetrical ligands used in stoichiometric reactions.

Sharpless reported the first generally useful catalytic version of the reaction in 1987 [71]. This landmark paper showed that the reaction could be rendered catalytic by combining modified cinchona ligands with the Upjohn process (Scheme 8.4). This use of *ligand-accelerated catalysis* is critical to the success of a catalytic AD reaction because of the preequilibrium present between OsO_4 and OsO_4L^* in solution (Scheme 8.14). Unless the equilibrium lies so far to the latter species as to effectively lower the concentration of OsO_4 to zero, the nonselective reaction of OsO_4 with the



Scheme 8.15. An early example of a catalytic dihydroxylation reaction [71]. The chiral ligand used here is the *p*-chlorobenzoate ester of DHQD (Figure 8.4a).

olefin would compete with that of OsO_4L^* , lowering the enantioselectivity of the overall process. The ligand acceleration effect provided by the chiral amine sidesteps this issue by ensuring that the OsO_4L^* pathway is also the most kinetically competent.

An interesting contrast exists between the development of the Sharpless asymmetric epoxidation reaction and the asymmetric dihydroxylation process. In the former case, the original reagents and protocol for carrying out the reaction have basically survived in their original form. However, the AD has been subjected to a great deal of optimization since its introduction, both in terms of ligand design and modification of conditions. In particular, protocols that cut down on interference by non-selective pathways have helped raise the utility of the overall procedure to its current high level. For example, the intrusion of a second catalytic cycle was proposed to lower overall stereoselectivity of the AD (Scheme 8.16). In this second cycle, the osmate ester formed by the reaction of one olefin with the chiral *Os*-cinchona complex was proposed to undergo oxidation and become itself a reactive dihydroxylation reagent, albeit one that had little enantiofacial selection. This pathway could be minimized by mandating slow addition of the alkene (allowing the osmate ester time to undergo hydrolysis and reoxidation [72]), through the use of $\text{K}_3\text{Fe}(\text{CN})_6$ as the reoxidant in place of NMO [73], or by increasing the rate of hydrolysis by adding MeSO_2NH_2 to the reaction mixture [74]. In particular, the use of the iron-based reoxidant remands the job of *Os* reoxidation to the aqueous portion

of a biphasic reaction mixture, thus “protecting” the organic osmate ester from inopportune oxidation prior to hydrolysis. The addition of sulfonamide is doubly useful because it increases the turnover rate of the reaction and facilitates the dihydroxylation of otherwise sluggish substrates.

Finally, a mind-boggling number of analogs of the original catalysts have been prepared and tested. Although the progression through this series makes for interesting reading [62-64], only the most generally efficacious catalysts are cited in Figure 8.5. The most striking advance is the use of dimeric species featured in PHAL and PYR, the most general of the catalysts (Figures 8.5a and b). The former ligand has been formulated along with $\text{K}_2\text{OsO}_2(\text{OH})_4$ (a non-volatile source of Os), $\text{K}_3\text{Fe}(\text{CN})_6$, and either DHQ or DHQD, respectively; these stable, storable powders contain all of the necessary ingredients for AD reactions and are known as AD-mix- α or AD-mix- β . These mixtures are commercially available. Interestingly, although the hydroxyl substituent on the cinchona alkaloid platforms for these catalysts tolerates and benefits from a great many variations, the rest of the alkaloid has proven much less flexible [64], and this portion of the catalytic system can (conveniently) be left alone.

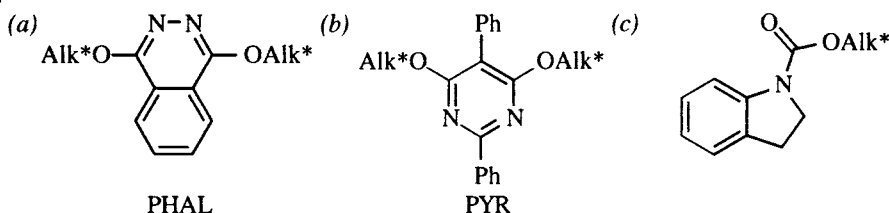
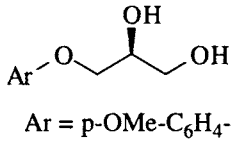
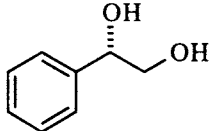
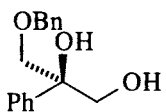
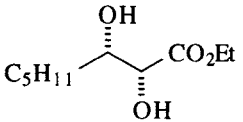
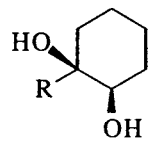
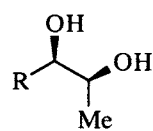
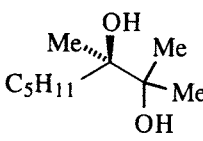
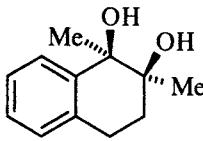


Figure 8.5. Ligands for the Sharpless AD process. (a) The phthalazine ligand (PHAL class), recommended for most substitution types [74,75]. (b) The diphenylpyrimidine ligand (PYR class), used for mono- and tetrasubstituted olefins [76,77] (along with PHAL ligands). (c) Indoline ligand (IND class), best for *cis*-disubstituted olefins [78]. For each, the Alk^* bound to each position is DHQD or DHQ (Figure 8.4).

The results of many dihydroxylation reactions have resulted in the compilation of a mnemonic device for the prediction of the direction of attack with catalysts based on each alkaloid (Scheme 8.17). Although this model is very useful, there can be some ambiguity as to which group is the large one and which is the medium (especially with *trans*-disubstituted olefins) and electronic characteristics cannot be ignored [63]. This is a byproduct of the lack of an unambiguous group to orient the molecule (*cf.* the AE reaction, Scheme 8.1).

Some useful generalizations are that the “large” group is very often aromatic, and indeed, aromatic olefins make up some of the best substrates for this reaction. Results from modifying other sites of substitution have led to the suggestion that the loaded catalyst is very forgiving for *trans* olefins (the best substrates), but that it begins to experience some interference at the R_S position. That the binding site is even less favorable toward substituents *cis* to the R_L position (H in Scheme 8.17) is surmised by the difficulty of carrying out AD reactions with fully substituted [77] and *cis* olefins (there are only a few really good examples, and those top out at about 90% *es* [78]). However, very good to excellent results have been wrestled from all alkene

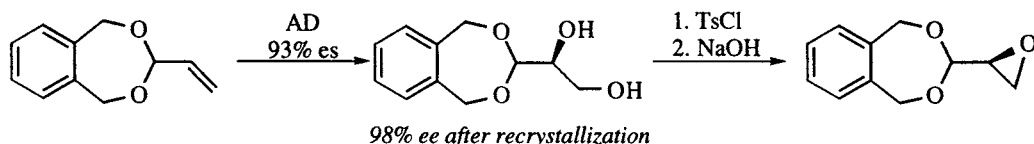
Table 8.3. Examples of Asymmetric Dihydroxylation Reactions. See Figure 8.5 for catalyst structures.

Entry	Diol	Catalyst	% es	Ref.
1	 <p>Ar = p-OMe-C₆H₄-</p>	(DHQD) ₂ -PHAL	95	[83]
2		(DHQ) ₂ -PHAL	98.5	[74,76]
3		(DHQD) ₂ -PHAL	89	[84]
4		(DHQ) ₂ -PHAL	97.5	[74]
5		(DHQD) ₂ -PHAL	79 (R = Me) >99 (R = phenyl)	[64,74]
6		DHQD-IND	78 (R = <i>c</i> -C ₆ H ₁₁) 86 (R = Ph)	[78]
7		(DHQD) ₂ -PYR	61	[77]
8		(DHQD) ₂ -PYR	92.5	[77]

8.3.2 Applications of enantioselective dihydroxylations

As in the asymmetric epoxidation reaction, the development of such a powerful tool for the enantioselective preparation of diols spurred its application to a very wide variety of synthetic problems and the invention of new methods of manipulating the diol products [64]. A few examples confer some of the flavor of this work.

Like the AE, the AD has obvious utility to those contemplating the synthesis or use of carbohydrates as synthons. For one, glyceraldehyde and its acetonides have found very wide acceptance as chiralons for asymmetric synthesis [85]. A clever utilization of the AD affords a building block that nicely complements the use of the naturally occurring material (Scheme 8.18) [86].

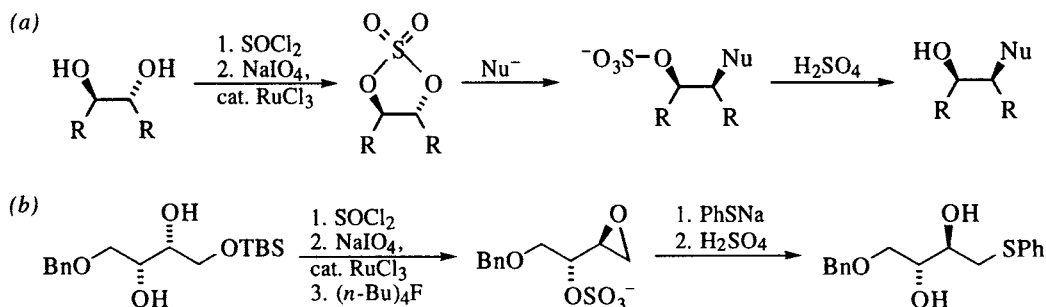


Scheme 8.18. Synthesis of a glyceraldehyde equivalent and its conversion to an epoxide [86]. This AD used the 5-phenanthryl ether of DHQD as the ligand.

Note that:

1. The AD technique allows the synthesis of either enantiomer of the diol by simply switching catalyst.
2. The formation of the epoxide occurs with retention due to specific tosylation of the primary alcohol. (A variety of conditions have been developed for the conversion of 1,2-diols into epoxides [64].)
3. The use of the aromatic protecting group of the aldehyde both increasing the efficiency of the AD reaction and allows for its ready removal by hydrogenation.

Instead of activating diols by converting them to epoxides, an alternative is to activate the diols themselves to nucleophilic attack; this has been accomplished by converting them into cyclic sulfates (Scheme 8.19) [64,87]. These highly reactive species are subject to substitution by many nucleophiles, including halides, azides, reducing agents, and sulfur and carbon nucleophiles. Scheme 8.19b depicts a strategy involving irreversible epoxide formation (*cf.* the Payne rearrangement (section 8.2.4)) [88].



Scheme 8.19. (a) Formation and reactivity of cyclic sulfates. (b) Application of cyclic sulfates to the synthesis of erythrose [88]. Note that the epoxide formation is irreversible because the sulfate leaving group is no longer nucleophilic.

The reliably high selectivity of *trans*-olefins makes these substrates particularly amenable to synthetic schemes that depend on reagent control for the installation of new stereocenters. Unlike the AE reaction, there are no strict limitations on which diastereoisomers can be prepared. However, issues of double asymmetric induction [89] often arise because the reactions of alkenes bearing allylic electron-withdrawing groups can be highly diastereoselective. Prior to the development of this asymmetric dihydroxylation, the dependence of diastereofacial selection in alkenes bearing allylic substitution had been catalogued by Kishi (Scheme 8.20) [90,91]. When AD reactions are carried out on substrates already bearing stereogenic centers, matched vs. mismatched situations develop (Section 1.5), with the former affording very high selectivity. However, the ability of the AD system to induce enantiofacial selectivity is often high enough that varying levels of selectivity in either direction can be obtained. Although a few cases have been published (and summarized [641])

aryl groups so that they can only undergo intramolecular biaryl coupling to give one configuration about the newly formed single bond. Diol oxidation removed the original stereocenters installed by the AD reaction.

8.4 Oxidation of enolates and enol ethers

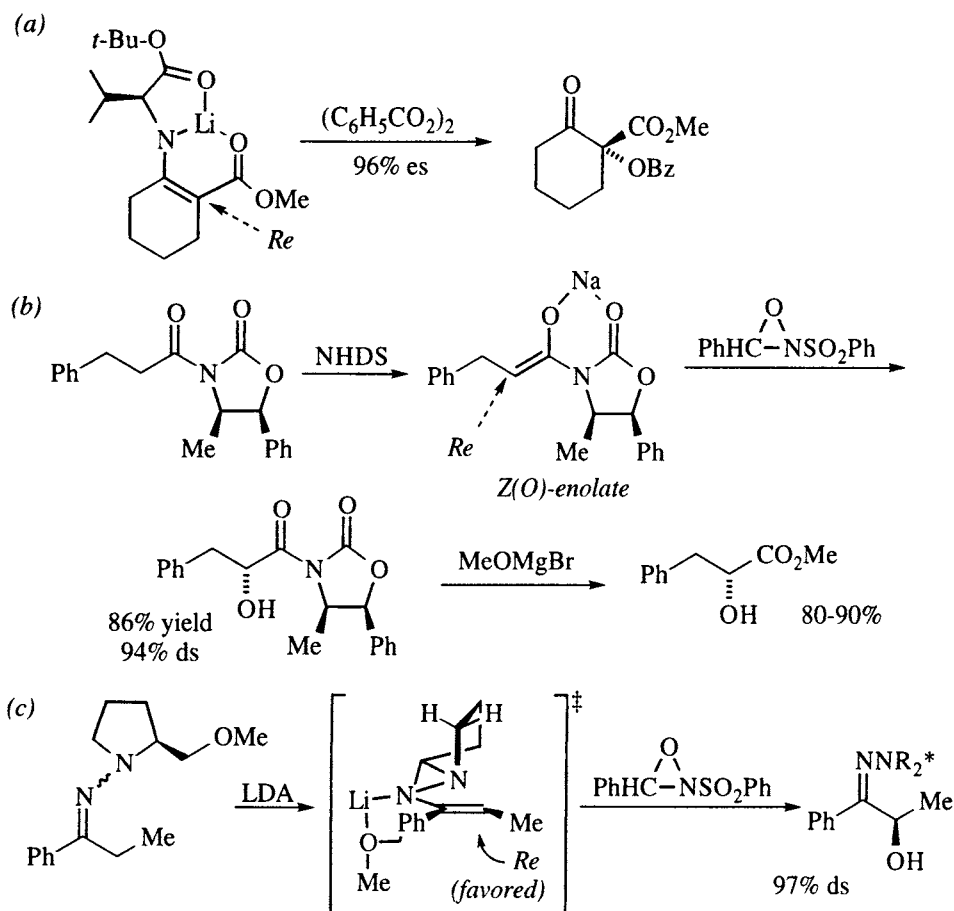
The asymmetric α -functionalization of carbonyl compounds with OR and NR₂ through their enolates has become another standard method for the synthesis of chiral 1,2-dioxygenated compounds. Most such methods utilize the rich chemistry developed for the asymmetric alkylation of carbonyls (Chapter 3), although one important class of chiral reagents has been developed for just this purpose.

8.4.1 Hydroxylations

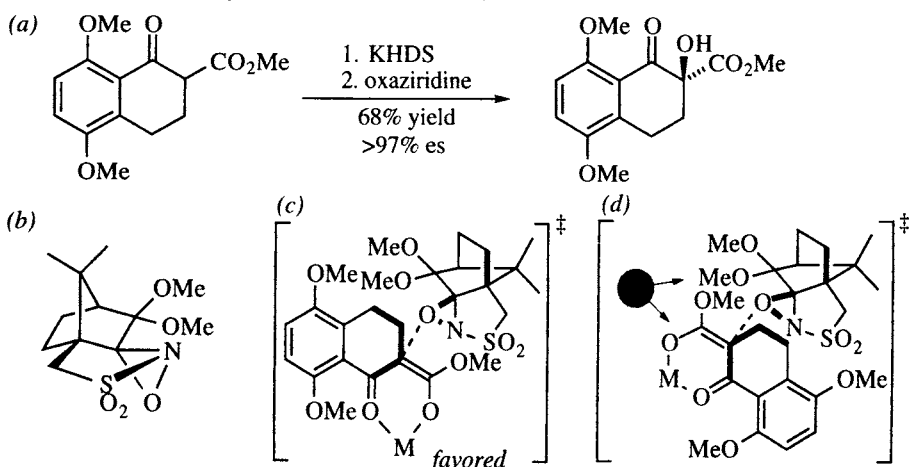
In cases where chiral auxiliaries are used to differentiate the two faces of an enolate, oxygen-transfer agents produce α -hydroxy ketones or esters after cleavage of the auxiliary. Some examples are shown in Scheme 8.22. In each case, the chiral auxiliary had been previously developed for reaction with alkyl halide electrophiles, and is applied to oxidation chemistry in these examples. For example, the metallocenamine shown in Scheme 8.22a was originally developed by Koga [94]; its use in the illustrated oxidation was reported by Snyder [95]. Scheme 8.22b illustrates the application of Evans's imides to hydroxylations [96] (*cf.* Scheme 3.17). Enders's SAMP hydrazone enolates are also amenable to oxidation, as shown in Scheme 8.22c (*cf.* Scheme 3.21 and 3.22) [97]. All three of these reactions presumably involve mechanisms for diastereofacial discrimination similar to those involved in carbon-carbon bond-forming reactions (Chapters 3 and 5). In addition to reagents such as MoOPh or benzoyl peroxide, *N*-sulfonyl oxaziridines have become especially useful for this purpose (Scheme 8.22b and c) [98]. Note that, although this oxaziridine is chiral, its configuration is not important, and it is generally used in racemic form for this purpose.⁷

The utility of oxaziridines in asymmetric α -hydroxylation also extends to reactions with achiral enolates. This has been made possible by the discovery that certain chiral *N*-sulfonyl oxaziridines can react with enolates to afford α -hydroxy carbon compounds in excellent yield and enantioselectivity. An application of a highly selective sulfonyloxaziridine derived from camphor to the synthesis of daunomycin is shown in Scheme 8.23. Attack of the oxaziridine presumably occurs such that the enolate ester avoids nonbonded interactions with the *exo* methoxy group on the bicyclic ring system (*cf.* Schemes 8.23c and d). This is a very useful reaction of wide scope, and can be carried out on both stabilized enolates derived from keto esters (shown) and simple ketone enolates [99].

⁷ These reactions are, therefore, examples of double asymmetric induction whereby the selectivity of one chiral reactant is overwhelmed by the facial bias of another (*cf.* Section 1.5).

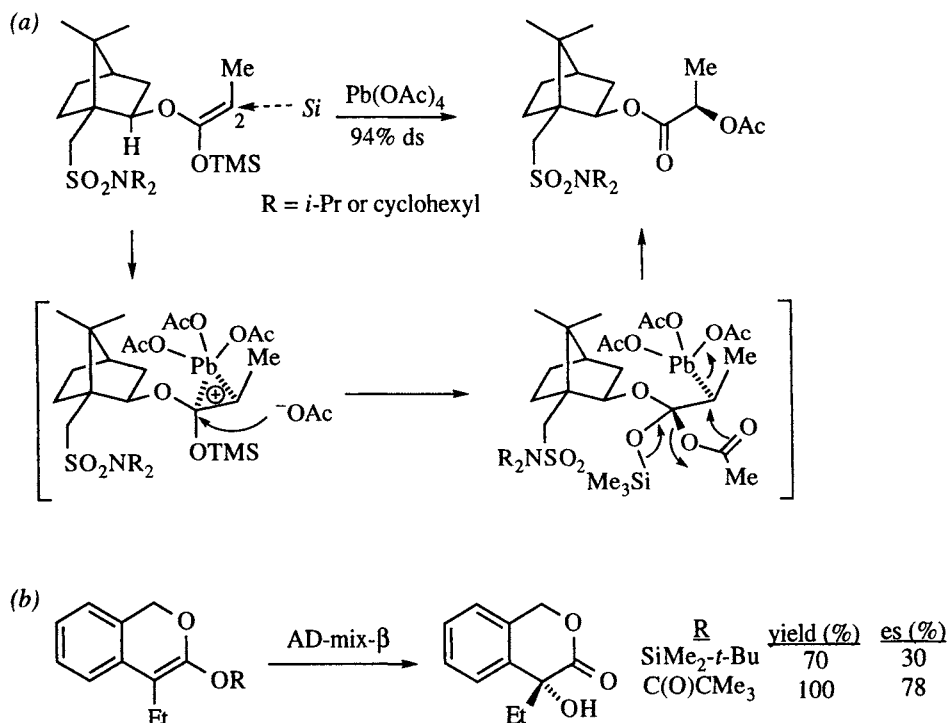


Scheme 8.22. Representative hydroxylation reactions of chiral enolates, using (a) metallocenamine [95] (cf. Scheme 5.33), (b) oxazolidinone [96] (cf. Scheme 3.17), and (c) hydrazone [97] (cf. Scheme 3.21 and 3.22) auxiliaries.



Scheme 8.23. (a) Application of enolate oxidation reactions of a chiral oxaziridine to the synthesis of an AB ring synthon of daunomycin [100]. (b) Structure of the oxaziridine used. Proposed (c) favored and (d) disfavored transition structures (see also ref. [101]).

An indirect route to α -hydroxy carbonyl compounds uses enol ethers as substrates for dihydroxylations (Scheme 8.24). The primary product is a vicinal hydroxy-hemiacetal which fragments to afford an α -hydroxyketone, rendering the overall route a two-step conversion of ketone to α -hydroxy ketone. The stereochemically important step can use a chiral auxiliary or enantioselective catalysis [64]. The sense of asymmetric induction found in Oppolzer's sulfonamide, shown in Scheme 8.24a [102], deserves comment, since this auxiliary is one seen previously in the Diels-Alder reaction (Figure 6.12f), and the topicity is not obvious [103]. The illustrated conformation is the most stable (*cf.* Figure 4.21, Figure 6.23, and the accompanying discussion). In this conformation, the sulfonamide shields the *Re* face of C-2 (toward the viewer), so that the lead then adds to the *Si* face. Opening of the plumbacycle with acetate affords an intermediate that suffers fragmentation and acetate migration to give the *R* isomer by the mechanism shown [102]. The Sharpless asymmetric dihydroxylation shown in Scheme 8.24b follows the topicity suggested by the mnemonic of Scheme 8.17, with the aromatic moiety playing the part of the large (R_L) substituent.

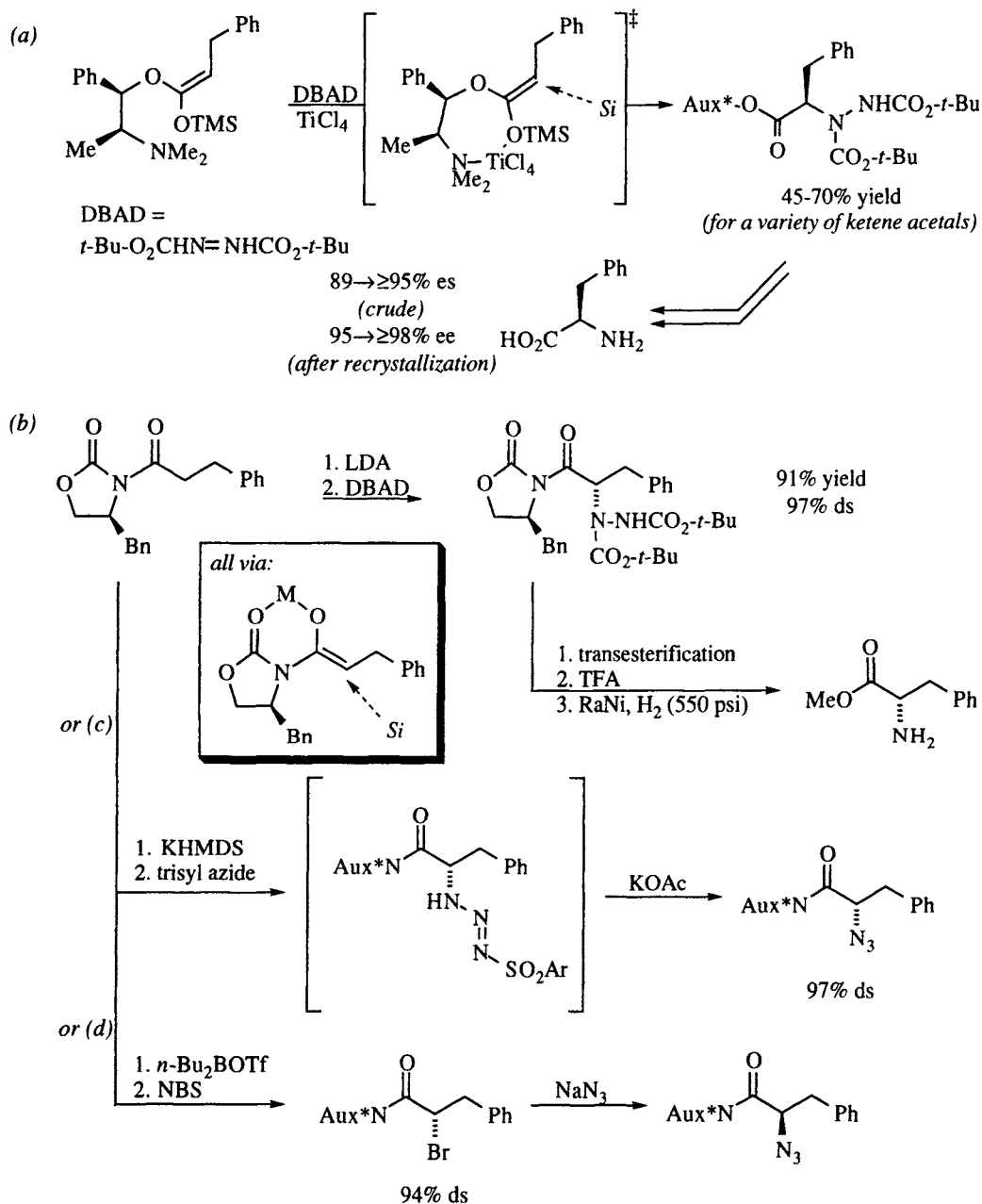


Scheme 8.24. Dihydroxylation reactions used for the synthesis of α -hydroxy carbonyl compounds. (a) A chiral auxiliary approach [102]. (b) Application of the Sharpless AD procedure to an intermediate for the synthesis of camptothecin [104].

8.4.2 Aminations

Amination reactions of carbonyl compounds provide access to useful building blocks for nitrogen-containing compounds, the conversion of esters to amino acid derivatives being particularly important [105]. In 1986, the groups of Gennari, Evans,

and Vederas simultaneously published routes to α -hydrazino ester derivatives by the addition of the electrophilic reagent di(*tert*-butyl)azodicarboxylate (DBAD) to enolates or trimethylsilyl ketene acetals (Scheme 8.25) [106–109]. Excellent yields were obtained, and the products were formed in accord with the diastereofacial selectivity of the nucleophiles in alkylation or aldol reactions (Chapters 3 and 5).



Scheme 8.25. α -Amidation of chiral ester enolates using di(*tert*-butyl)azodicarboxylate and (a) *N*-methylephedrine [106] or (b) oxazolidinone chiral auxiliaries [107]. Azidation of a chiral enolate (c) directly or (d) via bromination/azidation [110].

Unfortunately, the hydrazino esters or amides required inconveniently high pressures for their hydrogenolysis (500 psi; Schemes 8.25a and b). An improvement involved the direct azidation of the same enolates using arylazide derivatives, which were found to undergo reactions with enolate nucleophiles to provide a C-sulfonyltriazene intermediate which could be decomposed to the α -azido ester (Scheme 8.25c) [110]. Alternatively, azides may be obtained by enolate bromination followed by S_N2 azide displacement; note that these techniques are stereochemically complementary.

Similar chemistry has also been accomplished using 10-16% sodium azide in dimethyl sulfoxide.

8.5 Miscellaneous oxidations

8.5.1 Oxidation of sulfides

A great deal of effort has been expended in the development of ways to carry out the asymmetric oxidation of sulfides to sulfoxides; progress in this field has been exhaustively reviewed [114]. This is interesting from both a theoretical viewpoint and from the utility of certain chiral sulfoxides as reagents in asymmetric synthesis [115]. Some natural products also contain sulfoxide stereogenic centers.

The most common method for obtaining chiral sulfur compounds is the Anderson

An interesting application of this chemistry has been the subject of considerable work by the Aggarwal group. These workers prepared the *trans* isomer of 1,3-dithiane-1,3-dioxide in high ee; note the use of a temporary carbomethoxy group, which proved necessary for high enantioselectivity (Scheme 8.27c) [120]. Deprotonation gave an acyl anion equivalent which reacted with aromatic aldehydes with high diastereoselectivity [121]. Pummerer removal of the heterocycle followed by basic transesterification met with some isomerization and loss of enantiomeric purity, although this problem could be mitigated by a multistep procedure involving intermediate thioesters.

The reader is referred to the review literature for other applications of chiral sulfoxides in diastereoselective synthesis, including their use as directing groups for a wide variety of organometallic reactions [122,123] and the related chemistry of chiral sulfoxonium salts [115]. Although the vast majority of these efforts have to date obtained the stereogenic sulfur atom through the Andersen procedure or a variant thereof, one expects chiral catalysis to play an increasing role in the future.

8.5.2 Group-selective oxidation of C-H and C-C σ bonds

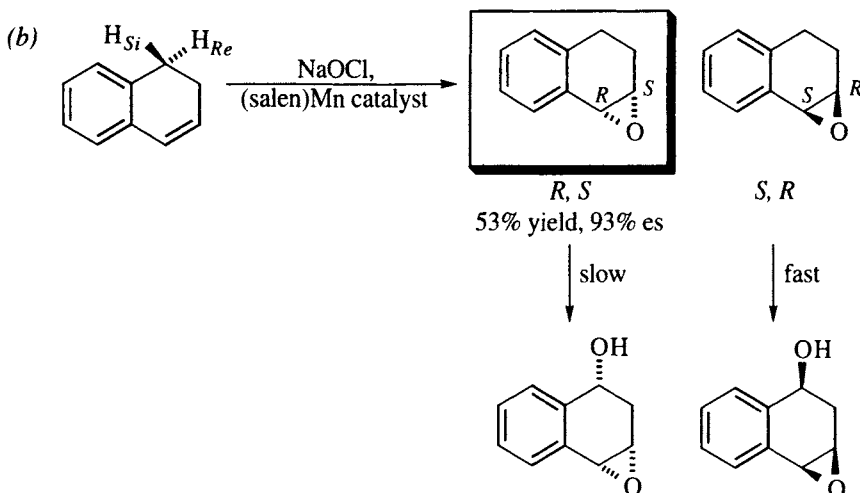
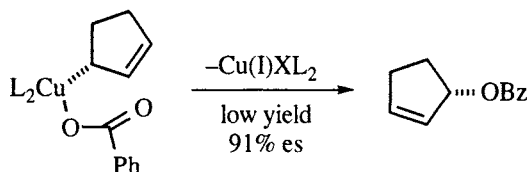
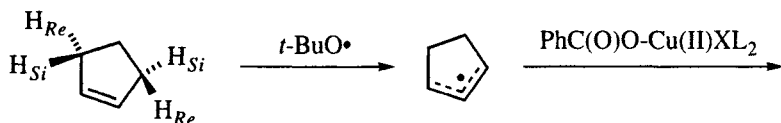
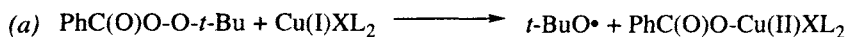
The oxidation of enantiotopic alkyl groups is only rarely accomplished through chemical means, although group selectivity is very commonly utilized in enzymatic reactions. This is partly because the conceptually simplest kind of group-selective reaction involves the formal cleavage of C-H or C-C σ bonds, which is still difficult to do with useful levels of chemo- or regioselectivity, much less enantioselectivity. Due to the significant potential of this strategy in asymmetric synthesis, a few early results are presented below.

A few non-enzymatic methods that permit the formal group-selective insertion of oxygen into enantiotopic C-H bonds are shown in Scheme 8.28. The asymmetric Kharash reaction in Scheme 8.28a uses a chiral bisoxazoline complex of copper similar to that employed by Evans in his approach to asymmetric aziridination (*cf.* Scheme 8.12) [124]. Without going too deeply into the details of the mechanism, note that although the overall reaction selectively replaces one of the enantiotopic hydrogen atoms with a benzyloxy group, the actual enantioselective step entails the face-selective recombination of the allylic radical with the copper(II)-benzoate salt! According to this hypothesis, the oxygen is delivered suprafacially and intramolecularly with expulsion of the original catalyst. Note that this example proceeds in low yield. Should more reactive catalyst systems that proceed with higher turnovers be found, this might provide a useful route to allylic oxidation.

The benzylic oxidation depicted in the second step of Scheme 8.28b is actually a formal group-selective differentiation of diastereotopic C-H bonds, since asymmetric epoxidation occurs prior to hydroxylation [125]. However, the reaction is an interesting example of a kinetic resolution that depends on the fact that the catalyst used reacts with the two epoxides at different rates, apparently because the chiral catalyst system:

1. Prefers to remove a hydrogen atom from the same face as the epoxide oxygen, possibly because of conformational effects.
2. Is selective for the removal of the H_S hydrogen.

Since the salen(Mn) catalyst used promotes both epoxidation and hydroxylation reactions (although not with the same efficiency), the net effect is to stereoselectively oxidize the *S,R*-monoepoxide in order to increase the enantiomeric purity of the *R,S*-epoxide.

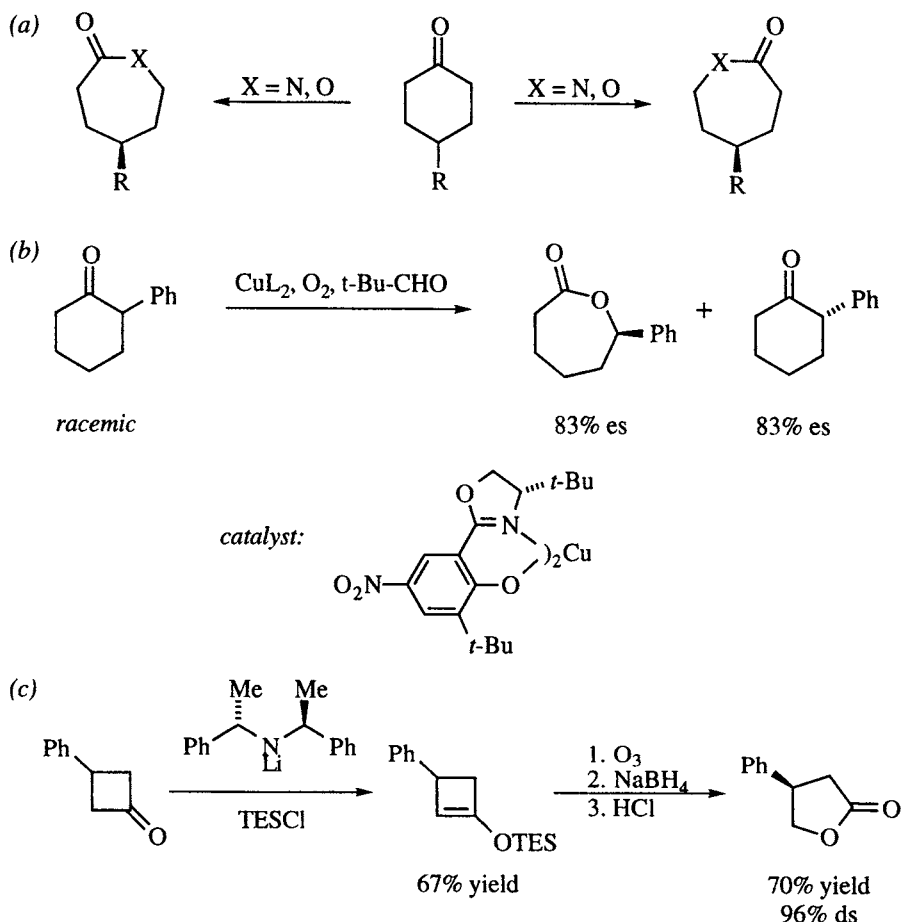


Scheme 8.28. Formally group-selection insertion of oxygen into enantiotopic C-H bonds. (a) An asymmetric Kharasch reaction [124]. The catalyst is similar to that shown in Scheme 8.12, except that each oxazoline bears two methyl substituents at C-5. (b) Kinetic resolution of dihydronaphthalenes [125]. The reaction uses a Jacobsen epoxidation catalyst (Scheme 8.6, type A).

The group-selective stereodifferentiation of C-C bonds has been investigated in the context of ring-expansion chemistry. In a symmetrical ketone like 4-*tert*-butylcyclohexanone, the two methylene groups adjacent to the ketone are enantiotopic. Several groups interested in the overall “oxidation” of these bonds have developed asymmetric versions of the classical Baeyer-Villiger and Beckmann reactions (Scheme 8.29a).

Although highly efficient enzymatic Baeyer-Villiger reactions have been accomplished using cyclohexanone oxygenase [126,127], only one method using an abiotic method has been reported [128]. A chiral copper complex is used to activate the oxidizing agent, this time molecular oxygen itself. In the example shown, a kinetic resolution of a 2-substituted cyclohexanone is carried out to afford both product lactone and the starting cyclohexanone with reasonable enantioselectivities.

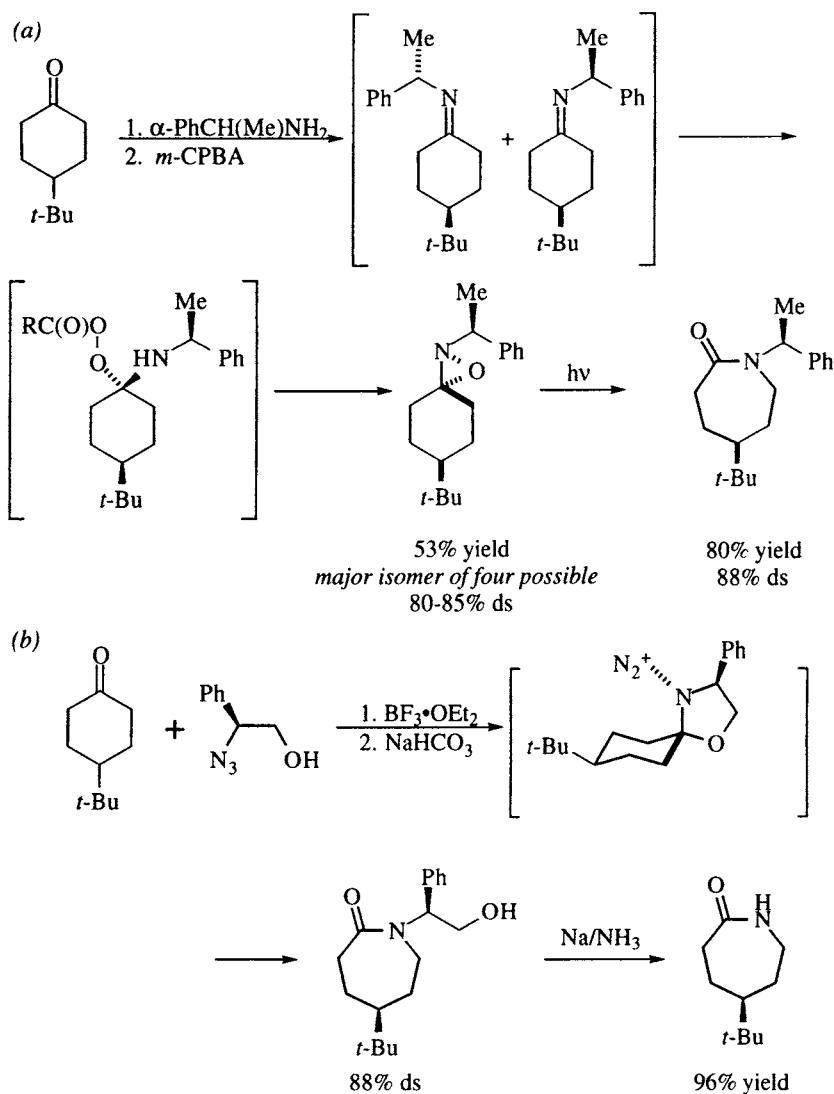
Such reactions have not yet found their way into the arsenals of synthetic organic chemists; instead, multistep sequences such as the chiral base-mediated method shown in Scheme 8.29c are usually used to achieve the net result of enantioselective oxygen insertion [129].



Scheme 8.29. (a) A generic asymmetric ring-expansion reaction. (b) A kinetic resolution using an asymmetric Baeyer-Villiger catalyst [128]. (c) A synthetic equivalent of an asymmetric Baeyer-Villiger reaction [129].

In contrast, there is no known enzymatic version of an asymmetric nitrogen insertion process. Rather, there are two methods available that utilize variations on known ring-expansion processes (Scheme 8.30). The first utilizes oxaziridines as the first isolated intermediate in a three-step overall sequence [130]. Axially dissymmetric spirocyclic oxaziridines are available by the oxidation of imines derived from the starting ketone and α -methylbenzylamine. The reaction utilizes one element of diastereofacial selectivity (interpreted here as equatorial attack of the peracid oxidizing agent) and an interesting kind of selectivity whereby intramolecular attack of the now-secondary nitrogen causes ejection of a carboxylic acid; in this latter reaction, the stereogenic nitrogen atom of the oxaziridine [131] is formed with good diastereoselectivity. The oxaziridine is then photolyzed, which causes the molecule to undergo bond reorganization to give the lactam. This reaction takes

advantage of the known (but not well-understood) tendency of the oxaziridine to react with regioselective migration of the bond antiperiplanar to the lone pair on the nitrogen atom (**emboldened** in the scheme) [132]. Reductive removal of the chiral substituent on nitrogen then finishes off the overall ring-expansion protocol.



Scheme 8.30. Asymmetric nitrogen ring-expansion reactions of ketones utilizing (a) oxaziridine synthesis and photolysis [130] and (b) an azide-Schmidt reaction [133].

A few examples of a similar conversion utilizing an azide-based variant of the Schmidt reaction have also appeared [133]. The reaction is thought to entail the formation of a hemiketal between the hydroxyl group of the reagent and the ketone; dehydration of the hemiketal leads to an oxonium ion that is subject to attack by the now-tethered azido group. Migration of the bond antiperiplanar to the departing N_2 substituent, possibly through a conformation such as that depicted, was proposed to

lead to the observed lactam. Again, removal of the chiral substituent on nitrogen afforded the formal asymmetric Schmidt reaction product.

8.6 References

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