Chapter 8

Oxidations

Some of the most commonly-used asymmetric transformations are oxidation reactions. The reason for this is the widespread existence of heteroatoms in interesting organic molecules and the high utility of oxygenated compounds as synthetic intermediates. For example, ring strain means that epoxides are excellent partners for substitution reactions by a wide variety of nucleophiles; they can also be readily converted to allylic alcohols by elimination or to ketones by rearrangement. Given all of this, it is no wonder that K. Barry Sharpless's contributions to oxidation chemistry were celebrated by his recognition, along with William S. Knowles and Ryoji Noyori (both for reduction reactions) by the 2001 Nobel Prize in Chemistry [1].

Some of the most pertinent virtues of asymmetric epoxidations and dihydroxylations were already present in their classical versions. Both reactions are highly chemoselective 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.

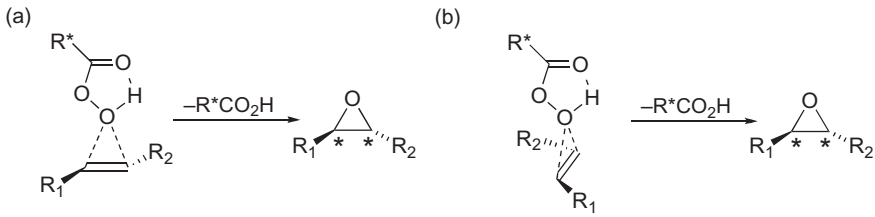
This chapter summarizes a variety of important asymmetric oxidation reactions, concentrating mainly on the most commonly-used examples such as epoxidation and dihydroxylation reactions but also glancing at some paths less traveled (*e.g.*, asymmetric ring-expansion reactions). Throughout our book, since most of these reactions have been thoroughly reviewed, coverage is selective. Once again, the emphasis is on utility and rationales of stereoselectivity.

8.1 EPOXIDATIONS AND RELATED REACTIONS

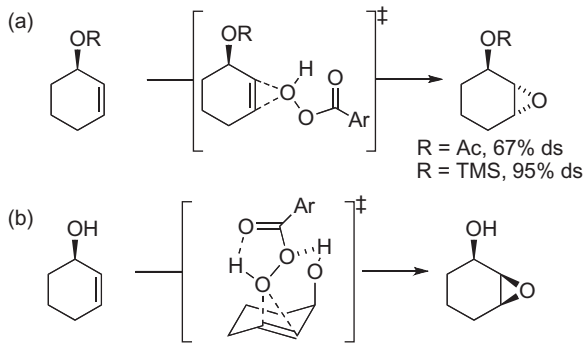
8.1.1 Early Approaches

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 [2]. 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*CO_3H, any stereogenic center on R* is too far away from the developing

Principles of Asymmetric Synthesis.



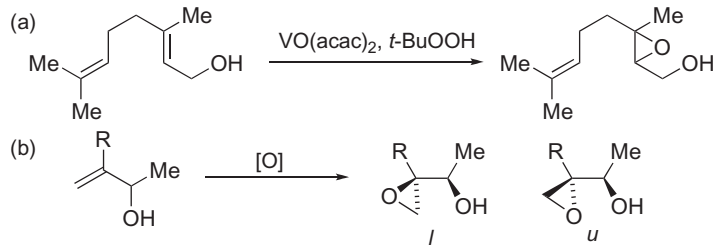
SCHEME 8.1 Generalized illustration of epoxidation of a *trans*-alkene using a chiral peracid; R* = a generic chiral substituent (in early work, monoperoxycamphoric acid was often used). (a) Butterfly and (b) spiro arrangements.



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 [7,8].

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, Scheme 8.1a) or within planes perpendicular to each other (the spiro arrangement, Scheme 8.1b). Clearly, a transition state in which the chirality in the reagent is closer to the reacting olefin was required.

An important clue as to how this could be attained was provided by Henbest and co-workers [3]. 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 [4]. 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; Scheme 8.2a). 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, reagent delivery might be expected to lower the activation barrier of the reaction due to favorable entropy. Thus, rather than achieving selectivity by blocking an unfavorable path relative to an achiral model system, one might affect 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 [5] and other reactions [6].



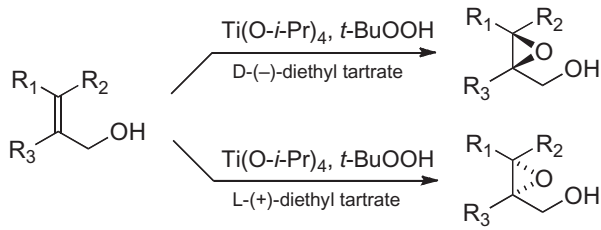
R	[O]	*l*:*u* ratio
H	*m*-CPBA	60 : 40
H	$VO(acac)_2$, *t*-BuOOH	20 : 80
CH_3	*m*-CPBA	45 : 55
CH_3	$VO(acac)_2$, *t*-BuOOH	5 : 95

SCHEME 8.3 Some examples of V^{+5}-mediated reactions of allylic alcohols with *t*-BuOOH. (a) A chemoselective reaction [10]. (b) Stereoselective reactions of acyclic allylic alcohols, compared to results obtained using *m*-CPBA [11]. 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.

This idea was later extended by Sharpless to include epoxidation reactions mediated by transition metals, notably those based on vanadium [8] (for a general review of transition metal mediated epoxidations, see ref. [9]). These diastereoselective epoxidation reactions laid the groundwork for the development of the catalytic asymmetric epoxidation reactions. Thus, soluble metal complexes such as $VO(acac)_2$ 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: other 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 [8]. 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 substantial rate acceleration for suitable substrates. In addition, this phenomenon allowed the useful chemoselective differentiation between allylic alcohols and other olefins. These experiments set the stage for the development of an efficient asymmetric epoxidation reaction.

8.1.2 Epoxidations

Katsuki–Sharpless asymmetric epoxidation. Upon its introduction in 1980 [12], the Katsuki–Sharpless asymmetric epoxidation (AE) reaction of allylic alcohols quickly became one of the most popular methods in asymmetric synthesis [13–16]. 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 low substoichiometric amounts of the titanium–tartrate complex), this recipe has persisted to this writing.



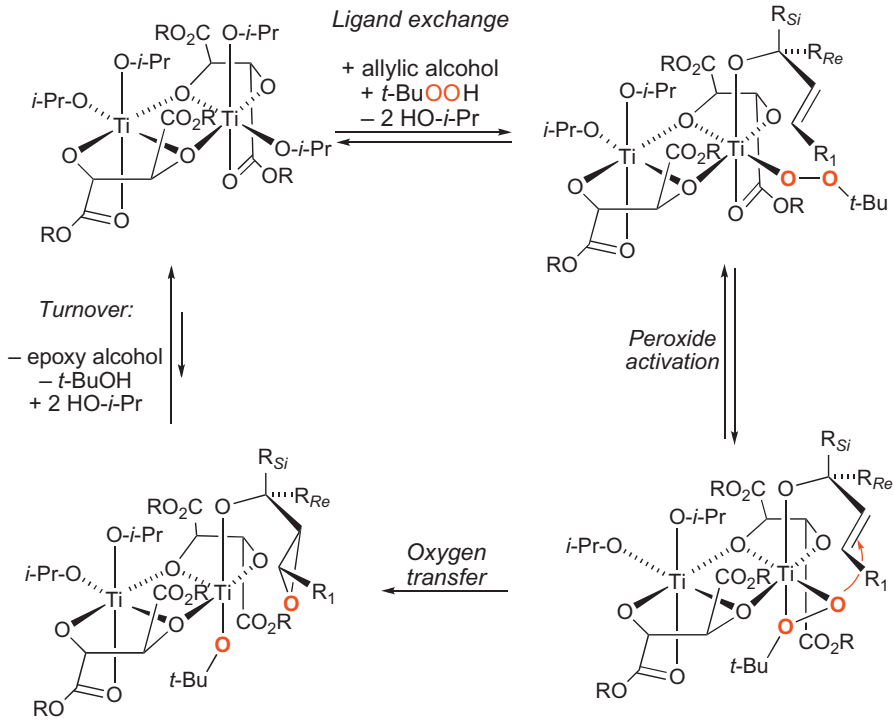
SCHEME 8.4 The asymmetric epoxidation reaction of allylic alcohols generally affords the product epoxides in excellent yields (>70%) and enantioselectivities (>95%). In addition, the reaction is predictable with respect to the predominant enantiomer obtained as shown.

In general, the reaction accomplishes the efficient asymmetric synthesis of hydroxymethyl epoxides from allylic alcohols (Scheme 8.4). Operationally, the catalyst is prepared by combining titanium isopropoxide, diethyl or diisopropyltartrate (DET or DIPT, respectively), and molecular sieves in CH_2Cl_2 at −20 °C, followed by addition of the allylic alcohol or *t*-BuOOH. After a brief waiting period (presumably to allow the ligand equilibration to occur on titanium), the final component of the reaction is added. 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 pertinent, allowing the synthesis of either enantiomer of a desired product. A key feature in this regard is the predictability of the enantioselectivity as shown in Scheme 8.4. And the experimental simplicity of standard epoxidation reactions has been effectively retained, since 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 the reaction has been reviewed [13]. Evidence in support of this mechanism has included extensive kinetic studies, spectroscopy, molecular weight determinations, and theoretical investigations [15,17−22].[1] A very important aspect of this mechanism, not shown in the scheme, is the formation of the titanium−tartrate species from its commercially available precursors, Ti(O-*i*-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 similar to that observed in the X-ray structure of a related tartramide complex [24].

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. 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 ($R_{Si} = R_{Re} = H$), 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

1. An alternative mechanism involving a monomeric complex has also appeared [23].



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

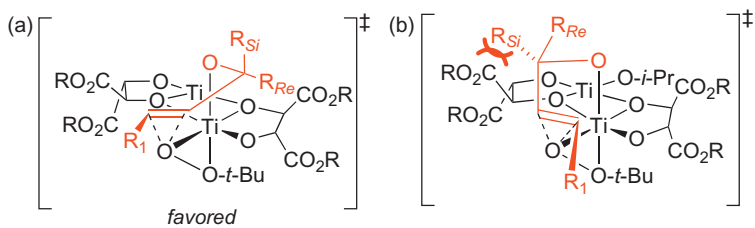


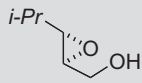
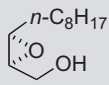
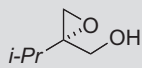
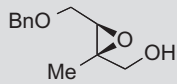
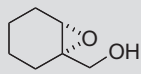
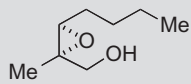
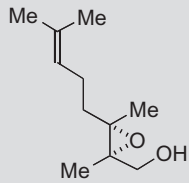
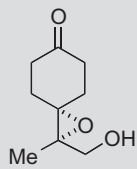
FIGURE 8.1 Proposed steric interactions leading to enantioselectivity in the Sharpless AE reaction.

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.

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 $R_2 \neq H$ 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 levels of 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). The epoxidation of the allylic alcohol in the presence of another olefin in entry 9 exemplifies the chemoselectivity that is inherent in this reaction.

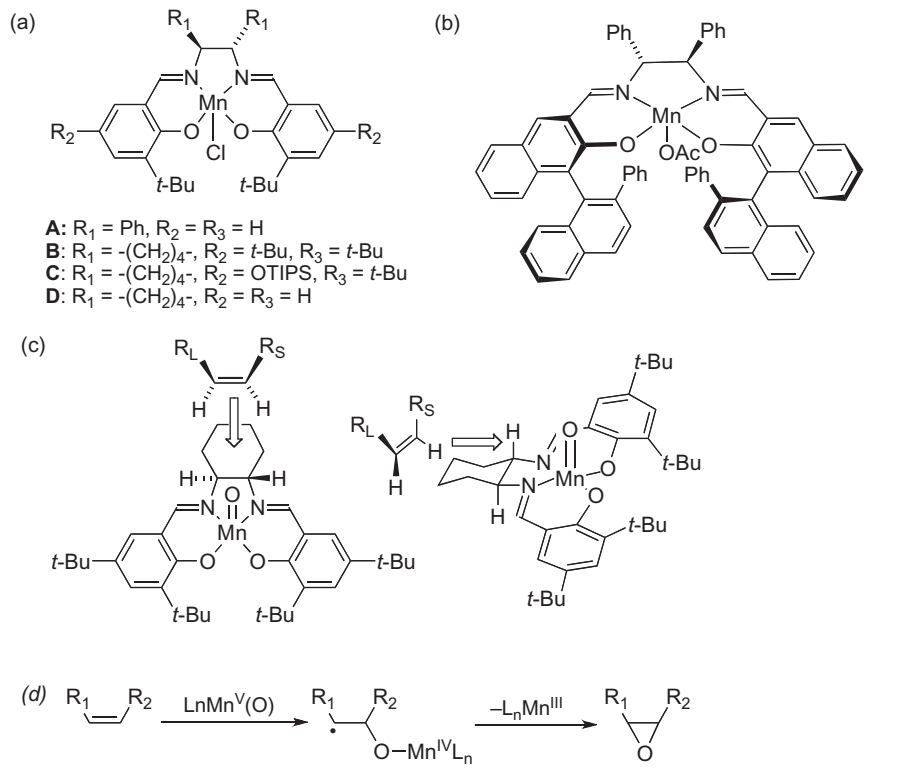
TABLE 8.1 Examples of Sharpless AE Reactions[a]

Entry	Product	Tartrate	% Yield	% es	Ref.
1		(−)-DIPT	50–60	94–96	[25]
2		(+)-DET	85	97	[25]
3		(+)-DET	54	83	[26]
4		(+)-DIPT	63	>90	[25]
5		(+)-DET	88	97	[25]
6		(−)-DIPT	87	95	[27]
7		(+)-DET	77	96	[25]
8		(+)-DET	80	94	[12]
9		(+)-DET	95	95	[25]
10		(+)-DET	*Not reported*	>95	[28]

[a]*These reactions were carried out under catalytic conditions (<10 mol% of $Ti(OR)_4$ and tartrate), except for entry 8 (done using stoichiometric catalyst).*

Asymmetric epoxidation reactions of simple olefins. Since the discovery of the Katsuki-Sharpless AE reaction, a major goal became to obviate the need for an allylic alcohol. Attempts to carry out asymmetric epoxidation reactions on simple olefins began with the ill-fated chiral peracid approaches noted in Section 8.1.1. In addition, numerous attempts using transition-metal-containing catalysts such as porphyrins as stoichiometric chiral reagents have been reported, with various degrees of success (peroxides, dioxiranes, and oxaziridines). These approaches have been summarized [29]. We concentrate here on the two catalytic methods that have found the most use by practicing synthetic organic chemists: the salen-catalyzed reactions of activated oxygen donors and reactions of chiral dioxiranes.

The introduction of salen catalysts for epoxidation reactions was a major breakthrough in the field, with the key papers being published by Jacobsen [30,31] and Katsuki in 1990 and 1991 [32–34]; for reviews, see refs. [29,35–37]. The Jacobsen–Katsuki epoxidation uses chiral and typically C_2-symmetric (salen)Mn complexes, such as those shown in Scheme 8.6 (the initial discovery of salen-based catalysis in oxidation reactions is generally attributed to Kochi [38]). The chiral salen catalysts 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 permit

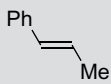
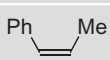
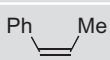
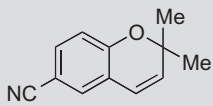
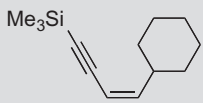
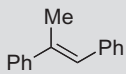
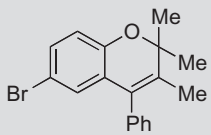
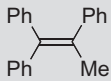


SCHEME 8.6 Jacobsen–Katsuki epoxidation of simple olefins. Examples of (salen)Mn(III) epoxidation catalysts prior to reaction with NaOCl by (a) Jacobsen [29–31,41,44] and (b) Katsuki [32–34]. (c) Two views of the proposed side-on approach of a generic *cis* olefin to the loaded catalyst. (d) Proposed stepwise mechanism of the reaction [44].

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 many outstanding results have been obtained, there are some limitations to the scope of this process (Table 8.2). The reaction works best with *cis*-olefins and affords the highest selectivities with conjugated, preferentially cyclic olefins. Further improvements resulted in a substantial broadening of this profile, obtaining some good-to-excellent selectivities from styrene [39] and certain tri- and tetra-substituted olefins (especially those that are not subject to isomerization due to symmetry or by constraining the double bond in a ring) [40,41].

TABLE 8.2 Examples of Jacobsen AE Reactions[a]

Entry	Olefin	Catalyst	% Yield (*cis*/*trans*)	% es	Ref.
1		A	71 (*trans* only)	60	[30]
2		B	84 (92:8)	96 (*cis*), 92 (*trans*)	[29,31]
3		C[b]	Not reported (5:95)	90 (*trans*)	[44]
4		B	96	98	[29,31]
5		B	65 (16:84)	82 (*cis*), 99 (*trans*)	[45]
6		B	73	82	[46]
7		B	87	94	[40]
8		D	72	90	[41]
9		A	12	72	[41]

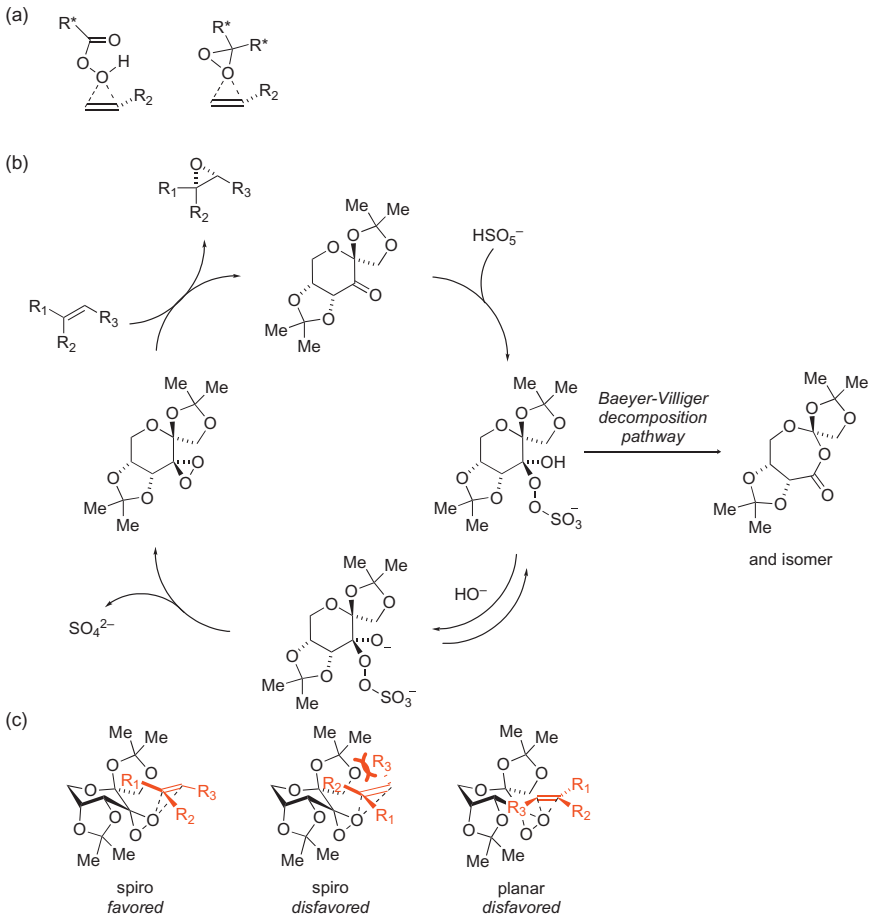
[a] *See Scheme 8.6a for catalyst structures.*
[b] *A cinchona alkaloid additive was used.*

Jacobsen proposed the approach vector for substrate shown in Scheme 8.6c, with selectivity arising from the minimization of steric interactions when the smaller alkene substituent R_S is closer to the *syn* axial hydrogen atom of the catalyst than R_L [31]. While Katsuki proposed a different approach from the side of the catalyst (not shown, ref. [32]), both models are consistent with the observed sense of stereoinduction (this issue is extensively considered in ref. [42]). Some acyclic *cis*-olefins were found to afford various amounts of *trans* epoxides, one observation that led to a radical mechanism being proposed for some substrates and supported through a radical probe study (Scheme 8.6d [43]). This isomerization could be facilitated by the addition of chiral quaternary ammonium salts, leading to synthetically useful ($>10{:}1$ *trans*:*cis*, $>90\%$ es) conversions of *cis*-olefins to *trans*-dialkyl epoxides (*cf.* entries 2 and 3 in Table 8.2) [44].

The 1990s also saw significant efforts toward the development of chiral dioxiranes for epoxidations (reviews: refs. [47–49]). Dioxiranes are highly active oxidizing agents that can be generated *in situ* by reacting a ketone precursor with inorganic Oxone, a commercially available form of potassium peroxomonosulfate ($KHSO_5$) formulated as $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. In contrast to simple peracids, the 3-membered ring of a dioxirane places the elements of the chiral ketone precursor closer to the reacting olefin, and in principle high enantioselectivity can result (Scheme 8.7a). In practice, the development of appropriate catalysts proved challenging, with the carbohydrate-derived system developed by Shi being the predominant version used in laboratories today [50–52]. The design features that led to this particular ketone, which is prepared from fructose [50], include highly differentiated α and β faces of the ring system, the presence of σ electron-withdrawing groups adjacent to the carbonyl to facilitate the formation of the dioxirane group, and the confinement of the latter in fused rings or upon a quaternary center to avoid epimerization of the ketone during the course of the reaction. In practice, the Shi ketone is mixed with Oxone under buffered conditions of pH *ca.* 7–10, found to minimize decomposition of the Oxone on one hand and to avoid the destruction of the catalyst *via* a Baeyer–Villiger reaction on the other [51]. Table 8.3 shows that the Shi epoxidation works well with a variety of olefin types, notably providing needed complementarity to the Jacobsen epoxidation due to its utility with *trans*-substituted olefins. Although the reaction does succeed with electron-deficient olefins (Table 8.3, entry 10 – more about those shortly), it preferentially reacts with a more electron-rich one when there is a choice (entry 8). While the enantiomer of the catalyst shown is most easily prepared from D-fructose, L-fructose is available from sorbose and can be used to prepare the opposite enantiomer of the Shi catalyst [53]. Additionally, other ketones and means of generating the active species have been studied [48].

The reaction is generally considered to proceed with a more or less concerted transfer of the active oxygen from the dioxirane to the substrate *via* one of the transition states shown in Scheme 8.7c. Shi has rationalized the preferred enantioselectivity of the reaction in the context of the spiro transition structure in which nonbonded interactions are minimized. One of several disfavored spiro structures shows an unfavorable steric interaction between one of the alkene substituents and a nearby oxygen atom on the catalyst, while one of the four analogous planar transition states is also depicted. This planar structure was proposed to be on the predominant minor pathway and presumably disfavored for subtle electronic and structural reasons. Kinetic isotope effects and calculations have been carried out by Singleton, who has emphasized the importance of reaction asynchronicity in rationalizing the results [60].

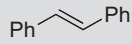
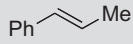
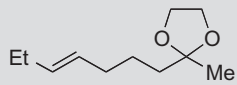
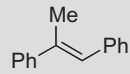
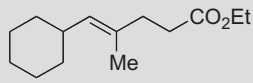
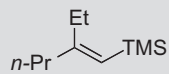
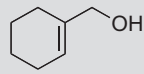
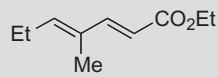
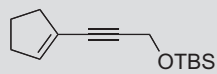
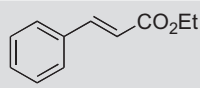
Epoxidation of electron-deficient olefins. In contrast to the oxidation reactions of electron-rich olefins just described, highly selective nucleophilic epoxidation reactions of α,β-unsaturated carbonyl compounds were slower to appear on the scene (Scheme 8.8, for reviews, see refs. [61–65]).



SCHEME 8.7 (a) Comparison of generalized transition structures for peracid-mediated *vs.* dioxirane-mediated epoxidations. (b) Shi catalyst structure and catalytic cycle, including the Baeyer–Villiger pathway for catalyst decomposition. (c) Comparison of three possible orientations leading to epoxidation. Two spiro pathways are shown (out of four), with the leftmost one being the most favorable. The one planar orientation shown (again, out of four possible) is cited as the second-most favored overall pathway; it leads to the opposite enantiomer of that resulting from the most favored spiro pathway. For a full discussion, see ref. [54].

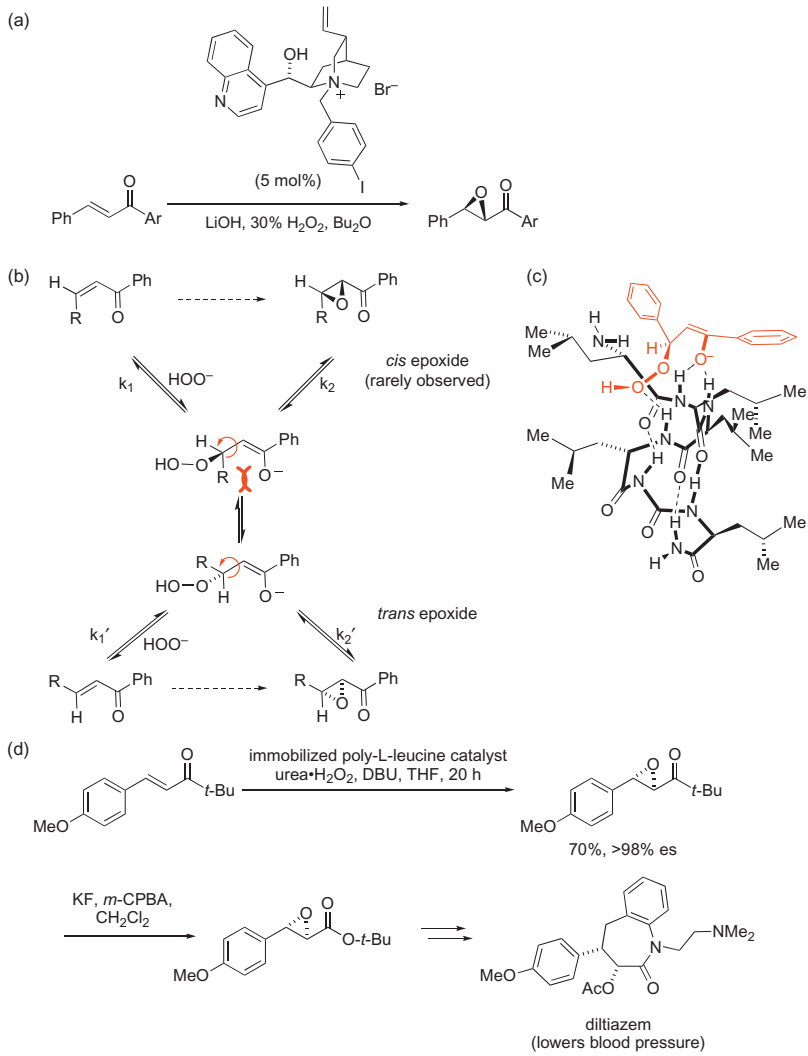
The most successful early attempts were carried out on chalcones, using standard basic peroxidation conditions with additives such as a quinine-derived phase-transfer catalyst first reported by Wynberg in 1976 [66] and explored by others (*e.g.*, Scheme 8.8a [67]). This constituted an early example of organocatalysis, as were reactions promoted by the unusual catalyst poly-L-leucine, first reported in 1980 and now known as the Juliá–Colonna epoxidation [68]. Mechanistically, epoxidations of most electron-poor olefins do not take place by concerted (if highly asynchronous) bond formation across both olefin carbons typical for other epoxidations. Instead, most occur by asymmetric conjugate addition of a peroxide anion followed by nucleophilic ring closure onto oxygen, which is now acting as an electrophile (Scheme 8.8b). When this happens, the configuration of the double bond is lost and *trans* epoxide is normally formed; in such cases the reaction is stereoselective but *not* stereospecific. Although exceptions exist

TABLE 8.3 Shi Epoxidation Reaction

Entry	Substrate	% Yield	% es	Ref.
1[a]		85	99 (*R,R*)	[52]
2[a]		94	98 (*R,R*)	[52]
3[a]		92	96 (*R,R*)	[52]
4[a]		89	98 (*R,R*)	[52]
5[a]		89	97 (*R,R*)	[52]
6[b]		51	95 (*R,R*)	[55]
7[a]		93	97 (*R*)	[56]
8[a,c]		82	97 (*R,R*)	[57]
9[a]		97	88 (*R,R*)	[58]
10		62[d]	91 (*R,R*)	[59]

[a]*Conditions: Ketone (0.3 equiv), Oxone (1.38 equiv), K_2CO_3 (5.8 equiv), MeCN–DMM–0.05 M $Na_2B_4O_7 \cdot 10H_2O$ of aq. Na_2EDTA (1:2:2, v/v).*
[b]*Conditions: Ketone (0.65 equiv), Oxone (1.38 equiv), K_2CO_3 (5.8 equiv), MeCN–DMM–0.05 M $Na_2B_4O_7 \cdot 10H_2O$ of aq. Na_2EDTA (1:2:2, v/v).*
[c]*Epoxidizes across the γ, δ-unsaturated double bond.*
[d]*Conditions: Ketone (0.3 equiv), Oxone (3 equiv), K_2CO_3 (6 equiv), dioxane/H_2O, 6 h, rt.*

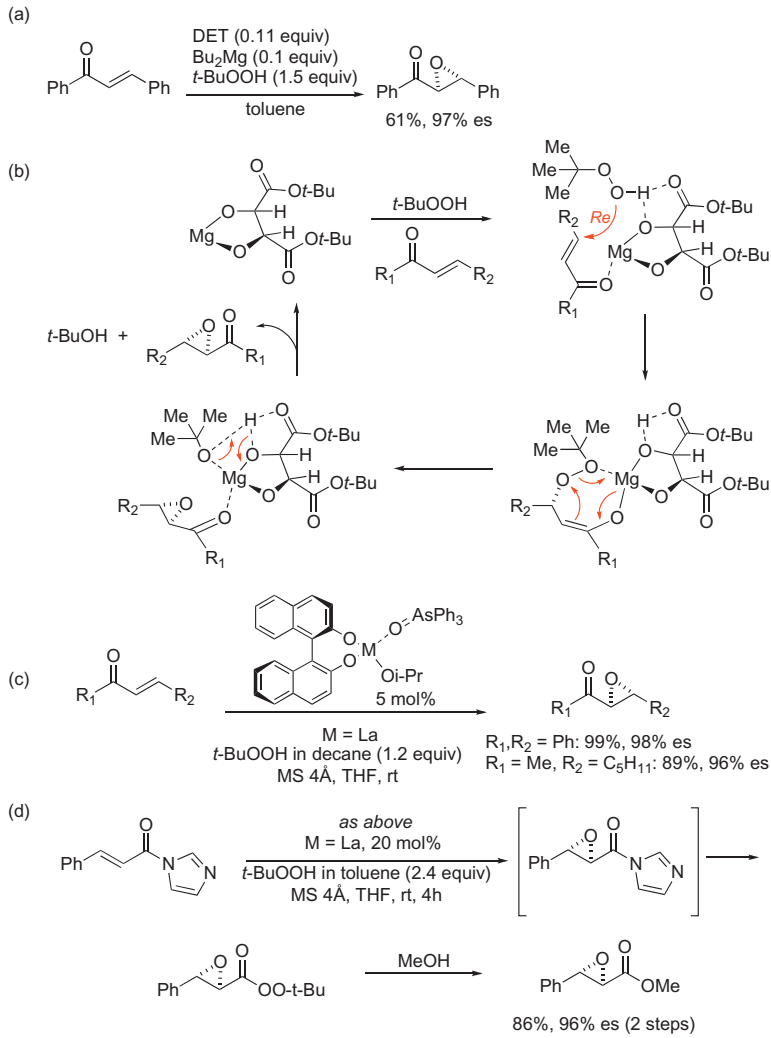
(obviously for cyclic substrates but also in a few acyclic examples [69,70]), the stereospecificity or lack thereof of a given reaction is generally taken as evidence for a concerted or a two-step mechanism, respectively. In a two-stage mechanism, the absolute configuration can in principle be set in the first step *via* a kinetically controlled enantiofacially selective conjugate addition reaction. However, in his extensive explorations of the Juliá–Colonna epoxidation [62,71], Roberts' analysis showed that this first step was reversible and that the high stereoselectivity could be best explained by a kinetic resolution of the initially formed β adduct isomers through a stereoselective ring closure of the substrate bound to the leucine oligomer, which adopts a highly helical structure in solution (Scheme 8.8c). Although



SCHEME 8.8 Nucleophilic epoxidation reactions of enones using (a) phase transfer catalysis [67] or the Juliá–Colonna epoxidation, for which is shown (b) the kinetic profile, (c) Roberts' proposed model for the helical peptide complexed to a β-peroxy adduct (shown in red), and (d) an example used in the synthesis of diltiazem [73].

limited to α,β-unsaturated ketones, the products can often be converted to the corresponding α,β-epoxy esters *via* a regioselective Baeyer–Villiger oxidation, a reaction that was central to the use of the Juliá–Colonna epoxidation in the synthesis of the blood pressure regulator diltiazem (Scheme 8.8d [72]).

More recent work has centered on catalysts that activate the electrophilic alkene to nucleophilic attack; although little mechanistic information is available, it is reasonable to expect that the stereoselectivity of these reactions occurs *via* a kinetically controlled addition of the peroxide to the α,β-unsaturated ketone. An early selective example was published by Jackson using a tartrate ligand (Scheme 8.9a [74]) who later proposed the



SCHEME 8.9 Metal-promoted epoxidations of electron-poor olefins by (a) [74], (b) [75], (c) [76], and (d) [77].

magnesium-coordinated delivery of *tert*-butylhydroperoxide as shown in Scheme 8.9b [75]. Probably the most general approach to this problem is Shibasaki's BINOL coordinated lanthanides, which were first applied to chalcone epoxidation (Scheme 8.9c, ref. [76]) and later extended to other substrate types [77,78]. Note the unusual use of a triarylarsine as a ligand; this proved more effective than other additives. This catalyst did not initially give good results with α,β-unsaturated esters. The apparent need for steric bulk on either side of the carbonyl group led to the ingenious work-around shown in Scheme 8.9d [77]. Here, a imidazoyl-substituted substrate was converted under the reaction conditions by *tert*-butyl hydroperoxide to a mixed perester that could be subsequently converted to the methyl ester. Later papers described the versions that could be used for the direct and selective epoxidation of α,β-unsaturated amides [78] and esters [79].

8.1.3 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_{Si} to be well-tolerated because this group points away from the catalyst, whereas R_{Re} should be much more sterically encumbered (Figure 8.2). Some experimental observations that address this issue and permit the application of the Katsuki–Sharpless catalyst to kinetic resolution reactions are shown in Scheme 8.10 [80].

Like the vanadium-based catalysts, the Sharpless AE system intrinsically favors 1,2-*anti* products; this is because the cyclohexyl group in Scheme 8.10a occupies the position denoted by group R_{Si} in Figure 8.2, away from the catalyst. In fact, this diastereoselectivity is somewhat amplified relative to achiral titanium catalysts. When the *S* allylic alcohol is used with (+)-DIPT, a matched pair results (Scheme 8.10a). The strong enantiofacial selectivity of the L-(+)-DIPT catalyst clashes with the *R* substrate's resident chirality (this is the case shown in Figure 8.2 with R_{Re} = cyclohexyl). In this mismatched pair, the preference of the chiral catalyst for α attack moderately exceeds that of the allylic alcohol for 1,2-*anti* product (Scheme 8.10b). The most important consequence is that *the mismatched reaction is 140 times slower than the matched one*. That is, the selectivity factor, **s** = 140 (see Section 1.7).

Using a racemic allylic alcohol, one can take advantage of this rate differential to selectively epoxidize the more reactive *S* isomer in the presence of its enantiomer. This procedure is known as a Sharpless kinetic resolution (KR) [80]. The KR has very wide applicability for the preparation of both 1,2-*anti* epoxy alcohols and the unreacted allylic alcohol, often with very high enantioselectivities (note that the diastereomeric 1,2-*syn* series is not generally available by this technique). In general terms, carrying out the reaction to lower conversions will maximize the enantiomeric purity of the epoxide, while greater conversions sometimes lead to very high (>99%) enantiomeric purities of the allylic alcohol, albeit in a reduced yield.[2] Scheme 8.10c 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

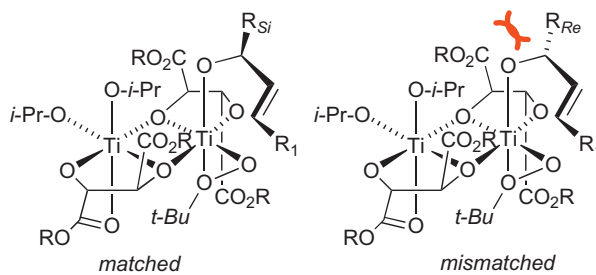
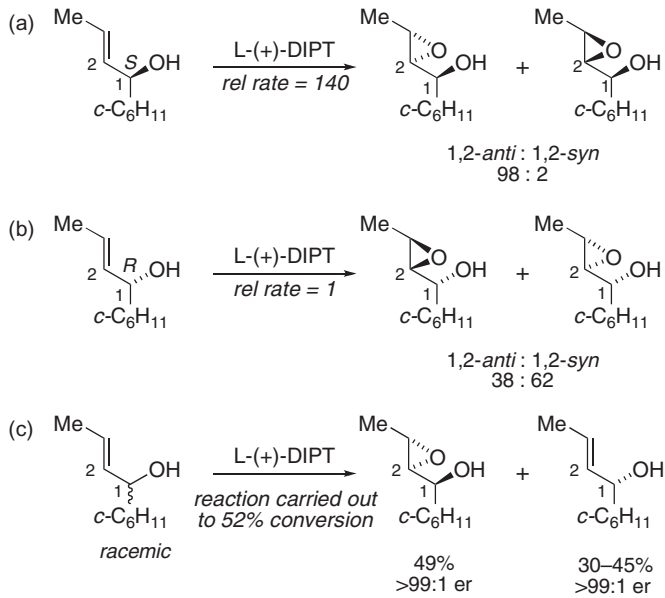


FIGURE 8.2 Origins of selectivity in the Sharpless kinetic resolution.

2. Interested readers are directed to the original literature for a quantitative treatment [15,80].

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



SCHEME 8.10 Reactions of a chiral allylic alcohol under Sharpless epoxidation conditions (Ti(O-*i*-Pr)$_4$, *t*-BuOOH) using the chiral tartrates given (DIPT = diisopropyltartrate, ref. [80]). (a) The "matched" case, in which the preferred approach of the asymmetric catalyst and the diastereoselectivity of the substrate are the same. (b) The "mismatched" case. (c) An example of a Sharpless kinetic resolution (KR).

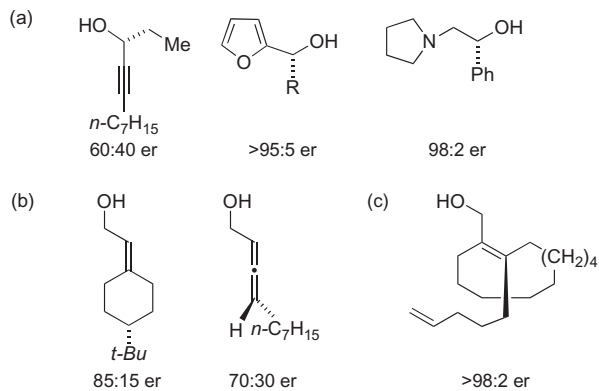


FIGURE 8.3 Examples of molecules prepared in enantiomerically enriched form using Sharpless KR procedure. (a) Compounds having alternative sites of oxidation; the enantioenriched (unreacted isomers) products of kinetic resolutions of an acetylene [82], a furan [83], and an amine [84] are shown. (b) Compounds bearing axial chirality [82]. (c) An alkene with planar chirality following KR enrichment [85].

chirality. Finally, some success has been seen in extending both the AE and KR procedures to homoallylic alcohols [81].

8.1.4 Some Applications of Asymmetric Epoxidation and Kinetic Resolution Procedures

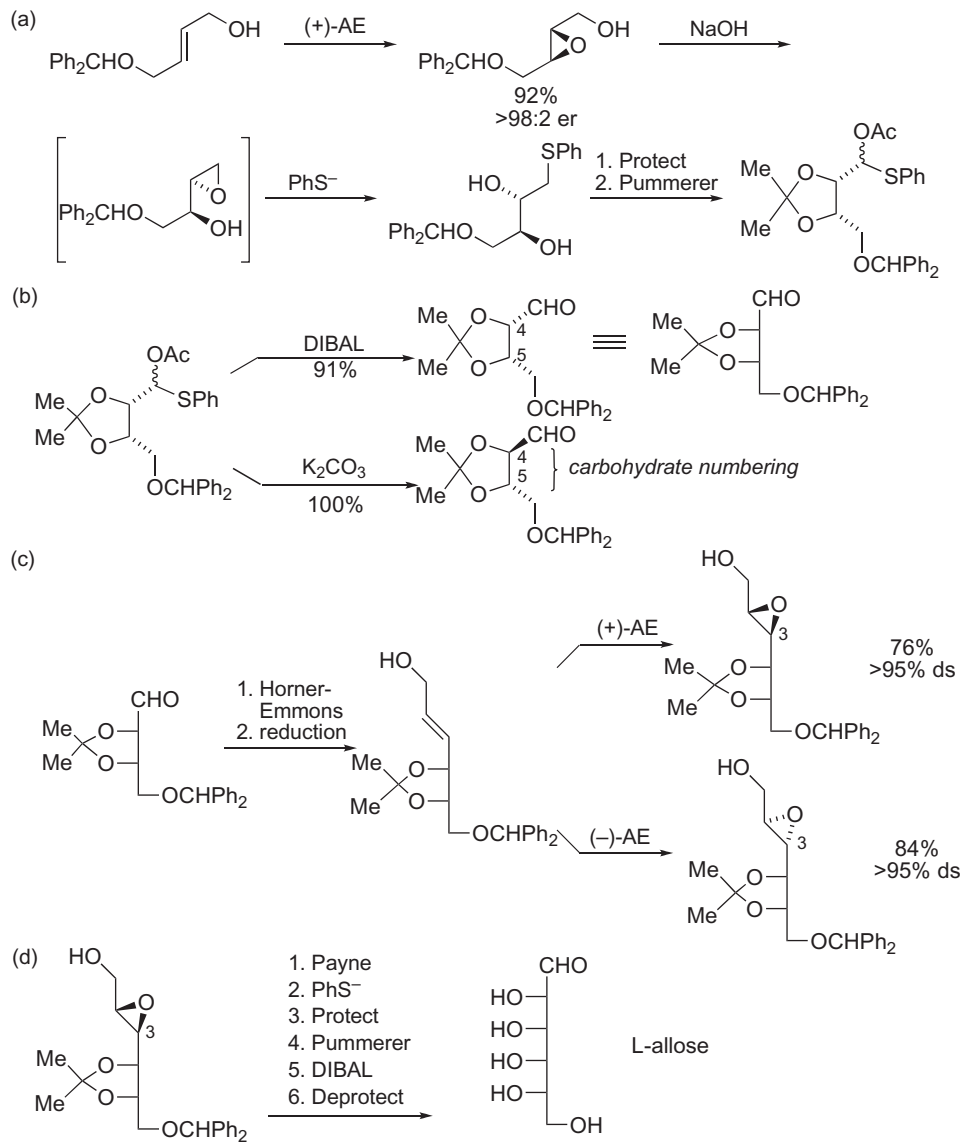
The influence of asymmetric epoxidations has been far too pervasive to allow even a partial representative listing here. However, it's worth recalling a few illustrations of the power of epoxidation chemistry in organic synthesis.

Carbohydrate synthesis. Save the all-important hydroxymethyl group that the titanium reagent uses as its handle, the Sharpless AE is remarkably insensitive to 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 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 1.6). This strategy was beautifully illustrated by the synthesis of all eight isomeric hexoses in their unnaturally-occurring L-series, summarized for L-allose in Scheme 8.11 [86,87]. This iterative sequence prepares the target carbohydrate in the C-6 → 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 using base, which isomerized the epoxy alcohol with 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]

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 has been termed *ancillary stereocontrol* [89]). 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 5-membered ring. Alternatively, basic deprotection led to epimerization to the *trans* isomer. This was possible in this case because of poor overlap between the aldehyde enolate and the σ* orbital associated with the C-5 carbon−oxygen bond − otherwise β-elimination of one of the acetal oxygens might have occurred. Also, using an epimerization step obviated the necessity of preparing and working with the less reactive *cis*-olefins to switch between diastereomeric series. Overall, the conversions in Schemes 8.11a and b constitute a single iteration of the synthesis.

Scheme 8.11c 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

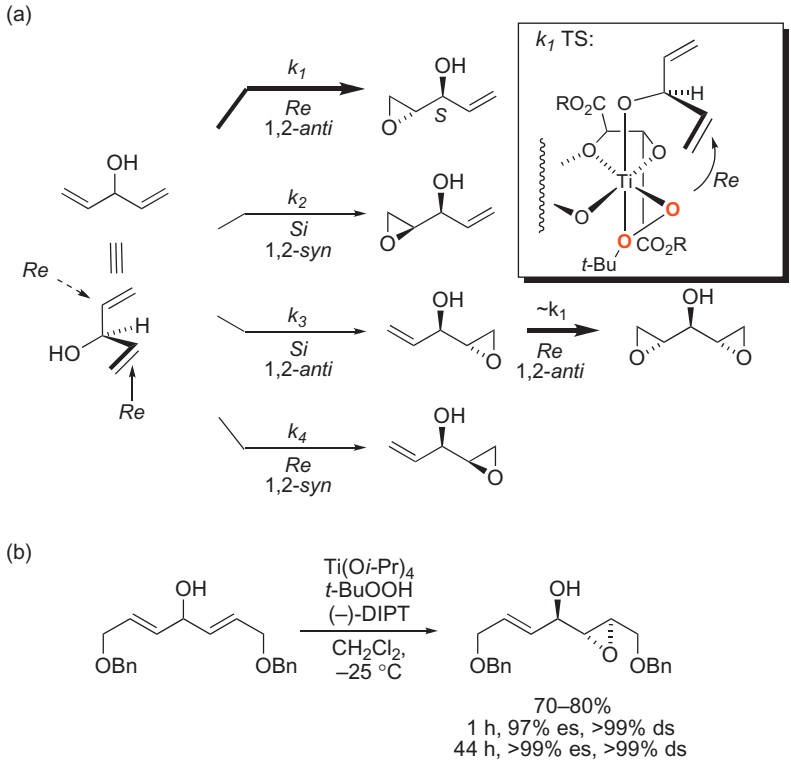
3. Although known prior to the discovery of the Sharpless AE, this use of the Payne rearrangement is a good example of how the availability of a particular functional array by asymmetric synthesis provoked a reaction's further development [88]. In this case, the product sulfide allows the chemoselective conversion of this carbon to the oxidation state of the aldehyde, in the guise of an acetoxy sulfide.



SCHEME 8.11 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.

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 [90].

Group-selective reactions of divinyl carbinols. Recall that the reagent control strategy is inapplicable to situations where the resident chirality is on the allylic position bearing the



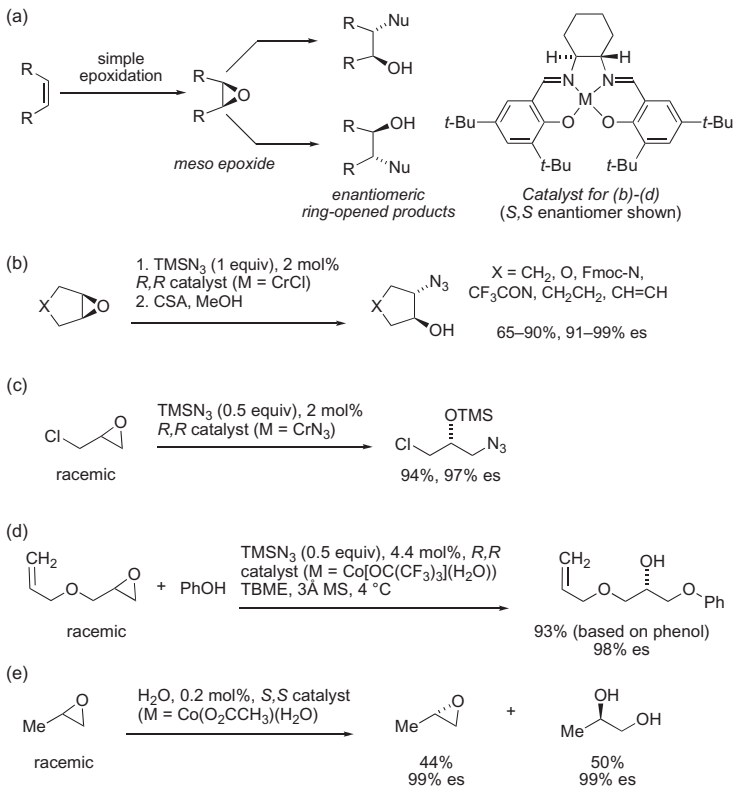
SCHEME 8.12 Reaction of divinyl carbinol under (+)-AE conditions as an example of enantiotopic group selectivity in epoxidation chemistry. Matched cases of enantiofacial selectivity are shown with bold arrows, *via* the k_1 partial transition structure shown in the inset (see also Scheme 8.5). Qualitative 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). Note that the products arising from the pairs k_1/k_3 and k_2/k_4 are enantiomers. (a) Theoretical treatment and (b) an experimental example [94].

hydroxyl "handle" for the catalyst. However, the preference for 1,2-*anti* product has been cleverly applied to a problem in diastereotopic group selectivity (Scheme 8.12) [91–95]. The two olefins carry a total of two enantiomeric pairs of diastereotopic faces. When a tartrate–titanium epoxidation system is allowed to react with this substrate, approach to only one of these four faces simultaneously satisfies the requirements of both the catalyst (which prefers the *Re* face) and the substrate (which prefers 1,2-*anti* addition). To the extent that the rate of epoxidation at this face exceeds that of the others (k_1 in Scheme 8.12), one product predominates. Minor diastereomers result from pathways k_2 and k_4. However, note that the pathway with a rate of k_3 (mismatched: 1,2-*anti* diastereoselectivity combined with disfavored *Si* enantiofacial attack) affords the enantiomer of the major isomer.

Schreiber has noted that this group-selective process is expected to provide products with very high enantioselectivity because the disfavored enantiomer resulting from pathway k_3 *still has the most favorable face available for reaction* [94]. Thus, to the extent that product from pathway k_3 accumulates, it is rapidly siphoned off at a rate comparable to k_1. Thus, the problem of enantiomer separation at the end of the reaction can largely be replaced by the problem of diastereomer and side product separation (although itself never an issue to be taken lightly!). The availability of a path for selective destruction of the unwanted enantiomer

means that the desired product can be obtained with very high enantioselectivity when the reaction is pushed to higher conversions. However, this will come at the expense of overall yield because some of the desired product will also react further under such conditions [94,96]. Provided that one is able to distinguish either end of a developing chain, such reactions have promise in applications involving two-dimensional chain elongation strategies [97].

Epoxide-opening reactions. The most common use of epoxides is in S_N2 ring-opening reactions leading to 1,2-difunctionalized compounds.[4] As just discussed, 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 8.13a). One can open an epoxide with a chiral amine and separate the products [99] but catalytic means of carrying out the reaction enantioselectively have been reported by Nugent [100] and Jacobsen [101]. The salen-promoted epoxide openings by Jacobsen are also portable to the kinetic resolution of terminal epoxides by a variety of useful nucleophiles such as



SCHEME 8.13 (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 the salen−metal complexes shown in (a) [101]. Kinetic epoxide resolutions with (c) azide [102,103], (d) phenol [104], and (e) water [105].

4. For a review of such reactions in asymmetric synthesis, see ref. [98].

azide [102,103], phenol [104], and water [105]. The value of these procedures lies both in obtaining the ring-opened products in high enantiopurity and also in the isolation of the terminal epoxides, which are not generally accessible by direct asymmetric epoxidation.

8.1.5 Aziridinations

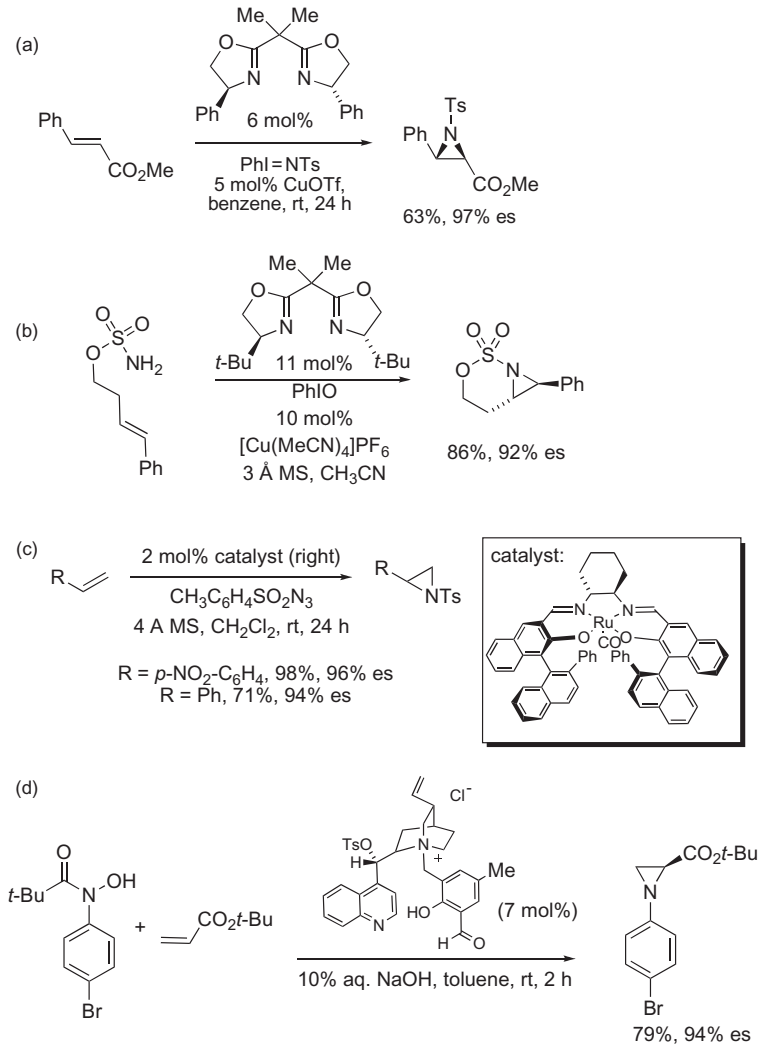
The asymmetric synthesis of aziridines has not received the same level of attention when compared to epoxides, not only because these reactions have posed particular challenges but also because their scope as synthetic intermediates is more narrow (various approaches have been reviewed in ref. [106]). Nonetheless, some catalytic, enantioselective aziridination reactions have been developed. In influential work, Evans showed that a copper bisoxazoline complex catalyzed the addition of *N*-(*p*-toluenesulfonylimino)phenyliodinane across an olefin (Scheme 8.14a [107]). Numerous investigators have examined similar ligands in aziridination reactions, *e.g.*, the intramolecular reaction shown in Scheme 8.14b [108]. In addition, chiral salen complexes of Mn [109], Cu [110], or Ru have been found to catalyze similar reactions with moderate to excellent enantioselectivities (Scheme 8.14c [108]). In all of these approaches, a metal-bound nitrene is generally assumed and has been supported by some mechanistic work [111]. Alternative approaches include the use of a cinchona alkaloid derivative to promote the conjugate addition of a hydroxamic acid as nitrogen source across an electron-deficient olefin followed by cyclization to aziridine product (Scheme 8.14d [112]).

8.2 ASYMMETRIC DIHYDROXYLATION (AD) REACTION

8.2.1 Reaction Development

The synthesis of vicinal diols from olefins using OsO_4 complements epoxidation/hydrolysis as a route to 1,2-diols (Scheme 8.15a, for reviews see refs. [115−120]). Both reagents effect *cis* bis-functionalization 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, was the first general method for the asymmetric oxygenation of unactivated olefins (*i.e.*, those without an allylic alcohol) and remains a valuable tool in synthesis. A general overview of the reaction sequence is outlined in Scheme 8.15b. All osmylation reactions ultimately afford an osmate ester[5] with concomitant reduction of osmium. Unlike most of the epoxidation reactions discussed earlier in this chapter, which require the formation of the active species in a chiral environment (either as a peroxo ligand or metal oxo species), the achiral precursor to most dihydroxylation catalysts, OsO_4, is itself a competent dihydroxylation reagent. An important antecedent for the development of the asymmetric osmylation was therefore the introduction of *achiral* means of accelerating the reaction rate and increasing turnover of osmium, with the goal of minimizing the amount of toxic metal necessary. Thus, catalytic methods using a variety of stoichiometric reoxidants for osmium were introduced, such as $KClO_4$ in 1912 [121] and the convenient Upjohn process, which uses *N*-methylmorpholine-*N*-oxide for this purpose [122]. Finally, a critical clue

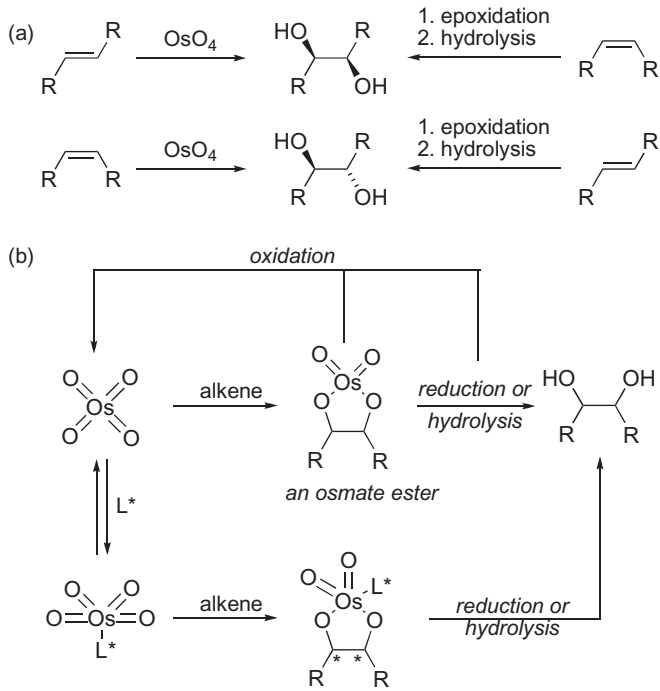
5. Both [3 + 2] concerted mechanisms and a stepwise process involving the formation of a metallooxetane intermediate by [2 + 2] cycloaddition followed by rearrangement were proposed, the latter most vigorously by Sharpless in his early papers introducing this reaction. On the strength of both theory and experiment, most now accept the simpler [3 + 2] mechanism.



SCHEME 8.14 Asymmetric aziridination reactions: (a) [113], (b) [108], (c) [114], and (d) [112].

was found in the work of Criegee, who had shown in 1942 that the reaction was accelerated by the addition of pyridine [123].

Taking this cue from Criegee, Sharpless reported that enantioselectivities of up to 97% could be realized when stoichiometric amounts of chiral amines were added to OsO_4-mediated oxidation reactions [124]. Sharpless used the cinchona alkaloids dihydroquinidine (DHQD) and dihydroquinine (DHQ) (Figures 8.4a and b). Note that although these ligands are nearly enantiomeric, their mirror symmetry is spoiled by the placement of the ethyl group on the bicyclic portion of the molecules. Nonetheless, they act as if they were enantiomers when applied to various asymmetric transformations. Other workers also reported a variety of



SCHEME 8.15 (a) 1,2-Diol synthesis from alkenes *via* direct osmylation or epoxidation followed by hydrolysis. (b) Generalized mechanism of the osmylation reaction.

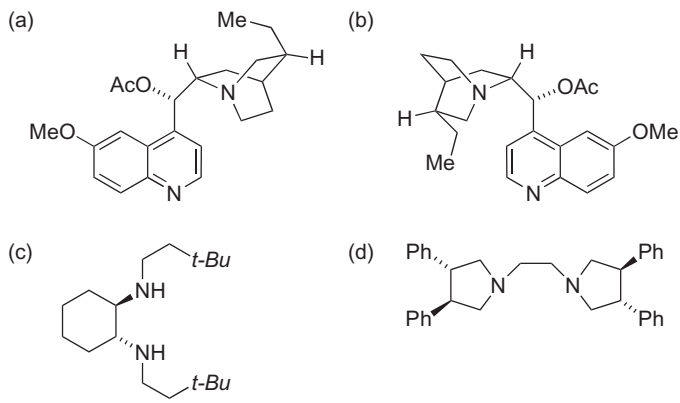
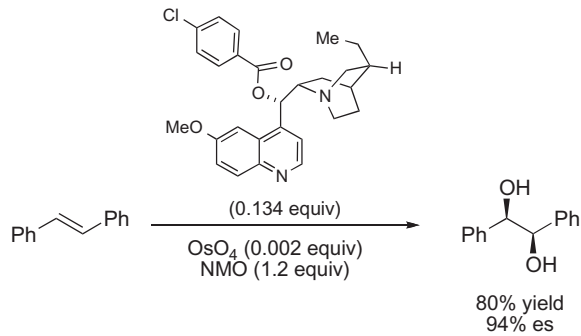


FIGURE 8.4 Representative ligands used in stoichiometric, asymmetric dihydroxylation reactions. (a) Dihydroquinidine (DHQD) and (b) dihydroquinine (DHQ) used by Sharpless [124]. Examples of C_2-symmetrical ligands used in stoichiometric osmylation reactions: (c) [125] and (d) [126]. These catalysts gave the following es values in dihydroxylation reaction of styrene: (a) 82%, (b) 80%, (c) $>99\%$, and (d) 95%.

additional 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).

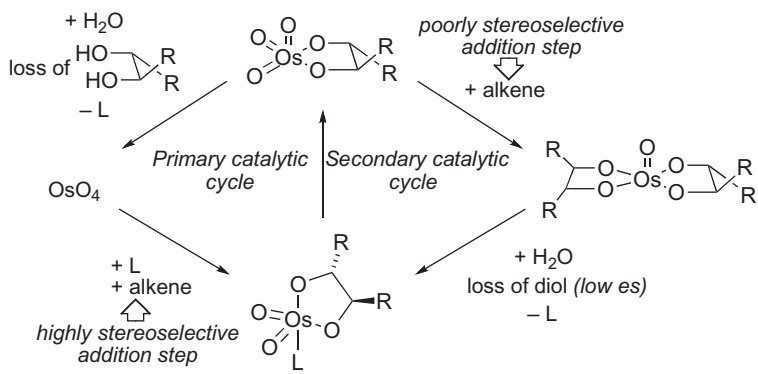
Sharpless reported the first generally useful catalytic version of the reaction in 1987 [127]. This landmark paper showed that the reaction could be rendered catalytic by



SCHEME 8.16 An early example of a catalytic asymmetric dihydroxylation reaction [127].

combining modified cinchona ligands with the Upjohn process (Scheme 8.16). This use of *ligand-accelerated catalysis* was critical to the success of this catalytic AD reaction because of the pre-equilibrium present between OsO_4 and OsO_4L^* in solution. Unless the equilibrium lies so far to the latter species as to effectively lower the concentration of OsO_4 to zero, the nonselective background reaction of OsO_4 with the olefin could compete with that of OsO_4L^*, lowering the enantioselectivity of the overall process. The ligand acceleration effect provided by the chiral amine ensured that the asymmetric pathway involving OsO_4L^* was 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 nonselective 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 8.17). 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



SCHEME 8.17 The two catalytic cycles proposed for the Sharpless AD reaction [128].

slow addition of the alkene (allowing the osmate ester time to undergo hydrolysis and reoxidation [128]), through the use of $K_3Fe(CN)_6$ as the reoxidant in place of NMO [129], or by increasing the rate of hydrolysis by adding $MeSO_2NH_2$ to the reaction mixture [130]. 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.

A mind-boggling number of AD catalysts have been examined. Some of the most commonly-used ligands are given in Figure 8.5 with a generalized correlation of ligand type with olefin class provided in Table 8.4. Examples of representative reactions are given in

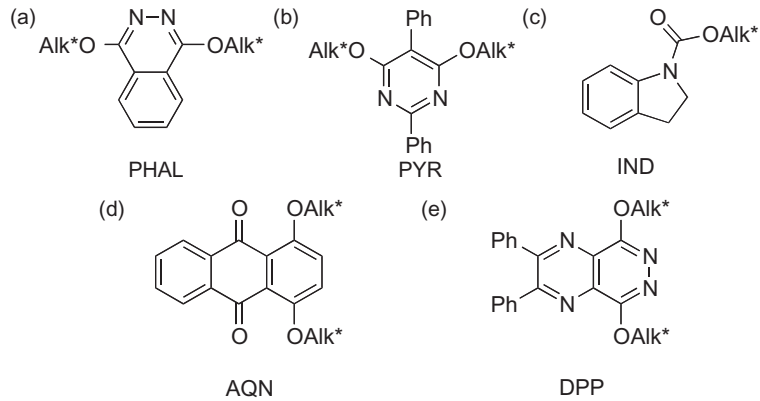


FIGURE 8.5 Ligands for the Sharpless AD process. (a) PHAL [130,131], (b) PYR [132,133], (c) IND [134], (d) AQN [135], and (e) DPP [136]. For each, the Alk* bound to each position is a cinchona alkaloid derivative (see Figures 8.4a and b).

TABLE 8.4 Generalized Utility of Ligand Types for AD Reactions According to Olefin Type [120]

	PHAL	PYR	IND	AQN	DPP
					
aromatic	X				X
aliphatic				X	
branched		X			
					
aromatic	X				X
aliphatic				X	
branched		X			

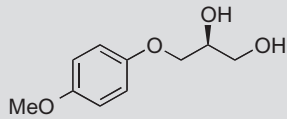
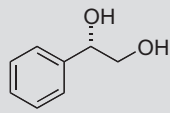
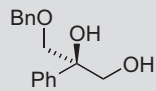
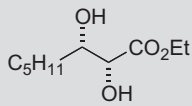
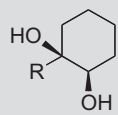
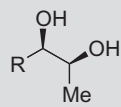
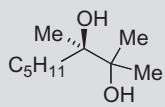
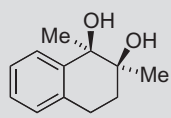
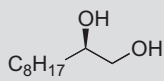
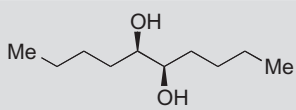
(*Continued*)

TABLE 8.4 (Continued)

					
acylic			X		
cyclic		X		X	X
					
aromatic	X				X
aliphatic				X	
	X			X	X
	X	X			
					
aromatic	X			X	X
aliphatic				X	
	X			X	X
	X	X			

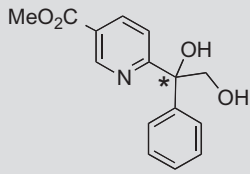
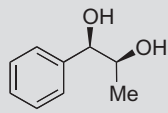
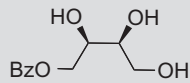
Table 8.5. The most striking advance was the use of dimeric species such as PHAL and PYR, which are still among the most general of the catalysts (Figures 8.5a and b). The former ligand has been formulated along with $K_2OsO_2(OH)_4$ (a nonvolatile source of Os), $K_3Fe(CN)_6$, and either DHQ or DHQD, respectively; these stable, storable powders contain all of the necessary ingredients for AD reactions and are marketed as AD-mix-α or AD-mix-β. 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 [118], and this portion of the catalytic system can usually be left alone. Numerous catalyst types have been devised to test mechanistic hypotheses or to provide various conveniences (such as immobilization for easy removal); the review literature may be consulted for leading references [120].

TABLE 8.5 Examples of Asymmetric Dihydroxylation Reactions

Entry	Diol product	Ligand[a]	% es	Ref.
1		$(DHQD)_2$-PHAL	95	[137]
2		$(DHQ)_2$-PHAL	98	[130,132]
3		$(DHQD)_2$-PHAL	89	[138]
4	 (from *trans* olefin)	$(DHQD)_2$-PHAL	98	[130]
5		$(DHQD)_2$-PHAL	79 (R = Me), > 99 (R = phenyl)	[118,130]
6	 (from *cis* olefin)	DHQD-IND	78 (R = *c*-C_6H_{11}), 86 (R = Ph)	[134]
7		$(DHQD)_2$-PYR	61	[133]
8		$(DHQD)_2$-PYR	92	[133]
9		$(DHQD)_2$-AQN	96	[135]
10		$(DHQD)_2$-AQN	99	[135]

(*Continued*)

TABLE 8.5 (Continued)

Entry	Diol product	Ligand[a]	% es	Ref.
11		$(DHQD)_2$-AQN	99	[139]
12	 (from *cis* olefin)	$(DHQD)_2$-DPP	84	[136]
13	 (from *cis* olefin)	$(DHQD)_2$-DPP	91	[136]

[a]*See Figure 8.5 for ligand structures.*

The results of many dihydroxylation reactions have led to mnemonic devices for the prediction of enantioselectivity (Figure 8.6a). The first such model was introduced by Sharpless [140] and was later modified by Norrby, following computational studies based on results obtained with an expanded set of ligands introduced in the late 1990s [140]. Although this model is 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 [117]. Some useful generalizations are that the "large" group is very often aromatic, and indeed, aromatic olefins are some of the best substrates for this reaction. Experimental results 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 Figure 8.6a) is surmised by the difficulty of carrying out AD reactions with fully substituted [133] and *cis*-olefins [134]. However, very good-to-excellent results have been wrested from all alkene types. In many cases, the enantiomeric purity of the diol products can be increased by simple recrystallization, which increases the practicality of the method.

The structural basis for enantioselectivity in the AD reaction has been the subject of vigorous debate over the years (for a review, see ref. [143]). One view of an intermediate proposed by the Sharpless school is given in Figure 8.6b, depicting the osmate ester of the reaction between styrene and a $(DHQD)_2$-PHAL-derived complex. In the transition state leading to this product, one DHQD binds the active osmium species and the other is a bystander ligand. Overall, the binding pocket is proposed to have an "L" shape, with the floor made up by the flat PHAL heterocycle (the better to accommodate aromatic alkenes) and one wall coming from the bystander DHQD ligand. Favorable aromatic stacking interactions along with the minimization of steric interactions between the alkene group and the methoxyquinone wall result in the observed diastereoselectivity. Corey has offered mechanistic proposals and

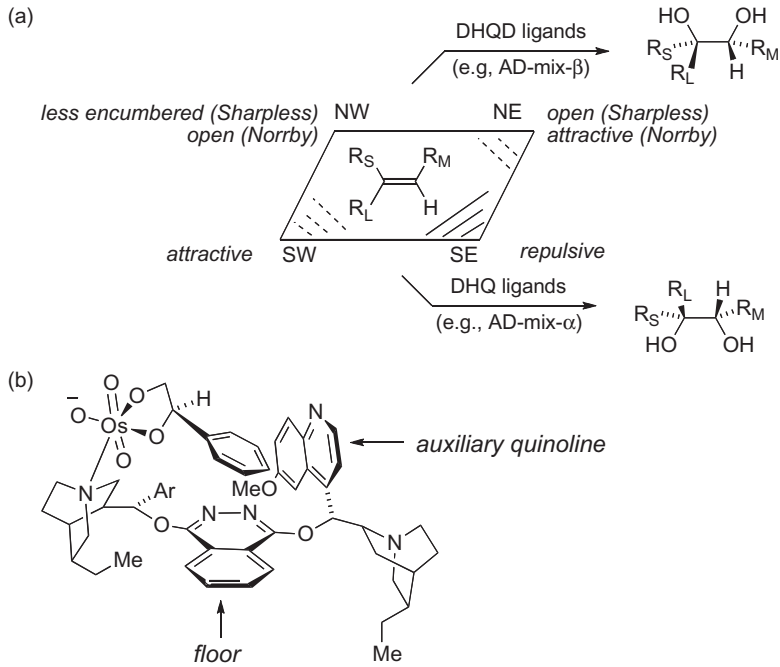
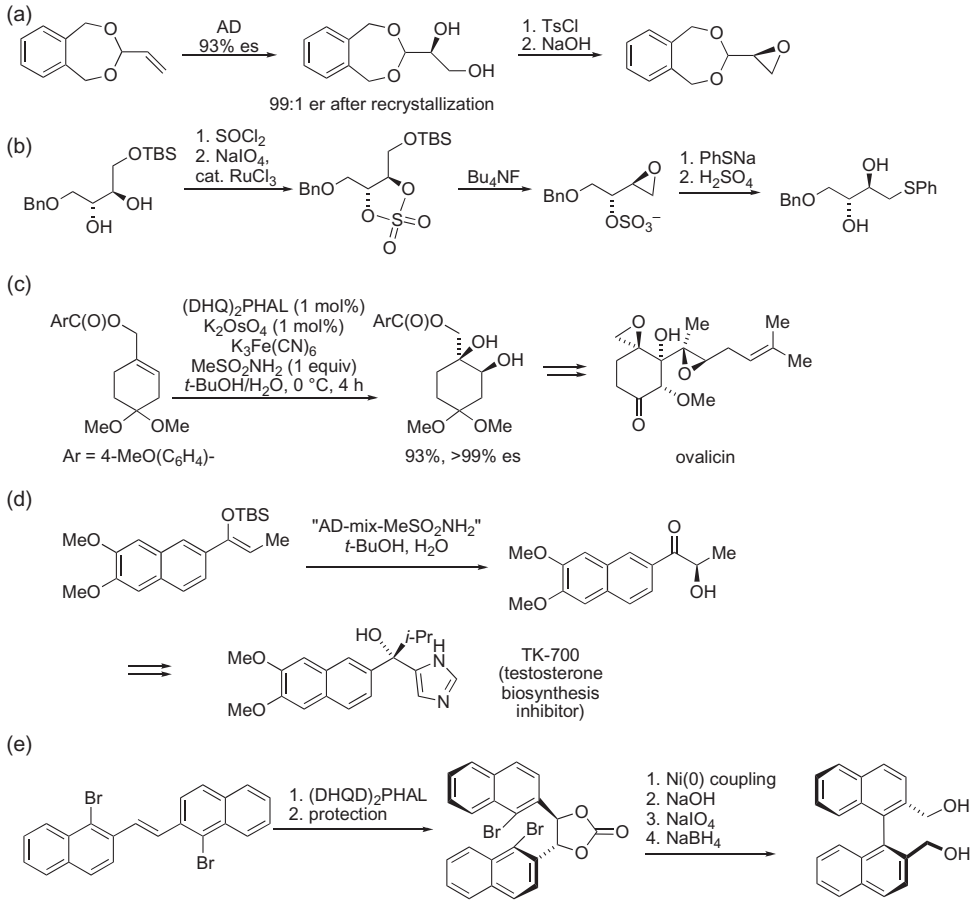


FIGURE 8.6 (a) The predicted enantioselectivity of Sharpless AD reactions using DHQD or DHQ ligands, as originally formulated by Sharpless [140] and modified by Norrby [141]. This model is used by orienting the substrate so that the large (often aromatic), medium, and small substituents match up best with the R_L, R_M, and R_S positions. Application of this model to some alkenes requires some compromises in placing the groups. (b) One view of a proposed intermediate in the Sharpless AD reaction of the $(DHQD)_2$-PHAL-derived osmium species reacting with styrene [142].

transition structures [144,145] that are also consistent with the observed course of the reaction, differing mostly in the relative orientations of the two cinchona moieties and in the orientation of the substrate prior to oxidation. A molecular mechanics study has determined the Sharpless and Corey transition states to be close in energy in numerous individual reactions [146].

8.2.2 Applications of Enantioselective Dihydroxylations

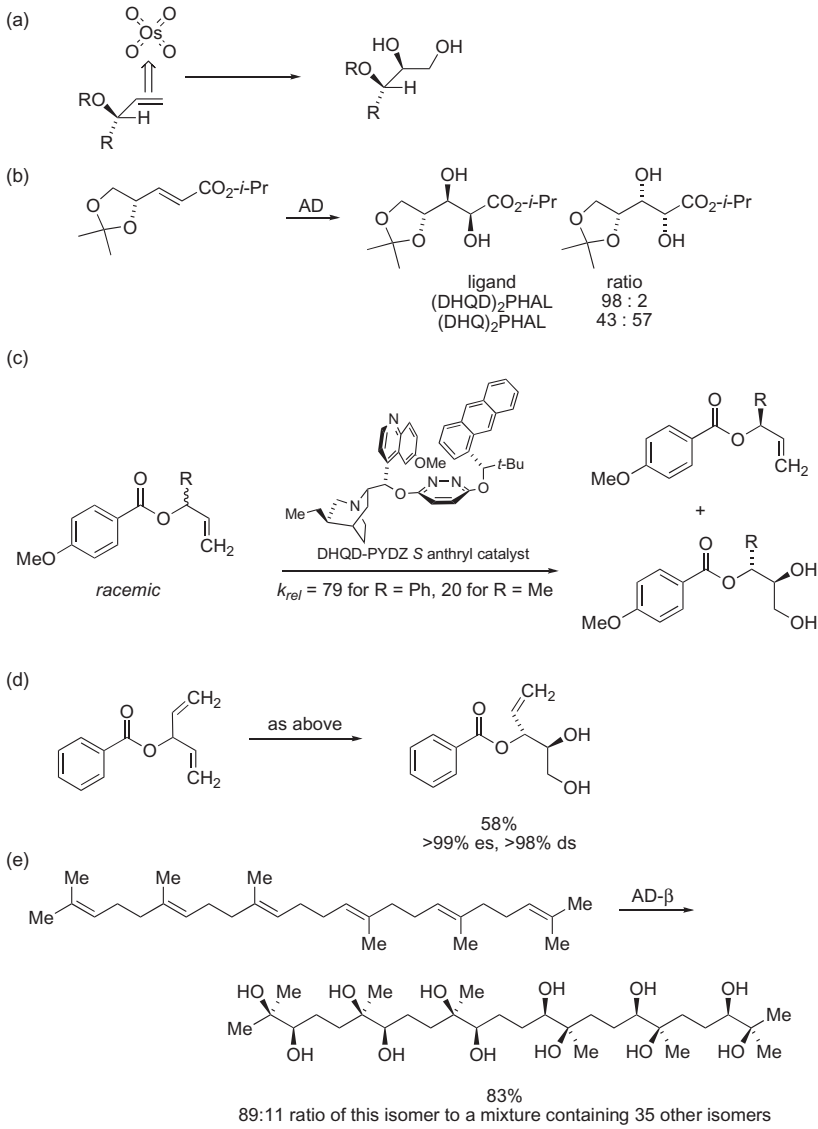
The diol products of an AD reaction are not intrinsically activated for further chemistry as are epoxides. Accordingly, it has proven necessary to develop schemes for the incorporation of the AD into synthetic programs. A few examples confer some of the flavor of this work (Scheme 8.18). For one, glyceraldehyde and its acetonides have found very wide acceptance as chiral starting materials in asymmetric synthesis [147]. The straightforward conversion of a diol to the epoxide afforded a building block that nicely complements the use of the naturally occurring material (Scheme 8.18a) [148]. An alternative to converting diols to reactive epoxides is to activate the diols themselves to nucleophilic attack; this has been accomplished by converting them into cyclic sulfates (Scheme 8.18b) [118,149]. These 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 8.1.4) [150]. Examples of using the reaction for



SCHEME 8.18 Synthetic applications of diols obtained by AD chemistry. (a) Synthesis of a glyceraldehyde equivalent and conversion to an epoxide [148]. (b) Formation and reactivity of cyclic sulfates. (b) Application of cyclic sulfates to the synthesis of erythrose [150]. Here, the epoxide formation is irreversible because the sulfate leaving group is no longer nucleophilic. (c) Synthesis of ovalicin [151]. (d) Synthesis of TK-700 [152]. (e) Synthesis of an enantiomerically enriched (>99% es) biaryl diol [153].

natural product (Scheme 8.19c, ref. [151]) or drug candidate synthesis (Scheme 8.19d, ref. [152]) are also provided – in neither case do both of the stereocenters generated during the AD reaction make it to the end product of the synthesis. In the latter example, directed toward a candidate for the treatment of prostate cancer, note the good results obtained for the oxidation of a silyl enol ether to afford an α-hydroxy ketone. Finally, a diastereofacially selective AD reaction affords a nice starting material for the preparation of an axially chiral binaphthyl derivative [153]. As shown in Scheme 8.18e, cyclization of the diol restricts the motion of the 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.

Issues of double asymmetric induction [154] and the potential for kinetic resolution arise in the reactions of chiral alkenes. Prior to the development of this asymmetric



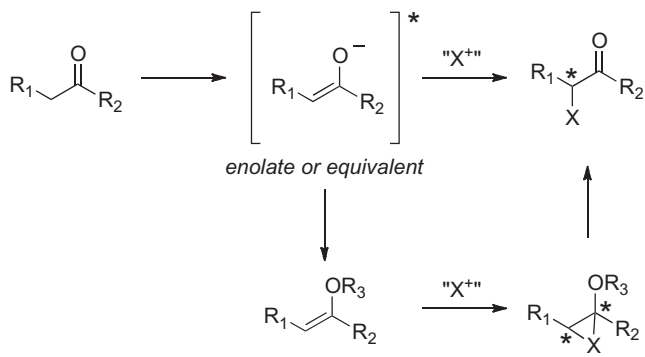
SCHEME 8.19 (a) Kishi model for acyclic control in osmylation reactions [155]. (b) Double diastereoselectivity in an AD reaction [160]. (c) Kinetic resolution or a chiral alkene and (d) group-selective conversion of an achiral substrate [157]. (e) Multiple AD reactions carried out on squalene [158].

dihydroxylation, the dependence of diastereofacial selection in alkenes bearing allylic substitution had been cataloged by Kishi (Scheme 8.19) [155,156]. When AD reactions were carried out on substrates already bearing stereogenic centers, matched *vs.* mismatched situations developed (Section 1.6), 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 the high tolerance of the standard

AD ligands for a wide variety of substrates translates to mediocre results in kinetic resolutions using those ligands [118], Corey has designed a more demanding version and showed it to be useful in both kinetic resolution and the selective reaction of one of the enantiotopic alkenes in a symmetrical starting material (Schemes 8.19c and d, ref. [157]). The high selectivity possible with trisubstituted alkenes was manifested in the multiple AD of a hexalkenyl substrate, squalene, which gave a high yield of 1 out of the 36 possible isomers for this substrate ([158]; for a thematically related example using the Shi epoxidation, see ref. [159]).[6]

8.3 α-FUNCTIONALIZATION OF CARBONYL GROUPS AND THEIR EQUIVALENTS

Most methods to formally oxidize the carbon adjacent to a carbonyl group by converting a C−H bond to a C−X group where X = OR, NR_2, or halogen leverage the rich chemistry developed for the asymmetric alkylation of carbonyl groups (Chapter 3) with the involvement of an appropriately electrophilic agent. Given the numerous ways of differentiating the faces of a ketone or aldehyde that have been developed (from chiral auxiliaries and coordinating ligands to catalysts, with or without metals), much of the innovation required in this field has been to identify appropriate reagents for adding the heteroatom of interest under the right reaction conditions ("X^+" in Scheme 8.20). Since most such routes involve the intermediacy of an enolate or its equivalent, another approach is to functionalize an electron-rich double bond present in a discretely trapped enol ether − another process having considerable precedent in epoxidation or dihydroxylation chemistry (see Scheme 8.18d for an example). This discussion will concentrate on those methods that have been developed particularly for these types of conversions.[7]

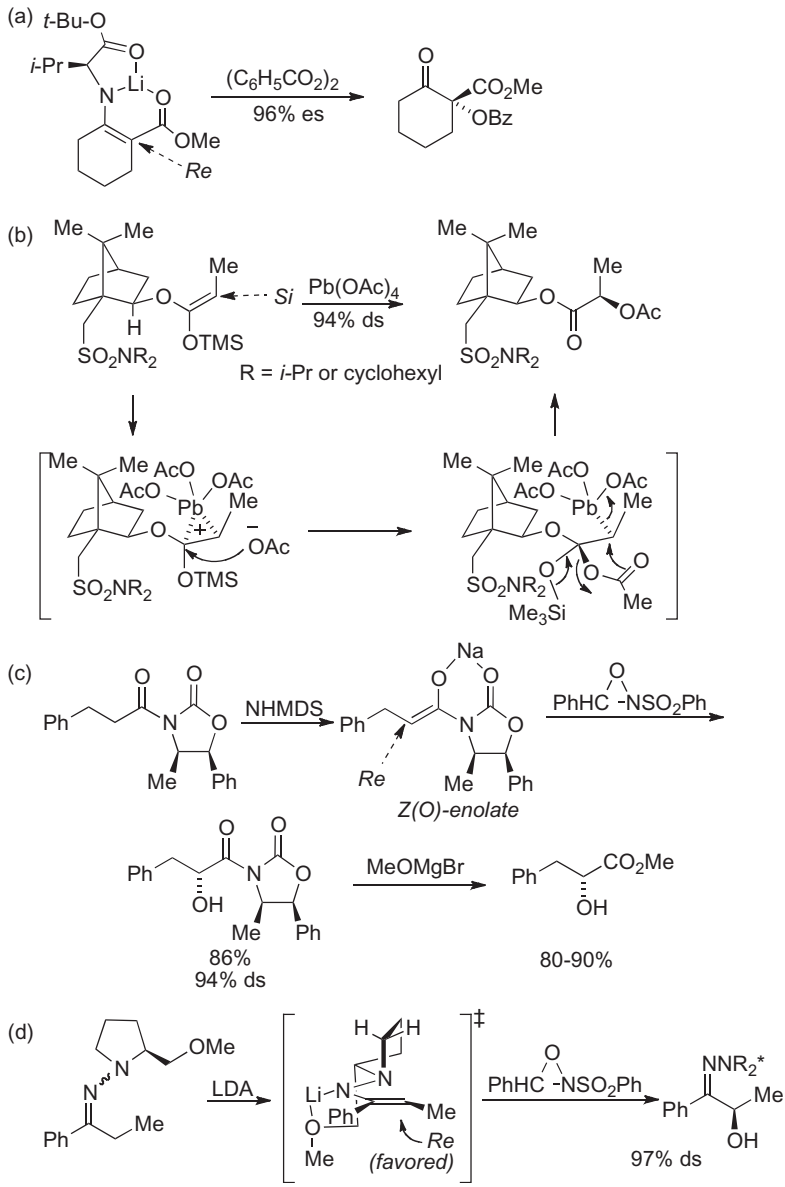


SCHEME 8.20 General approaches for α-functionalization of a ketone rendered chiral in a so far unspecified way.

6. Figuring out exactly why there are 36 possible isomers of this polyol is an entertaining way to spend a rainy day; see the discussion in ref. [158].
7. For general reviews, see refs. [161−163].

8.3.1 Hydroxylations

In general, chiral auxiliaries that are effective for alkylation reactions work well when combined with electrophilic sources of oxygen, and some of the usual suspects are shown in Scheme 8.21. All presumably involve mechanisms for diastereofacial discrimination similar to those involved in carbon–carbon bond-forming reactions (Chapters 3 and 5). These



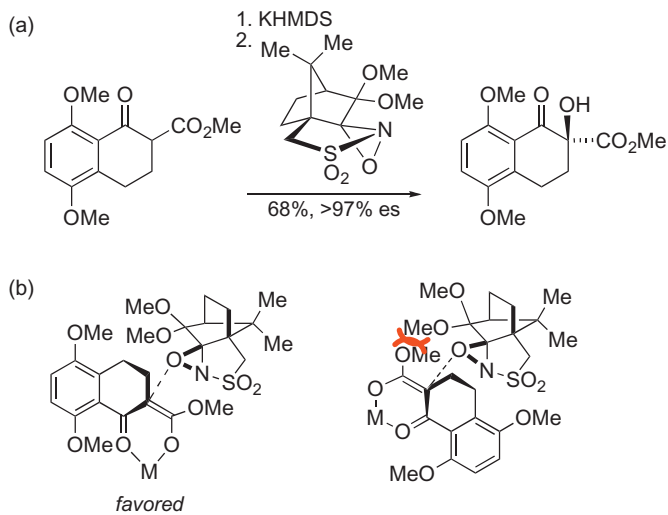
SCHEME 8.21 Representative hydroxylation reactions of chiral enolates, using (a) metalloenamine [166], (b) sulfonamide [167] (*cf.* Scheme 3.19), (c) oxazolidinone [168] (*cf.* Scheme 3.21), and (d) hydrazone [169] (*cf.* Scheme 3.27) auxiliaries.

examples show some of the reagents that have been used to transfer oxygen. In early years, chemists commonly used for this purpose reagents like MoOPh (the complex of oxodiperoxymolybdenum with pyridine and HMPA – not shown, but see ref. [164]), benzoyl peroxide (Scheme 8.21a), or $Pb(OAc)_4$ (demonstrated for the oxidation of a pre-formed silyl enol ether in Scheme 8.21b). Since their popularization by Davis in the 1990s, *N*-sulfonyl oxaziridines have become the reagents of choice (Scheme 8.21c and d; for a review, see ref. [165]).

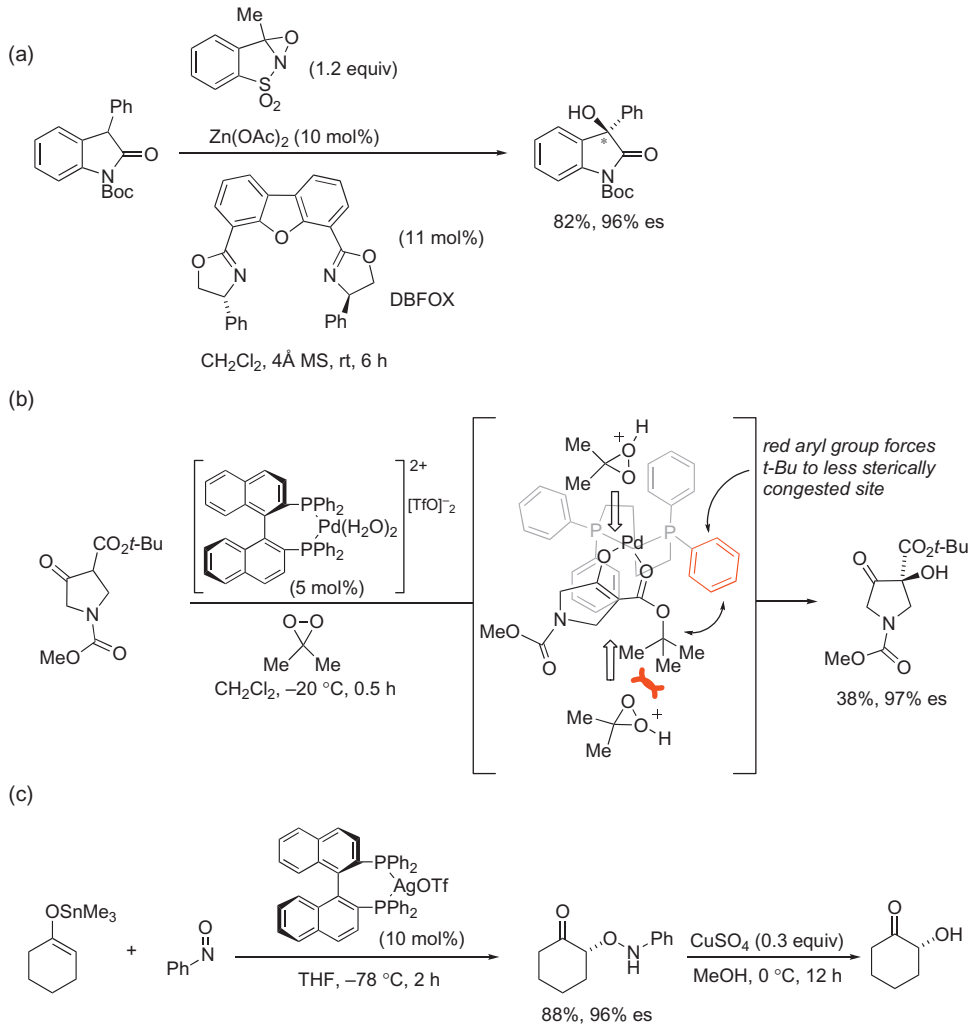
Chiral *N*-sulfonyl oxaziridines can react with enolates to afford α-hydroxy carbonyl compounds in excellent yield and enantioselectivity. An application of a highly selective sulfonyloxaziridine derived from camphor to the synthesis of daunomycin is shown in Scheme 8.22. Attack of the oxaziridine presumably occurs such that the enolate ester avoids nonbonded interactions with the *exo* methoxy group on the bicyclic ring system. This is a reaction of wide scope, and can be carried out on both stabilized enolates derived from keto esters as shown and simple ketone enolates [170].

Catalytic approaches to α-carbonyl oxygenation include epoxidation and dihydroxylation reactions, as discussed in the relevant sections earlier in this chapter (for a review, see ref. [162]). In addition, the catalytic generation of enolates and selective reaction through interligand chirality transfer has been reported using oxidants such as Davis' oxaziridines (Scheme 8.23a [173]), dimethyldioxirane (Scheme 8.23b [174]), or nitrosobenzene (Scheme 8.23c [175]). Note the use of either 1,3-dicarbonyl-containing compounds (which have high enol content) or the pre-formed tin enolate in Scheme 8.23b. Nitrosobenzene is an interesting oxidant that can in principle react with a nucleophile at either oxygen or nitrogen. Which one occurs depends on the particular conditions employed, although the majority of its use in asymmetric catalysts is for α-hydroxylation rather than α-amination.

Nitrosobenzene has also found considerable use in organocatalytic α-oxygenation reactions (reviewed in ref. [162]), such as the examples shown in Schemes 8.24a and b [176,177]. Both reactions use enamine catalysts to α-oxygenate an aldehyde or ketone, respectively; they also demonstrate how the nitroso adducts may be converted to more standard functional group arrays useful in synthesis. Mechanistically, these reactions involve reactive ensembles



SCHEME 8.22 (a) Application of enolate oxidation reactions of a chiral oxaziridine to the synthesis of an AB ring synthon of daunomycin [171]. (b) Proposed competing transition structures [172].

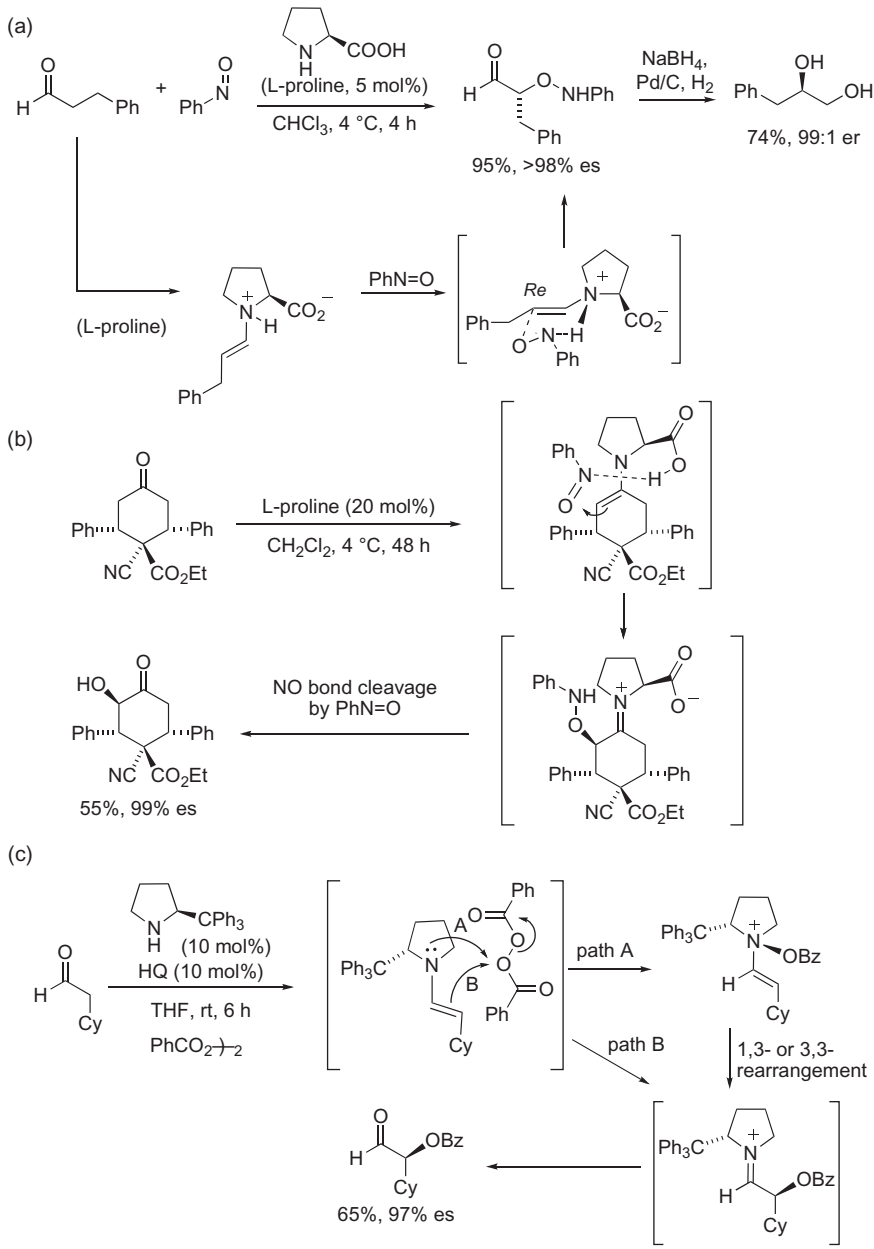


SCHEME 8.23 Catalytic methods for α-hydroxylation using a (a) an oxaziridine [173], (b) dimethyldioxirane [174], and (c) nitrosobenzene [175]. In (b), note the blockage of the bottom face due to steric interactions between catalyst and the *tert*-butyl ester.

that resemble those discussed for enamine-promoted aldol reactions (Section 5.2.3). In 2009, three groups reported a comeback for benzoyl peroxide as an α-hydroxylating agent in the context of organocatalysis (Scheme 8.24c, ref. [178]; also see refs. [179,180]). Mechanistically, these reactions might involve either direct nucleophilic attack at one of the oxygens of benzoyl peroxide or possible N-attack followed by a rearrangement in the resulting intermediate [178].

8.3.2 Aminations and Halogenations

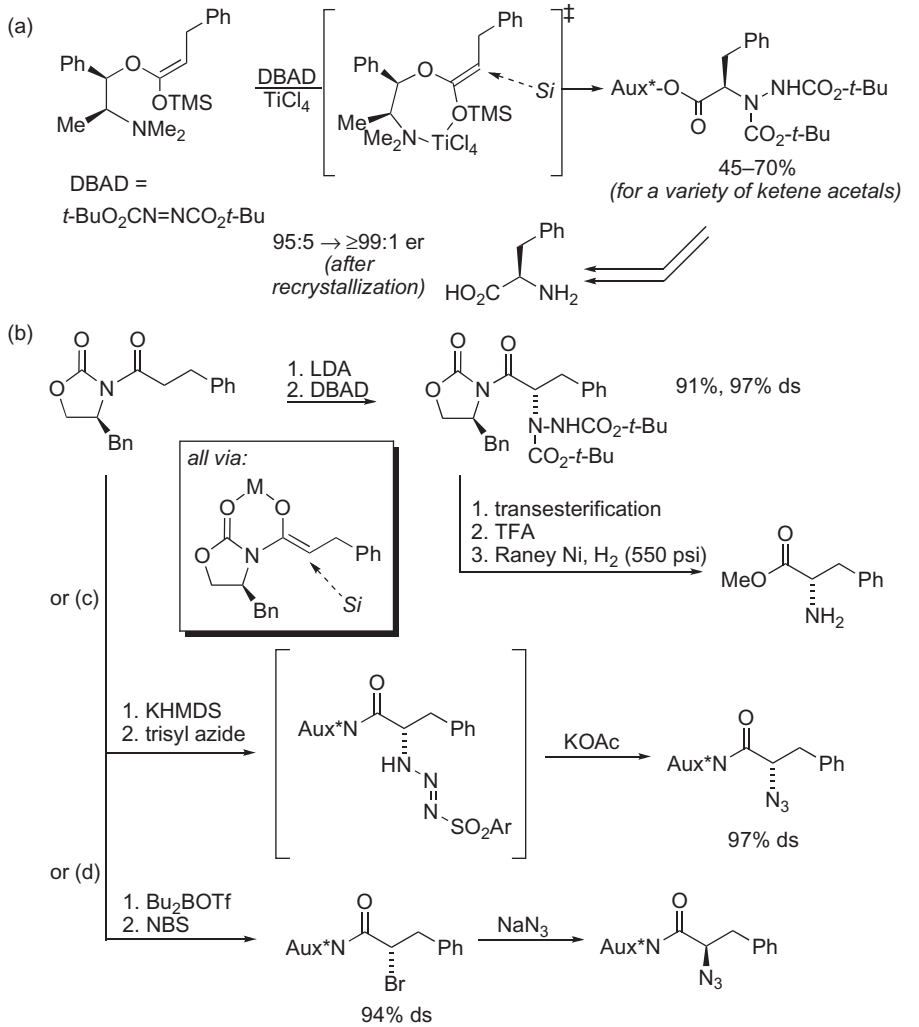
Amination reactions of carbonyl compounds provide access to useful building blocks for nitrogen-containing compounds, with the conversion of esters to amino acid derivatives being



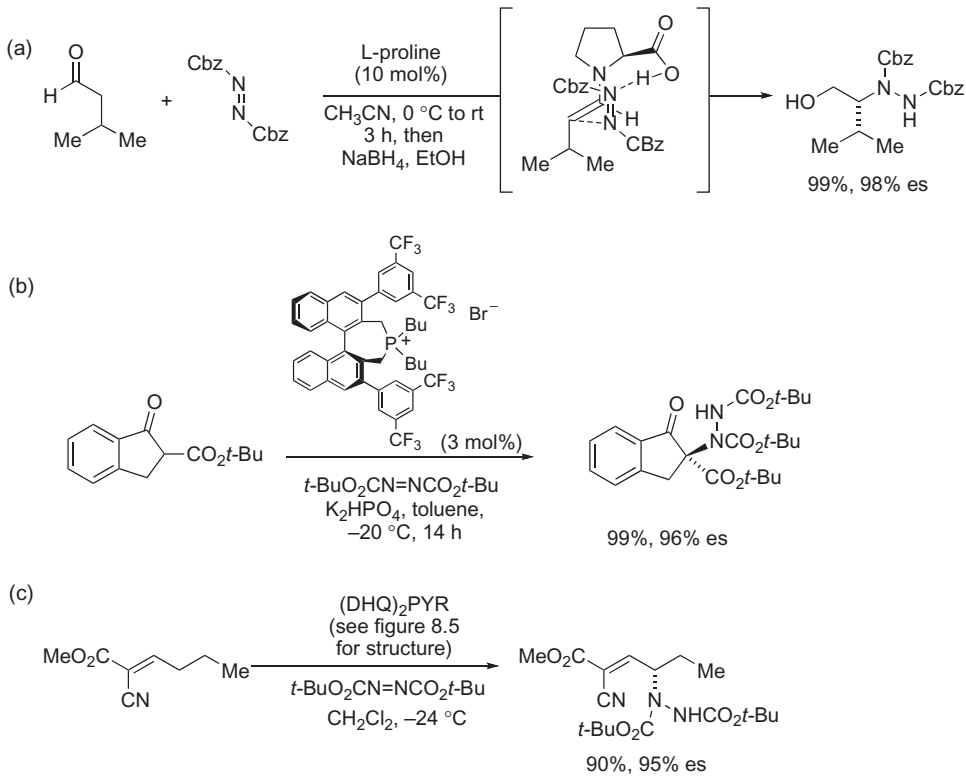
SCHEME 8.24 Organocatalytic α-oxygenations: (a) [176], (b) [177], and (c) [178]. Although not shown, the cleavage of the NO bond in (b) is caused by excess nitrosobenzene; see ref. [177] for a full mechanistic proposal.

particularly important. Likewise, the α-halogenation of carbonyl groups is a reaction of potentially enormous utility given the existence of the S_N2 reaction. Obviously, one useful way of installing a nitrogen into an organic molecule is through the displacement of a halide and for that reason we discuss these two methods together, although asymmetric halogenation chemistry was introduced much later than amination approaches.

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) [181–184]. 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 [181] or (b) oxazolidinone chiral auxiliaries [182]. Azidation of a chiral enolate (c) directly or (d) *via* bromination/azidation [185].



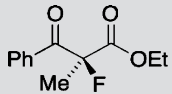
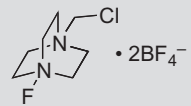
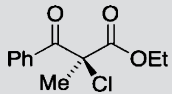
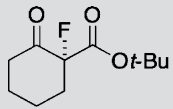
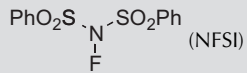
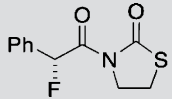
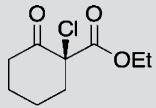
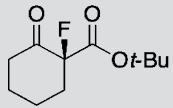
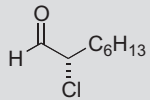
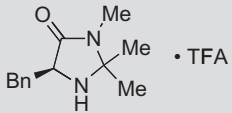
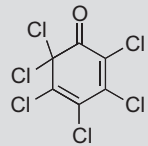
SCHEME 8.26 Asymmetric α-amination promoted by (a) enamine [186] and (b) phase transfer [188] catalysis. (c) An approach to formal allylic amination involving formation of an extended dienolate [189].

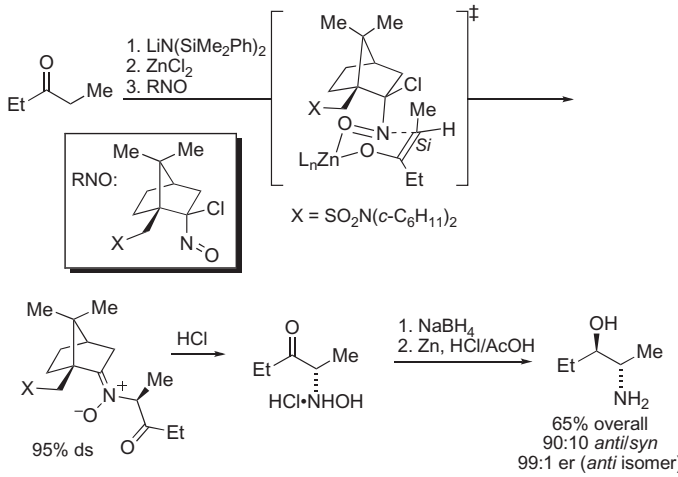
Unfortunately, the hydrazino esters or amides required inconveniently high pressures for their hydrogenolysis (500 psi). An improvement involved the direct azidation of the same enolates using arylazide derivatives, that were found to undergo reactions with enolate nucleophiles to provide a *C*-sulfonyltriazene intermediate that could be decomposed to the α-azido ester (Scheme 8.25c) [185]. Alternatively, azides may be obtained by enolate bromination followed by S_N2 azide displacement; this allows access to both enantiomers from the same auxiliary.

Azodicarboxylate esters are similarly useful electrophiles for organocatalytic α-aminations, two of the many examples reported are depicted in Schemes 8.26a and b (for an extensive review of this literature, see ref. [162]). Scheme 8.26a shows an early example of enamine catalysis in this context, which was discovered essentially simultaneously by List and Jørgensen [186,187]. Once again, the proposed transition structure resembles the cyclic intermediates suggested in the pioneering aldol organocatalysis literature (Section 5.2.3). Scheme 8.26b demonstrates a selective example of phase transfer catalysis in this context [188]. The concept may also be extended to dienolates for a formal allylic amination reaction (Scheme 8.26c, ref. [189]).

The extension of these concepts to halogenation chemistry requires the development of appropriate electrophilic donors of "X^+". Perhaps the most familiar of these are *N*-chloro- and *N*-bromosuccinimide (see Scheme 8.25 for an example of enolate bromination using the latter). Table 8.6 provides an introduction to the types of catalysts and reagents used for this

TABLE 8.6 Examples of Asymmetric α-Halogenation

Entry	Product	Catalyst type	Halogenating Agent	% Yield	% es	Ref.
1		Ti-TADDOL	 (SelectFluor™)	80–95	81	[191]
2		Ti-TADDOL	NCS	85	79	[190]
3		Pd-xylylBINAP	 (NFSI)	91	97	[194]
4		Ni-BINAP	NFSI	99	94	[195]
5		Cu-*t*-Bu-BOX	NCS	99	88	[196]
6		Ni-DBFOX	NFSI	86	99	[197]
7				93	94	[192]



SCHEME 8.27 Reaction of an achiral enolate with a chiral α-chloro-α-nitroso reagent [198].

purpose, beginning with Togni's early innovations in the field using TADDOL derivatives (entries 1 and 2, refs. [190,191]) and ending with an organocatalytic approach toward direct chlorination published by MacMillan (entry 7, ref. [192]). The increasing attention noted toward selective introduction of fluorine reflects not so much synthetic utility but rather the importance of fluorine in drugs and imaging agents (reviews: refs. [161,193]).

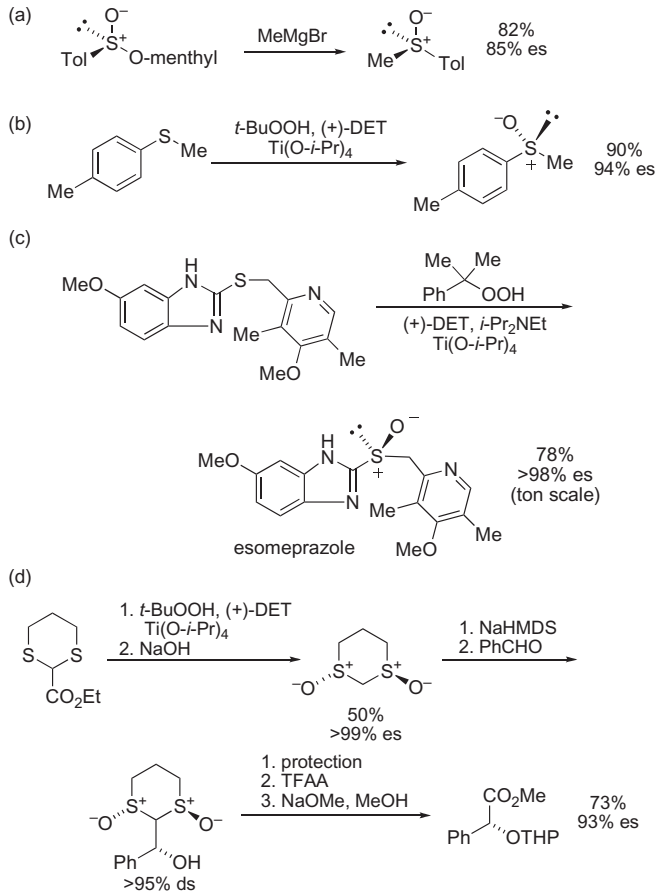
Finally, a different approach toward amination utilizes achiral enolates and a chiral amination reagent (interligand asymmetric induction) [198]. α-Chloro-α-nitrosocyclohexane had previously been used as an aminating reagent with chiral enolates, providing nitrones as the primary product [199]. The adaptation of this chemistry to chiral aminating agents gave the nitrones with high diastereoselectivity (Scheme 8.27), which could be hydrolyzed to give α-hydroxylamino ketones. These were further reduced to the amino alcohols using borohydride reagents and zinc/HCl. The reactions were proposed to proceed through a Zimmerman−Traxler-type transition structure in which the *Z(O)*-enolate of the ketone was coordinated *via* zinc to the nitroso group and the whole ensemble oriented to avoid steric interactions between the incoming nucleophile and the sulfonamide group.

8.4 MISCELLANEOUS OXIDATIONS THAT NECESSITATE DIFFERENTIATION OF ENANTIOTOPIC GROUPS

8.4.1 Oxidation of Sulfides[8]

A great deal of effort has been expended in the development of ways to carry out the asymmetric oxidation of sulfides to sulfoxides (for reviews, see refs. [200−205]). This is interesting from both a theoretical viewpoint and from the utility of certain chiral sulfoxides as reagents in asymmetric synthesis [206]. Some natural products and drugs also contain sulfoxide stereogenic centers.

8. Here the "enantiotopic groups" are the lone pairs on sulfur, which we acknowledge is stretching the section title a little bit.



SCHEME 8.28 (a) An example of the Andersen synthesis of chiral sulfoxides [216]. (b) Catalytic oxidation of an aromatic sulfide using a chiral titanium complex [209]. (c) Industrial-scale synthesis of esomeprazole, a proton pump inhibitor [211]. (d) Synthesis of a C_2-symmetrical *trans*-1,3-dithiane-1,3-dioxide and its use as an asymmetric acyl anion equivalent [214,215].

An important classical method for obtaining chiral sulfur compounds is the Andersen synthesis, which utilizes a chiral sulfinate ester such as that derived from menthol by diastereoselective oxidation and isomeric enrichment *via* epimerization and recrystallization [206,207]. Scheme 8.28a shows a simple example; note that the Grignard reaction occurs with inversion of configuration at the sulfur atom. Additional approaches use chiral reagents (*i.e.*, chiral *N*-sulfonyloxaziridines [208]) and catalytic systems to address this problem, such as the titanium-diethyl tartrate system (Scheme 8.28b); this reaction can proceed with high enantioselectivity when appropriate substrates such as aryl sulfides are used [200,209]. An important application is the industrial-scale preparation of esomeprazole, the active ingredient in Nexium®, a stomach acid reducing agent [210,211]. An interesting application of chiral sulfoxide chemistry has been reported by the Aggarwal group (reviewed in refs. [212,213]) and exemplified in Scheme 8.28d. These workers prepared the *trans* isomer of 1,3-dithiane-1,3-dioxide in high enantioselectivity;

note the use of a temporary carboethoxy group, which proved necessary for high enantioselectivity (Scheme 8.28d, ref. [214]). Deprotonation gave an acyl anion equivalent which reacted with aromatic aldehydes with high diastereoselectivity [215]. 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.

8.4.2 Group-Selective Oxidation of C—H Bonds

The functionalization of C—H bonds became a major area of expansion in the early twenty-first century due to the attractiveness of functionalizing both very basic building blocks (such as methanol [217]) or very complex ones (such as natural products [218]). Although the field is far beyond the scope of this book, it is worth providing the reader with a taste of how chemists have attempted the oxidative conversion of enantiotopic hydrogen atoms to provide chiral molecules (Scheme 8.29; for a review, see ref. [219]). It is worth noting that the oxidation of an apparently unactivated C—H bond is "business as usual" for the enzymes of metabolism, particularly those in the family of cytochrome P450. Since such reactions often occur with high levels of enantioselectivity, engineered versions of these enzymes can be attractive tools for particular applications (*e.g.*, ref. [220]).

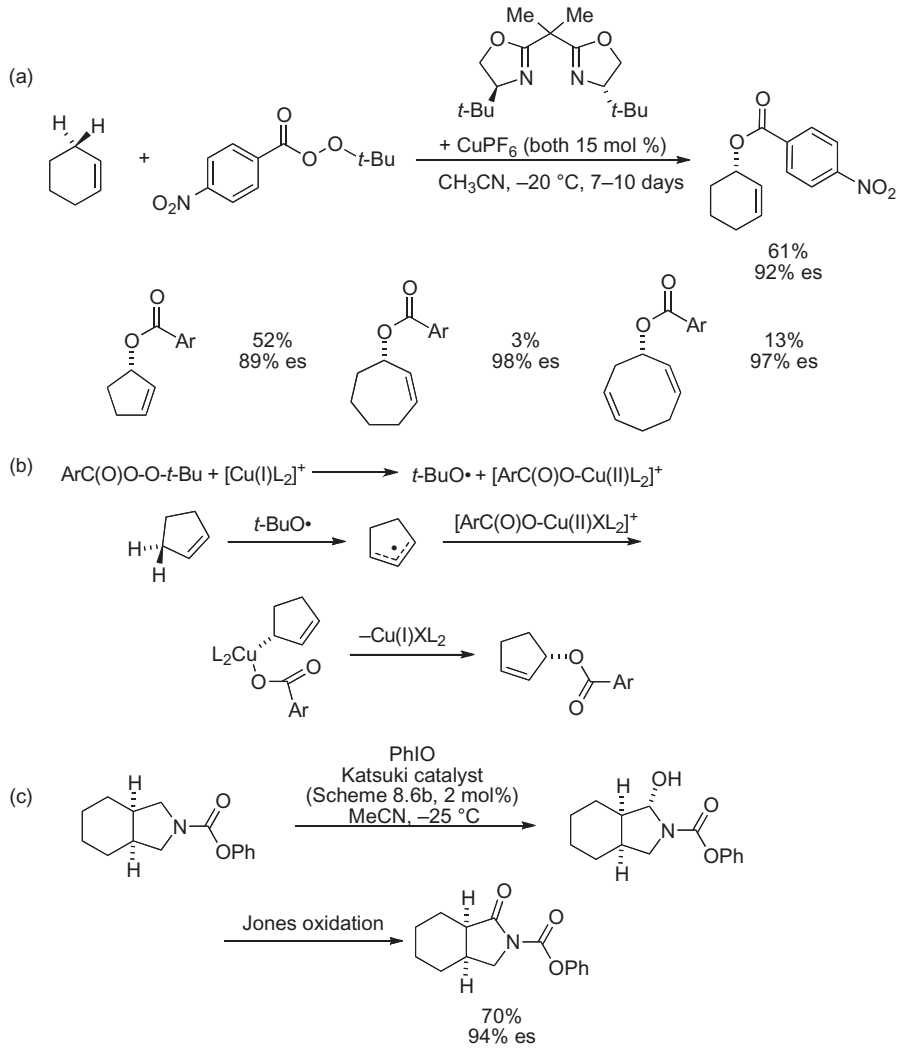
A few nonenzymatic methods that permit the formal group-selective oxidation of enantiotopic C—H bonds are shown in Scheme 8.29 (for a review, see ref. [219]). The asymmetric Kharasch reaction in Scheme 8.29a uses a chiral bisoxazoline ligand and a Cu(I) salt [221,222]. The reaction involves generation of an allylic radical that reacts with an *in situ*-generated Cu(II) complex with the chiral ligand (Scheme 8.29b). Note that although the overall reaction selectively replaces one of the enantiotopic hydrogen atoms with a benzyloxy group, the actual enantioselective step is the face-selective recombination of the allylic radical with the copper(II)-benzoate. The low reactivities and yields reported for some substrates suggest room for improvement (*e.g.*, see related work by Singh [223]). Katsuki has used the salen catalyst of his design to oxidize positions adjacent to heteroatoms in appropriate ring systems (Scheme 8.29c, refs. [224,225]). While formally another C—H oxidation, one cannot rule out the intermediacy of an sp^2 hybridized acyliminium ion that is attacked from the exo face of the bicyclic ring system to afford the product shown.

A truer sense of the promise inherent in direct C—H oxidation can be seen in the allylic/benzylic amination shown in Scheme 8.30a reported by Du Bois (Scheme 8.30 [226]).[9] Although these reactions require relatively weak C—H bonds, it is not thought that they proceed through radical intermediates. Rather, evidence suggests that this reaction proceeds *via* a rhodium nitrene complex that directly inserts into the C—H_{Si} bond. Impressive results were also registered in the diastereomeric manifold by Dodd and Dauban as shown in Scheme 8.30b [228].

8.4.3 Group-Selective Oxidative Ring Expansions

In a symmetrical ketone like 4-*tert*-butylcyclohexanone, the two methylene groups adjacent to the ketone are enantiotopic. The formal "oxidation" of these bonds through asymmetric

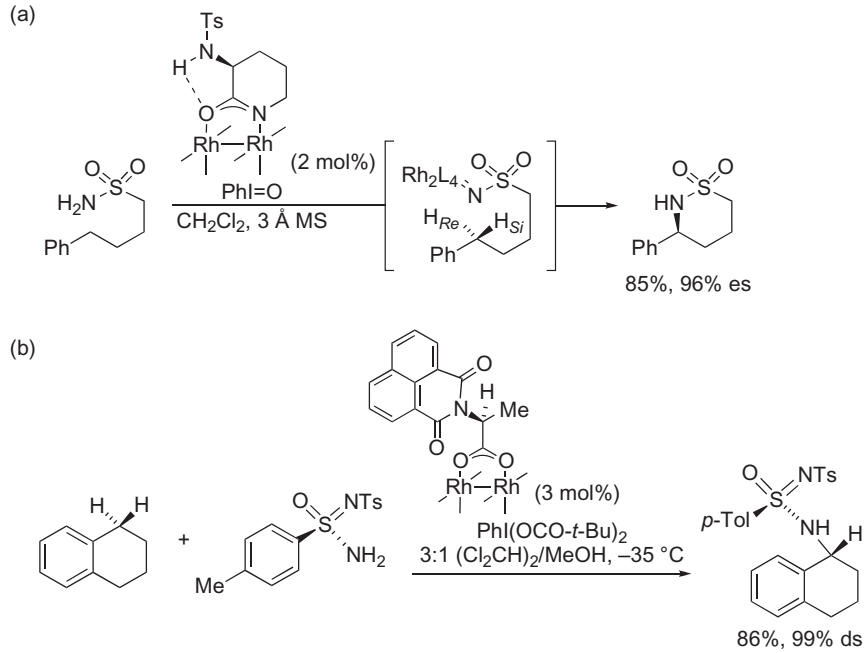
9. For a review of this field of insertion chemistry see ref. [227].



SCHEME 8.29 Formally group-selection insertion of oxygen into enantiotopic C—H bonds. (a) An asymmetric Kharasch reaction [221] and (b) its proposed mechanism [221,222]. (c) Oxidation of an isoindoline derivative [224,225].

versions of the classical Baeyer—Villiger and Schmidt reactions results in useful routes to lactones and lactams, respectively (Scheme 8.31a).

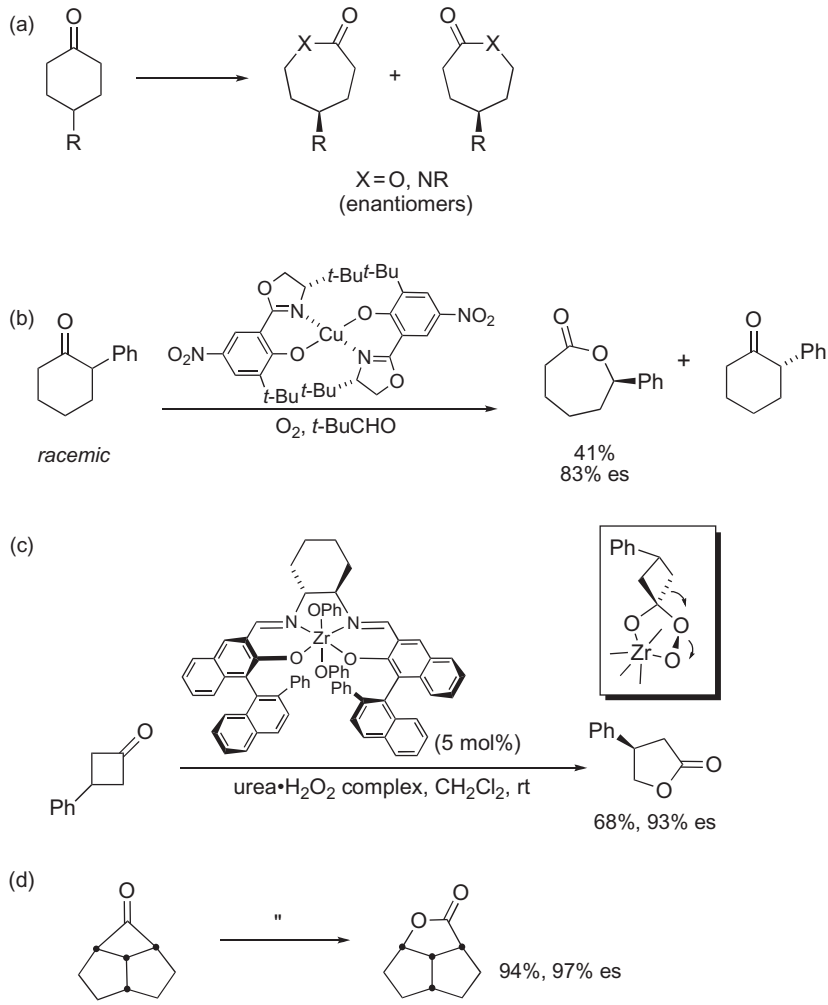
Although highly efficient enzymatic Baeyer—Villiger reactions have been reported [229—232], results of attempts using abiotic catalysts have been much less successful (reviews: [230,233,234]). In landmark work, an early kinetic resolution published by Bolm used a chiral copper complex to activate molecular oxygen for addition to racemic 2-substituted



SCHEME 8.30 (a) Enantioselective benzylic amination by Du Bois [226] and (b) a diastereoselective version by Dodd and Dauban [228]. The catalysts are formulated as Rh_2L_4, with only one of the four ligands explicitly shown.

cyclohexanone (Scheme 8.31b [235]). In this way, the corresponding lactone was prepared and enriched in the *R* isomer in good enantioselectivity. Numerous attempts to improve on these results were made over the next two decades but only rarely approached the selectivities routinely obtained by enzymes. One exception is shown in Scheme 8.31c. Katsuki and co-workers used a salen catalyst to promote the ring-expansion of 4-phenylcyclohexanone to the valerolactam analog with solid enantioselectivity [236]. The inset to Scheme 8.31c summarizes the issues that are necessary to obtain good selectivity: (1) facial selectivity for the addition of the hydroperoxide to the ketone and (2) selective orientation of one of the two potential migrating carbons *antiperiplanar* to the O—O being cleaved in the course of the reaction. The latter condition depends on the chiral environment formed by the large ligands of the catalyst, whereas the former is a function of the substrate's tendency to direct any reagent from a particular direction (which might be one factor leading to the highly selective reactions obtained on the niche ketone shown in Scheme 8.31d).

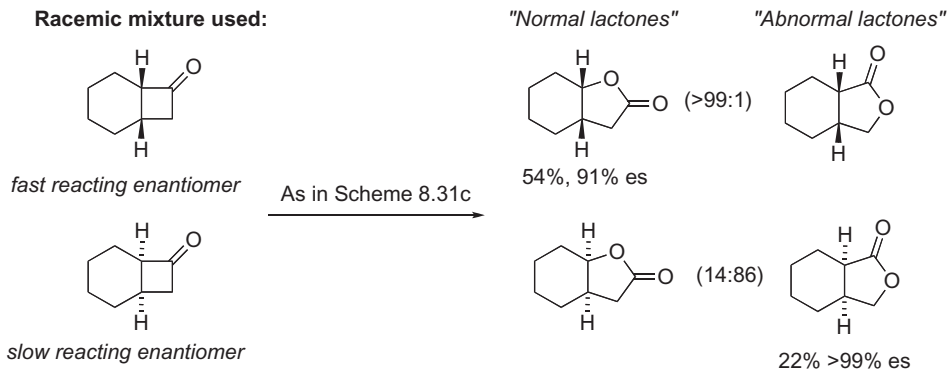
Similar systems have also been employed for the kinetic resolution of unsymmetrical ketones (Scheme 8.32 [237]). The particular results depicted were obtained using the



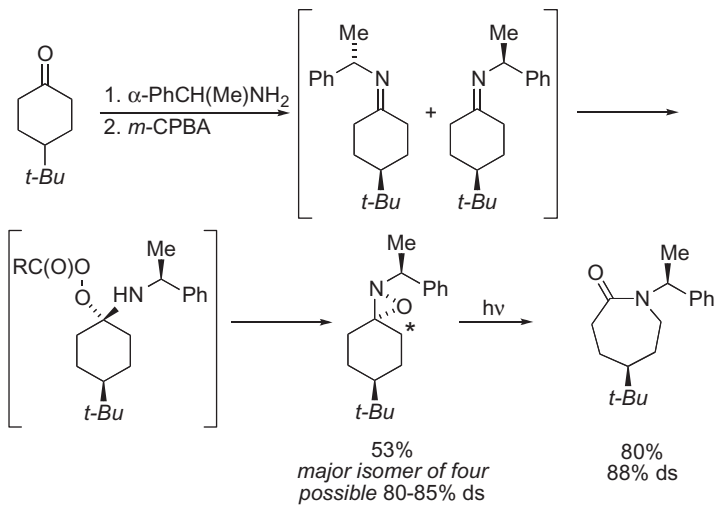
SCHEME 8.31 (a) A generic asymmetric ring-expansion reaction. (b) A kinetic resolution using an asymmetric Baeyer–Villiger catalyst [235]. (c) and (d) Asymmetric Baeyer–Villiger reactions [233,236].

above-noted Katsuki protocol. In this example, although the difference in reactivity between the two isomeric ketones was modest (**s** ~ 4.2), both isomers reacted with good-to-high stereoselectivity at 76% conversion. Note that in this chiral ketone, which group migrates is now viewed as a matter of regioselectivity (or product selectivity), with the preference of the catalyst edging out that of the substrate in determining which products are preferred (recall that standard Baeyer–Villiger oxidations generally occur with migration of the more substituted carbon, hence the designation of these products in Scheme 8.32 as "normal").

In contrast, there is no known enzymatic version of an asymmetric nitrogen insertion process, although two methods that utilize variations on known ring-expansion processes have been reported. The first utilizes oxaziridines as the first isolated intermediate in a three-step

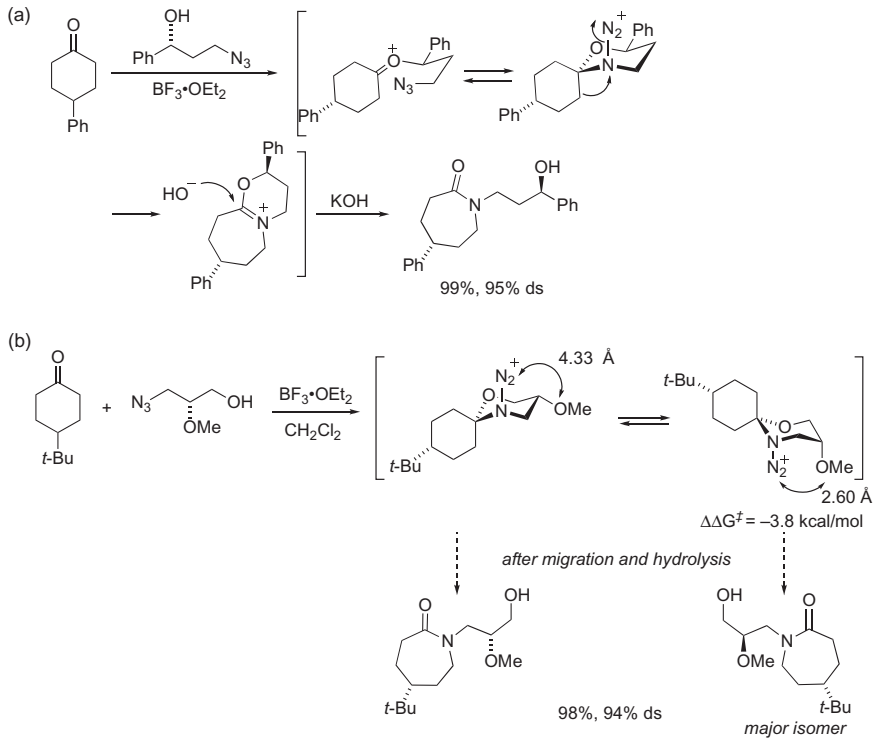


SCHEME 8.32 Kinetic resolution using enantioselective Baeyer–Villiger reactions [237].



SCHEME 8.33 Asymmetric nitrogen ring-expansion reactions of ketones utilizing oxaziridine synthesis and photolysis [238].

overall sequence (Scheme 8.33 [238]). 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 (which is not epimerizable at room temperature; [239]) 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



SCHEME 8.34 (a) Asymmetric ring-expansion azide-Schmidt reaction [241,242]. (b) Evidence for an attractive electrostatic interaction resulting from an n-cation interaction [243]. The energy differences noted were calculated using *ab initio* methods.

lone pair on the nitrogen atom (marked with an asterisk in the scheme) [240]. Reductive removal of the chiral substituent on nitrogen then finishes off this overall ring-expansion protocol.

A few examples of a similar conversion utilizing an azide-based variant of the Schmidt reaction have also appeared (Scheme 8.34 [241,242]). The reaction is thought to entail the formation of a hemiacetal between the hydroxyl group of the reagent and the ketone; dehydration of the hemiacetal leads to an oxonium ion that is subject to attack by the now-tethered azido group (Scheme 8.34a). Formation of the more stable spirocyclic intermediate followed by migration of the bond *antiperiplanar* to the departing N_2 substituent was proposed to lead to the observed lactam. Again, removal of the chiral substituent on nitrogen afforded the formal asymmetric Schmidt reaction product. A provocative element of this chemistry is that attractive interactions might have an effect on particular examples of this reaction specifically those in which the substituent on the newly-formed heterocyclic ring and the positively charged N_2^+ group have a 1,3-diaxial relationship in the intermediate.[10] In such cases,

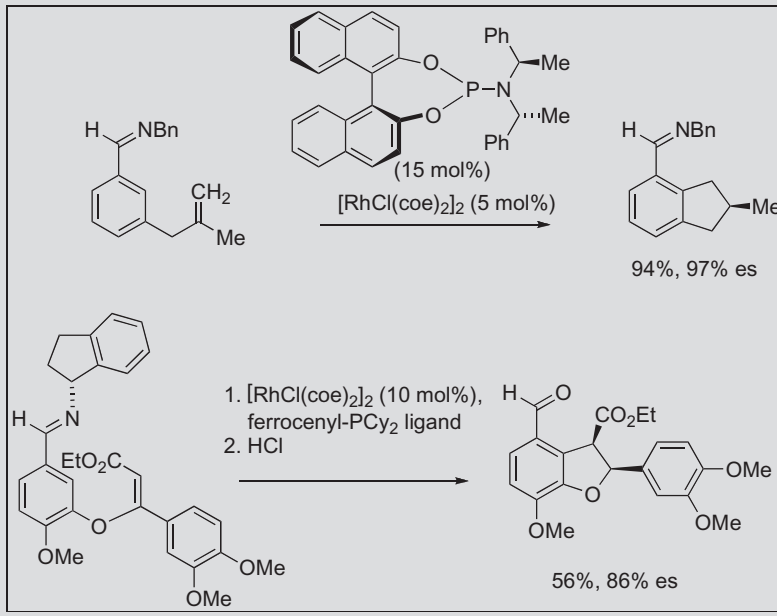
10. We can conservatively estimate that $>95\%$ of the asymmetric transformations described in this book depend ultimately on the relief of repelling through-space (steric) interactions of one type or another.

nonbonded stabilization of the intermediate that bears an electron-rich group in the axial orientation occurs, leading to the observed product (Scheme 8.34b); this can either be the interactions shown involving the oxygen nonbonded electrons and the cationic nitrogen [243], or analogous (and more common) π-cation interactions where the methoxy group in the scheme is replaced by an aromatic group [244,245].

C–C Bonds from C–H Bonds

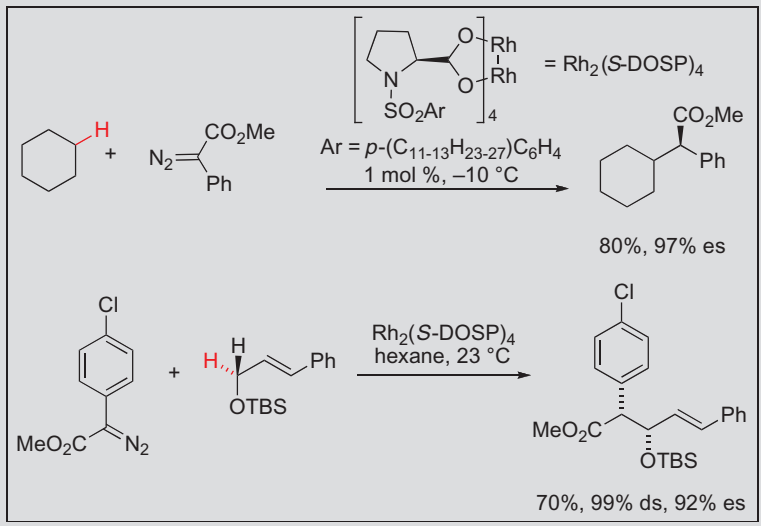
Forming C–C bonds is very often cited as an activity at the core of organic chemistry and the subject has accordingly received much attention throughout this book. Functionalizing "unactivated" C–H bonds is attractive from a synthetic planning perspective because it is desirable to inexorably increase complexity as one moves along a synthetic pathway and especially desirable to avoid introducing functional groups for the express purpose of converting them into something else.[1] The challenges of doing so in complex organic molecules, which may contain *numerous* unactivated C–H bonds, entail both obtaining appropriately chemoselective reactions and, if one is doing asymmetric synthesis, requiring that one differentiate between enantiotopic C–H bonds as well (the general issues involved in C–H functionalization have been thoughtfully reviewed by Baran [1]).

An early (2005!) example published by Ellman and Bergman utilized a chiral auxiliary approach that entailed the *in situ* generation of an imine and subsequent activation/cyclization using a rhodium catalyst system. The imine substituent plays a directing role in this reaction, which was able to afford high stereoselectivities in a variety of cases [2]. It proved necessary to employ a chiral auxiliary approach in the application of this reaction to a total synthesis of lithospermic acid [3]. Here the C–H bond substituted was the only one available for intramolecular cyclization.

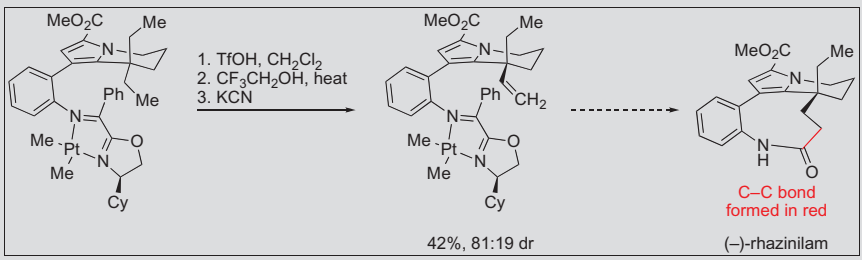


1. What actually constitutes an "unactivated" functional group is up for some debate. For example, are C–H bonds of an aromatic ring "unactivated" in the context of the Friedel–Crafts reaction? Here, we take a "we know it when we see it" stance in which obviously activated C–H bonds (such as those on a methylene next to a carbonyl) are excluded from discussion.

No one would accuse cyclohexane as being functionalized, which is one reason that the conversion of C_6H_{12} to the ester shown is so impressive [4]. Davies has utilized rhodium carbene complexes of the type shown to tremendous effect not only in insertion chemistry but also for cyclopropanations and other transformations (see Section 6.1.5.2 of the present book and also an instructive tutorial review [5]). In this case, one might reasonably consider the roles of "reagent" and "substrate" reversed from their usual understanding since the stereocenter ends up on the carbenoid precursor and not on the cyclohexane, but this is not a general limitation of the technology (*cf.* the corresponding diastereoselective reaction of a silyl enol ether [6]).



Finally, consider the differentiation of enantiotopic ethyl groups accomplished by Sames en route to (–)-rhazinilam [7]. Once again, the expedience of attaching a chiral auxiliary that controls the delivery of a metal to a particular group was needed for high selectivity; the auxiliary also allowed the separation of diastereomers prior to transamination, which afforded an aniline product. Carbonylation followed by amide bond formation finished off the total synthesis. In this case, the differentiation of the two ethyl groups took place *via* the equilibration of the heterocyclic ring prior to CH activation under strong acid promotion.



There is little doubt that a third edition of this book, 15 years after this writing, would be able to track the maturation of this field from dependence on chiral auxiliaries to the wide availability of truly effective and general catalysts, just as has been the case for numerous other reactions contained in this edition.

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