Catalytic Asymmetric Dihydroxylation

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1. Introduction and General Principles

During the last decade a number of powerful asymmetric reactions have emerged as a result of the growing need to develop efficient and practical syntheses of biologically active compounds. *Catalytic* asymmetric reactions provide an especially practical entry into the chiral world due to their economical use of asymmetry inducing agents.[1] A number of processes have gained wide acceptance, and some of them are even used on an industrial scale. Among the most prominent examples are the "Monsanto Process" for the asymmetric hydrogenation of dehydroamino acids[2] and the enantioselective isomerization of allylic amines,[3] used in the "Takasago Process" for the manufacture of (−)-menthol. The asymmetric epoxidation of unfunctionalized olefins, catalyzed by manganese−salen complexes, also has considerable potential.[4] Our own efforts in the field of asymmetric oxidation of olefins[5] have led to two useful reactions, the asymmetric epoxidation[6] (AE) and the osmium-catalyzed asymmetric dihydroxylation[7] (AD). While the former reaction requires the presence of a directing functional group in the substrate (allylic alcohols), the dihydroxylation process is much less limited in the choice of substrate, since it does not need any directing functional group to be present. Strikingly, both processes crucially depend on the ligand acceleration effect (LAE),[6b−d,8] which ensures that the reaction is funneled through a pathway involving the chiral catalyst. The principle of ligand acceleration is illustrated in Scheme 1 for the AD reaction.

In his pioneering work on the stoichiometric reaction of OsO_4 with olefins, Criegee showed that pyridine accelerates the reaction considerably.[9] However,

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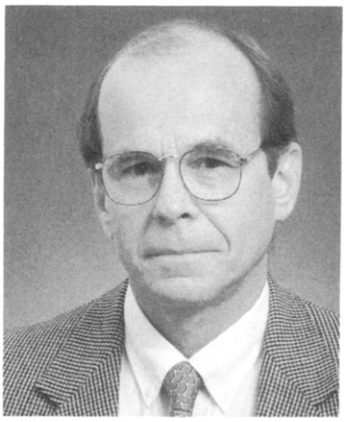
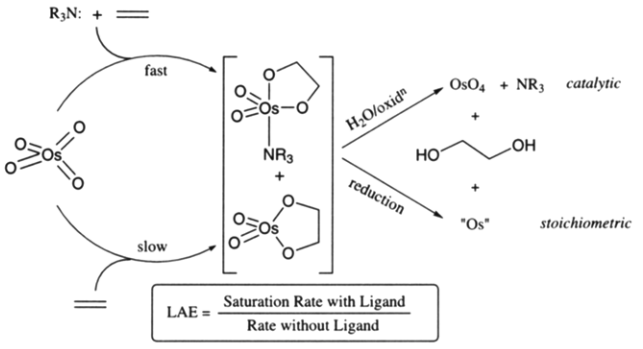
cost considerations make the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of the reaction, which employ relatively inexpensive reagents for the reoxidation of the osmium(VI) glycolate products, greatly enhance its synthetic utility.[10] Inorganic cooxidants, such as sodium or potassium chlorate[11] or hydrogen peroxide,[12] were the first to be introduced, but in some cases these reagents lead to diminished yields due to overoxidation. Much better results are obtained with alkaline *tert*-butyl hydroperoxide, introduced by Sharpless and Akashi,[13] or *N*-methylmorpholine *N*-oxide[14] (Upjohn Process). Recently, Minato, Yamamoto, and Tsuji demonstrated that $K_3Fe(CN)_6$ in the presence of K_2CO_3 provides a powerful system for the osmium-catalyzed dihydroxylation of olefins.[15]



K. Barry Sharpless (b. 1941), W. M. Keck Professor of Chemistry at the Scripps Research Institute, was deflected from pre-med to chemistry after doing research in Thomas A. Spencer's laboratory at Dartmouth College. Following a Stanford Ph.D. with E. E. van Tamelen and postdoctoral years with James P. Collman at Stanford and Konrad Bloch at Harvard, Sharpless joined the M.I.T. faculty. He taught there, as well as at Stanford in the 1970s, until moving to Scripps in 1990. Finding new metal-catalyzed transformations of use in organic synthesis is the main goal of his research.

Scheme 1. The Osmylation of Olefins



Initial efforts by Sharpless and Hentges to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4.[16a] It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. Consequently, quinuclidine derivatives were used instead of pyridines for further investigations due to their intrinsically higher affinity for OsO_4.[17] This logic proved correct, and in 1979 it allowed Hentges to isolate diols with moderate to good enantiomeric excesses using acetate esters of cinchona alkaloids as chiral ligands[16a] (Figure 1a, R = Ac).

Apart from the cinchona alkaloid catalyzed asymmetric dihydroxylation, there are very few other catalytic systems. Recently, Hirama *et al.* employed a monodentate 1,4-diazabicyclo[2.2.2]octane (DAB CO) derivative (Figure 1b) to effect dihydroxylation of olefins under catalytic conditions[16i] (1 mol % OsO_4, 5 mol % ligand). Unfortunately, the enantiomeric excesses are far from satisfactory (≤41% ee) even with stilbene. Better results were achieved by Murahashi and co-workers[16n] who employed chiral isoxazolidines (Figure 1) to effect the same transformation in up to 73% ee.

A number of recent methods employ chiral diamine ligands for the asymmetric osmylation of olefins[7,16b-m] (Figure 1c). Good results have been achieved very recently by Hanessian *et al.* with a simple, *trans*-1,2-

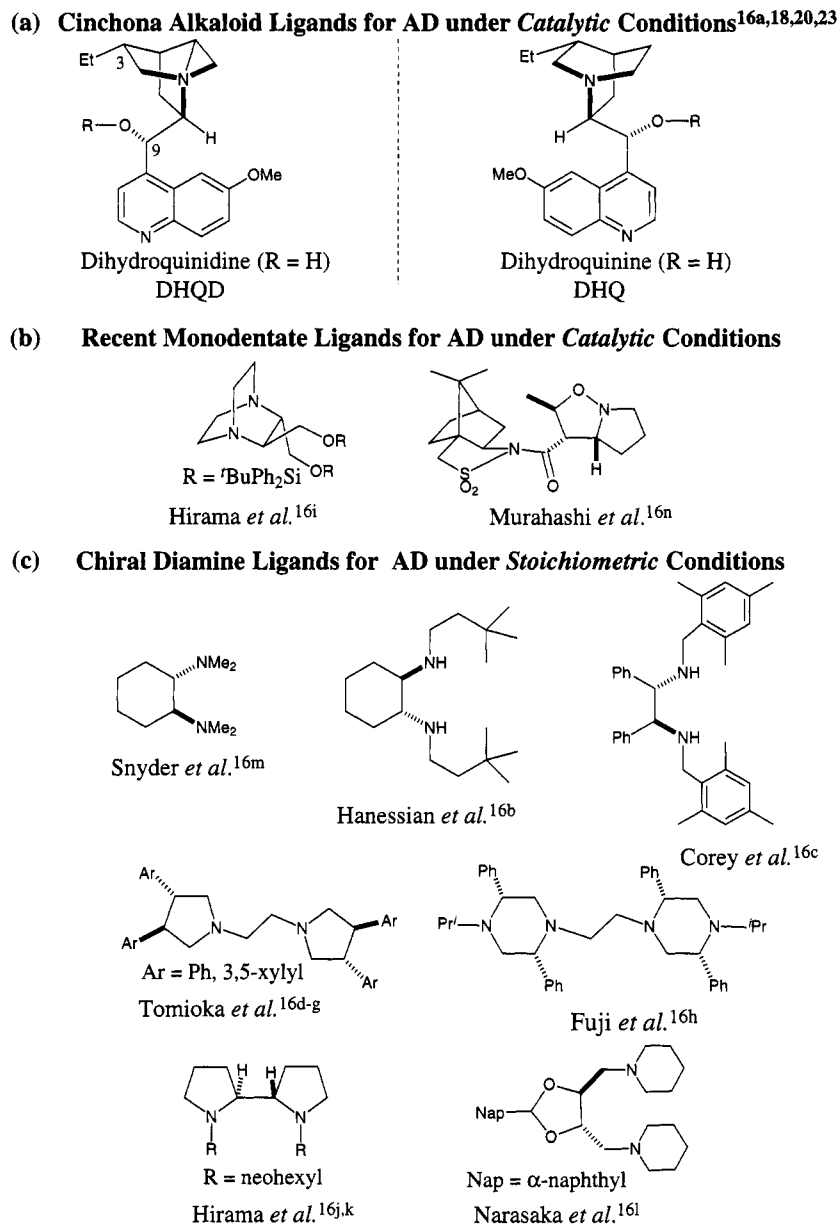


Figure 1. Some ligands for asymmetric dihydroxylation.[16] Only monodentate ligands allow a reaction under catalytic conditions. Note that DHQD and DHQ are *diastereomers* and not enantiomers due to the presence of the ethyl group at C3. Although ligands derived from these two "pseudoenantiomeric" alkaloids lead to diols of opposite configuration, the ee's are usually not identical.

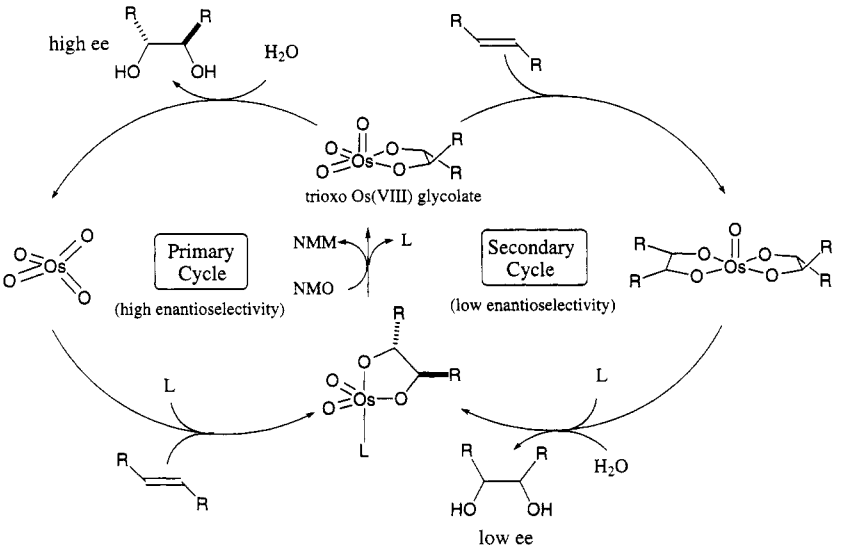
diaminocyclohexane derived ligand.[16b] Despite the good to excellent enantioselectivities that can be obtained with diamine ligands, a serious drawback results from their bidentate nature; they form very stable chelate complexes with the osmium(VI) glycolate products which leads to inhibition of hydrolysis and as a consequence prevents *in situ* recycling of the osmium and the ligand. Thus, all the reactions involving bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand.

Initially, the asymmetric dihydroxylation using derivatives of cinchona alkaloids was performed under stoichiometric conditions, but in 1987 Marko and Sharpless found that the process became catalytic when *N*-methylmorpholine *N*-oxide was employed as the cooxidant.[18] However, the enantiomeric excesses of the diol products obtained under these *catalytic* conditions were initially lower than those produced by the *stoichiometric* reaction. The origin of this discrepancy was found to be the presence of a second catalytic cycle,[19] which exhibited only low or no enantioselectivity (Scheme 2). A partial remedy was discovered by Wai in the slow addition of the olefin.[19]

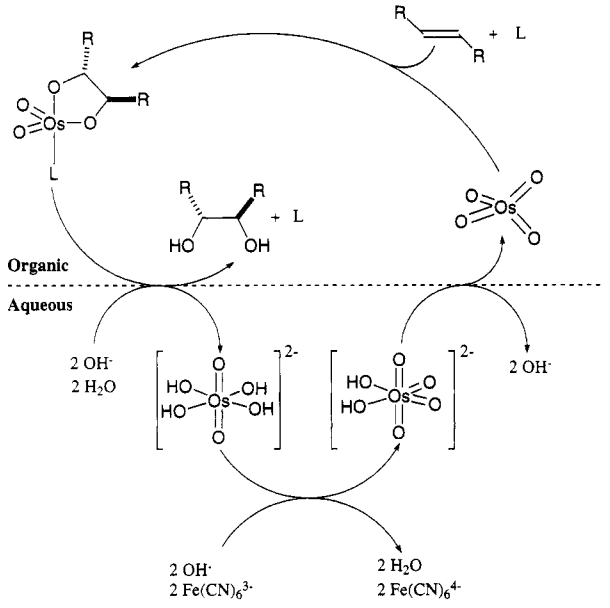
While the rate of progress in the development of this reaction was initially only moderate, our recent work has led to a dramatic increase in momentum. This was due mainly to three key discoveries in our group. First, Kwong found that the participation of the second catalytic cycle can be virtually eliminated by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric reoxidant (Scheme 3).[20]

Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO conditions (cf. Scheme 2). Since the actual osmylation takes place in this layer, the resulting osmium(VI) monoglycolate ester undergoes

Scheme 2. The Two Catalytic Cycles for the Asymmetric Dihydroxylation Using NMO as Cooxidant[19]



Scheme 3. Catalytic Cycle of the AD Reaction with $K_3Fe(CN)_6$ as the Cooxidant[20]



hydrolysis, releasing diol and ligand to the organic layer and Os(VI) to the aqueous layer before its reoxidation can occur, and consequently entry of the osmium glycolate into the second cycle is prevented. The use of $K_2OsO_2(OH)_4$ as a nonvolatile Os source in combination with an inorganic cooxidant [$K_3Fe(CN)_6$] has allowed us to formulate a premix containing all reagents, including the ligand. With this premix, which is commercially available under the name of "AD-mix", the reaction is extremely easy to carry out (cf. section 2.2.1).

The second key discovery was made by Amberg and Xu, who found that the hydrolysis of the osmium(VI) glycolate product can be accelerated considerably by $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in the presence of this additive.[21] This allows high catalytic turnovers even with sterically encumbered substrates, and tetrasubstituted olefins are now within the scope of the reaction (cf. section 2.2.2). Due to this "sulfonamide effect", most AD reactions can be carried out at 0 °C rather than

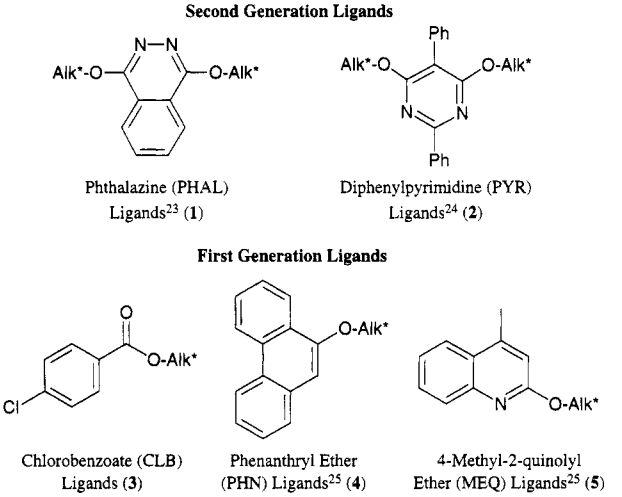


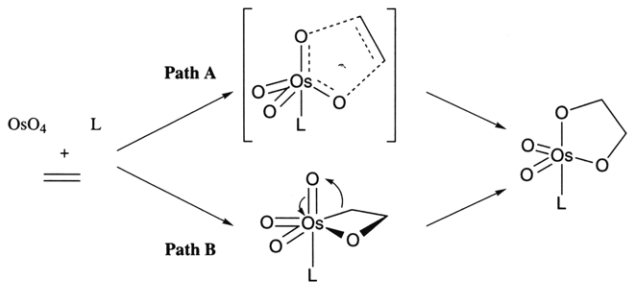
Figure 2. The latest generation of "dimeric" PHAL and PYR ligands and their predecessors (Alk* = DHQD or DHQ).

at room temperature, which normally has a beneficial influence on the selectivity.[22] We routinely add 1 equiv of $MeSO_2NH_2$ to the reaction mixture,[23a] except for terminal olefins (i.e., monosubstituted and 1,1-disubstituted olefins). Surprisingly, terminal olefins actually react slightly slower in the presence of $MeSO_2NH_2$. However, this weak inhibitory effect is noticeable only if a very small amount of OsO_4 (ca. 0.2 mol %) is employed.

Third, the discovery of ligands with two independent cinchona alkaloid units by Hartung[23] (phthalazine core) and Crispino[24] (diphenylpyrimidine core), attached to a heterocyclic spacer (Figure 2), has led to a considerable increase in both the enantioselectivity and the scope of the reaction. Due to these improvements it is now possible to obtain high enantioselectivities with a broad range of alkenes (see section 2). These two ligand classes have superseded our previous chlorobenzoate (CLB), phenanthryl ether (PHN), and 4-methyl-2-quinolyl (MEQ) ligands (Figure 2).[25]

The osmium-catalyzed dihydroxylation reaction has been the center of extensive mechanistic investigations and two different mechanisms have been

Scheme 4. Schematic Presentation of the Concerted [3 + 2] Mechanism[9e] (Path A) and the Stepwise Osmaoxetane Mechanism[9f,g] (Path B)



suggested: Böseken and Criegee originally proposed a concerted [3 + 2] pathway[9a−e] (Scheme 4, path A), while Sharpless *et al.* suggested a stepwise reaction[9f,g] which is initiated by a [2 + 2]-like addition of the olefin across an Os=O bond (path B), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.

The recent observation of a nonlinear Eyring relationship between ee and temperature[22] is inconsistent with Criegee's *one-step* [3 + 2] mechanism, but it can be explained by a reaction pathway with at least two selectivity determining steps which are weighted differently according to temperature, owing to their different activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. Hence, this observation suggests that the *stepwise* [2 + 2]-like mechanism is operative. High level *ab initio* calculations have indeed shown that osmaoxetanes are energetically accessible minima on the potential energy surface.[27a,c]

Recent ligand structure−activity studies have shed light on the origin of the enantioselectivity in the AD reaction[26] and demonstrated the importance of an enzyme-like binding pocket present in the "dimeric" cinchona alkaloid ligands, e.g., the phthalazine ligands (Figure 3).

The cinchona alkaloid backbone is ideally suited for providing high ligand acceleration as well as enantioselectivity and the relationship between ligand structure and activity is summarized in Figure 4.[26]

The investigations have further shown that the reaction rates are influenced chiefly by the nature of the O9 substituent of the cinchona alkaloid, with certain aromatic appendages giving especially large

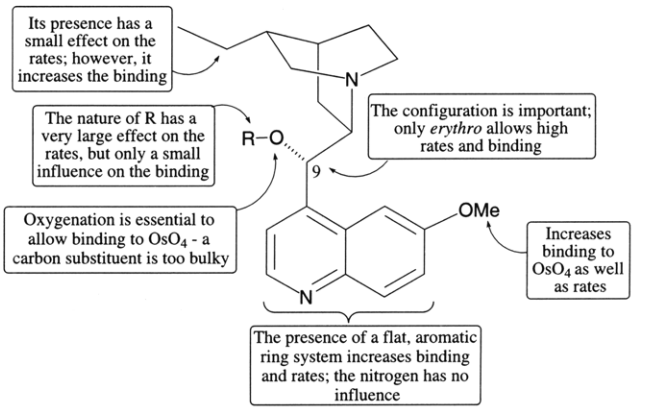


Figure 4. Relationship between ligand structure and binding and ceiling rate constants.[26] The alkaloid core is ideally set up to ensure high rates, binding, and solubility. The rates and enantioselectivities are influenced considerably by the nature of the O9 substituent, while the binding to OsO_4 is almost independent of that substituent.

rate accelerations for aromatic olefins. Further evidence from binding data suggests that the rate enhancement is not a ground-state effect, but rather caused by a stabilization of the transition state due to aromatic stacking interactions. Although this kind of stabilization is operative even in our monomeric first generation ligands (Figure 2), it is most effective in the dimeric second generation ligands due to the presence of a binding pocket or cleft. Thus, the almost perfect match between the phthalazine ligands and aromatic olefins with respect to rates and enantioselectivities can be readily explained by an especially good transition-state stabilization resulting from offset-parallel interactions between the aromatic substituent of the olefin and the phthalazine floor of the ligand, as well as favorable edge-to-face interactions with the "bystander" methoxyquinoline ring (Figure 3). The geometry of the binding pocket is such that it tolerates *one* large substituent in the meta position of the substrate's phenyl ring, since this substituent can be readily positioned away from the bystander methoxyquinoline ring without lowering the edge-to-face attractions. Thus *m-tert*-butylstyrene gives enantioselectivities comparable to styrene itself.[36] However, a second large meta substituent seriously interferes with the perpendicu-

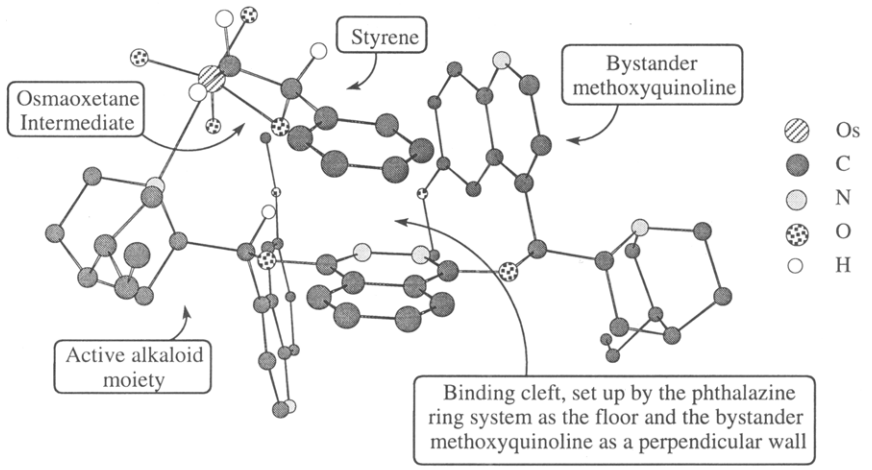


Figure 3. Structure of the osmaoxetane intermediate derived from styrene and $(DHQD)_2PHAL$, calculated using a modified MM2 force field.[27b] The aromatic portion of the olefin is positioned inside a chiral binding pocket.

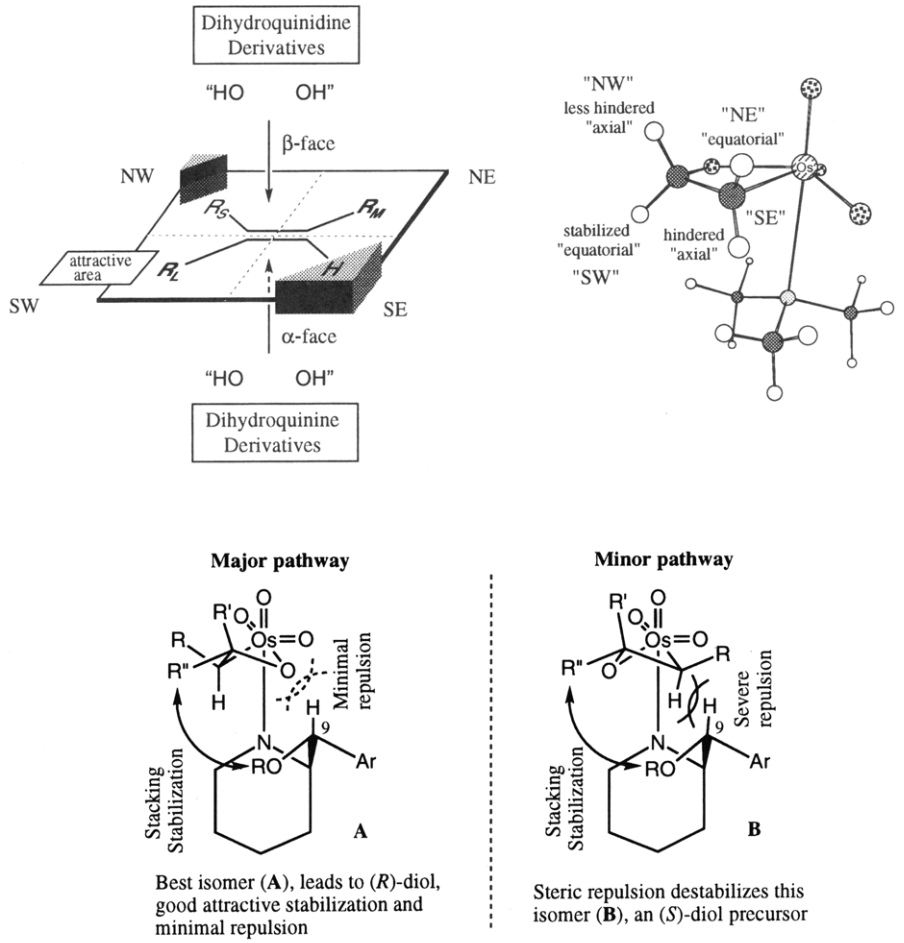


Figure 5. Rationalization for enantiofacial selectivity in the AD reaction (top left, empirical mnemonic device; top right, the proposed osmaoxetane intermediate with the sterically nonequivalent positions around the four membered ring and with trimethylamine in place of the alkaloid ligand; bottom, molecular mechanics model for explaining the enantioselectivity).

lar wall of the binding pocket, thereby disrupting it and leading to lower selectivities. These results are inconsistent with an alternative mechanistic proposal by Corey and Noe,[35b,c] which invokes sandwich-like stacking of the olefin between the methoxyquinolines of the ligand.

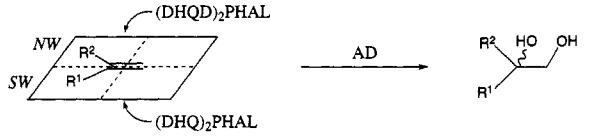
The above observations have led to a revised mnemonic device[26] (Figure 5) for predicting the enantiofacial selectivity in the reaction. The southeast quadrant and to a much lesser extent the northwest quadrant of this device present steric barriers, whereas the northeast quadrant is relatively open for olefin substituents of moderate size. The southwest quadrant is special in that it is regarded as being an *attractive* area, especially well-suited to accommodate flat, aromatic substituents or, in their absence, "large" aliphatic groups. An olefin positioned according to these constraints will be attacked either from the top face (i.e., the β-face), in the case of dihydroquinidine (DHQD) derivatives, or from the bottom face (i.e., the α-face), in the case of dihydroquinine (DHQ) derived ligands. Recent studies have shown, however, that the northwest quadrant, which is normally considered to present a modest steric barrier (*vide supra*), also can play an attractive role for certain allylic and homoallylic alcohols (see section 2.5).

Predictions for 1,1-disubstituted olefins using the empirical mnemonic device are not always unambiguous,[28] since it may be difficult to judge which of the two substituents prefers the attractive, southwest quadrant. For a group to be well suited for this quadrant it has to be "soft", large and/or flat. Thus, aryl groups are the ideal candidates, followed by alkyl groups. In contrast, oxygen-containing substituents normally have a relatively low tendency to occupy this position. Our results and a recent study by Hale et al.[28] suggest the trend shown in Scheme 5 for the tendency of a substituent to occupy the southwest quadrant.

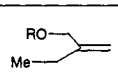
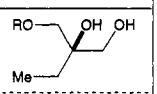
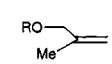
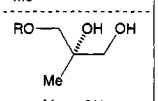
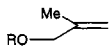
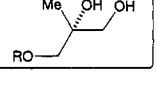
It should be noted, however, that predictions are less reliable for cases where methyl groups are in competition with $ROCH_2$ groups, and low enantioselectivities are normally obtained (entries 4−6).

Recently, a molecular mechanics model for explaining the facial selectivity and rate trends has been developed based on experimental observations (rate and ee data, X-ray crystal structures) as well as *ab initio* calculations.[27b] This model assumes that the reaction proceeds through the stepwise [2 + 2]-like pathway (cf. Scheme 4, path B), involving an osmaoxetane as an intermediate, since this is the mechanism which fits the experimental observations best.[22] The molecular mechanics model suggests that

Scheme 5. Application of the Mnemonic Device to 1,1-Disubstituted Olefins[28]



Tendency for a substituent to occupy the SW quadrant: Aryl > Alkyl > Me $BnOCH_2$, $PivOCH_2$, R_3SiOCH_2

Entry	Olefin	R	Ligand	%ee	Product
1		^{t}BuPh$_2$Si		91	
2		Bn	(DHQD)$_2$PHAL	31	
3		Py		11	
4		^{t}BuPh$_2$Si		47	
5		Py	(DHQ)$_2$PHAL	15	
6		Bn		45	

the enantiofacial selectivity is governed mainly by two factors; stabilizing stacking interactions between one of the substituents (R″) on the oxetane and the OR substituent on C9 of the ligand, and destabilizing repulsive interactions between another oxetane substituent (a hydrogen) and H9 of the ligand. These effects are depicted in structures **A** and **B** at the bottom of Figure 5. **A** and **B** are diastereomers whose only essential difference is that the carbon and oxygen atoms connected to osmium in the metallaoxetane have been interchanged. Both **A** and **B** are in rotameric forms which allow engagement of the attractive interactions between R″ and the C9 OR substituent, leading to overall enhancement of reaction rate in each case (ligand acceleration). However, partaking of these attractive interactions comes at a greater cost for **B** than for **A** because of an attendant repulsive interaction between the ligand's C9 hydrogen and the proximate oxetane substituent. For **A** this repulsion is minimal since the C9 hydrogen is juxtaposed with the oxetane oxygen. But due to the aforementioned oxetane "interchange", relating structures **A** and **B**, the C9 hydrogen in **B** experiences a bad repulsive interaction with an oxetane hydrogen. This model provides a simple rationale for the AD's face selectivity. If it is correct, then intriguingly the AD is primarily dependent on a noncovalent attractive interaction for its high selectivity. The role of the attractive interaction is to favor a transition state arrangement where a repulsive steric effect presents a substantial problem for one diastereomer (**B**), but not for the other (**A**). In this scenario, the AD's enantioselectivity arises from the interplay of two simple effects, attraction and repulsion. Primacy is assigned to the attractive effect since it ordains the decisive role played by the repulsive interaction.

An alternative mechanism was proposed by Corey *et al.*[30,35a] who suggested that a μ-oxo-bridged bis-OsO_4 complex is involved as the active component. However, this hypothesis is inconsistent with the kinetics of the reaction, which clearly show a first-order behavior in [OsO_4].[8a,b] Additionally, *ab initio* calculations by Frenking and Veldkamp have demonstrated that Corey's dimer is not a minimum on the potential energy hypersurface.[27c] Lohray *et al.*[31] have proposed an alternative model which envisages stacking of the olefinic double bond of the substrate with the central aromatic nucleus of the bis(dihydroquinidyl) terephthalate ligand. However, no convincing evidence for such a mode of reaction was offered.

Several stereochemical models have been developed for the rationalization of the *stoichiometric* asymmetric dihydroxylation with chiral diamine ligands. Tomioka *et al.* have concluded that the selectivity using their pyrrolidine ligands (cf. Figure 1) can be understood best on the basis of the osmaoxetane mechanism.[16d-g] In contrast, Houk *et al.* have developed a molecular mechanics model which is based on a [3 + 2] transition state.[27d] Their model is useful for explaining the stereoselectivity observed with various chiral diamine ligands.

Both the catalytic and stoichiometric versions of the asymmetric dihydroxylation have been reviewed recently.[7] However, the rapid progress in this area makes an update necessary, and this review deals with new developments in the field of *catalytic* asymmetric dihydroxylation. The next chapter addresses the enantioselective preparation of 1,2-diols employing the AD reaction, and is followed by another chapter covering synthetic applications for these chiral diols.

2. Enantioselective Preparation of Chiral 1,2-Diols from Olefins

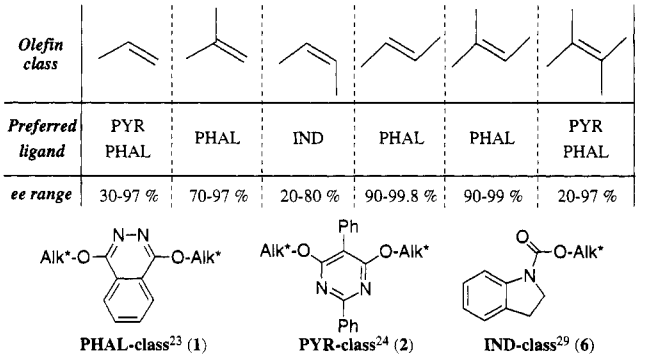
This section presents our current knowledge regarding the preparation of chiral 1,2-diols from olefins. In five different subsections we will address (1) our currently recommended "best" AD ligands, including their strong points and their weaknesses; (2) reaction conditions for "standard" substrates as well as for olefins that require special treatment; (3) double diastereodifferentiation and kinetic resolution; (4) the dihydroxylation of polyunsaturated substrates; and (5) the influence of free OH groups in the substrate on rate, stereoselectivity and chemoselectivity.

This section is intended to illustrate the broad scope of the AD reaction and the ease with which this reaction can be carried out. It is hoped that this information will be helpful to anyone interested in performing an AD reaction.

2.1. Preparation of Ligands, Choice of Ligand, Scope, and Limitations

In recent years approximately 350 cinchona-based ligands have been tested for the AD reaction. It was found that the enantioselectivity is influenced mainly by the nature of the O9 substituent of the cinchona alkaloid backbone (*vide supra*). A number of different ligands were proposed as the "best" ligand over the years (see Figure 2),[7] but our efforts have converged on only *three* different classes of ligands, which taken together are very effective for the dihydroxylation of almost any olefin. Scheme 6 shows our current ligand recommendations for each of the six olefin classes. It should be pointed out that five out of six olefin classes are well served by the PHAL (**1**) and PYR (**2**) ligands, and only *cis*-olefins

Scheme 6. The Recommended Ligands for Each Olefin Class



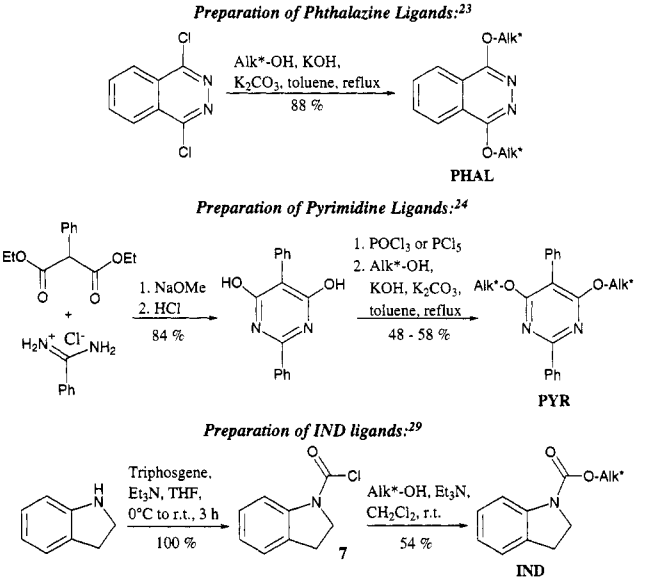
require a unique ligand [IND (**6**)]. Thus, the phthalazines and pyrimidines are by far the most general ligands.

In several recent reports from other laboratories, the use of other "dimeric" ligands, featuring a pyridazine[30] and a terephthalate spacer[31] have been proposed for the AD reaction.[32] However, a comparative study has shown that these ligands are inferior to the phthalazine- and pyrimidine-based ligands.[33]

2.1.1. Preparation of the Ligands

Most ligands are commercially available,[34] but they are also easily prepared from relatively inexpensive starting materials. The dimeric ligands are obtained by condensation of the alkaloid with the dichloride of the heterocyclic spacer in refluxing toluene using

Scheme 7. Preparation of the AD Ligands (Alk* = DHQD or DHQ)[34]



a mixture of solid K_2CO_3 and KOH as the base (Scheme 7). The indoline ligands are readily available by reaction of *N*-indolinecarbonyl chloride (**7**) with the alkaloid in the presence of triethylamine.[29]

2.1.2. Ligand Choice and Enantioselectivity Data

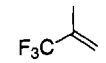
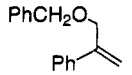
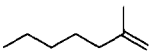
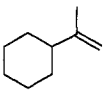
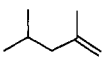
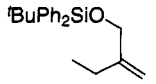
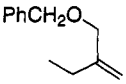
One striking feature of the PHAL and PYR ligands is their "dimeric" structure, which is in contrast to

Table 1. Asymmetric Dihydroxylation of Monosubstituted Olefins†

Entry	Olefin	PHAL DHQD	PHAL DHQ	PYR DHQD	PYR DHQ
1[a]	H_3C	36 (*R*)		**49** (*R*)	
2[a]	F_3C	63 (*S*)		64 (*S*)	63 (R)
3[a]	Cl_3C	70 (*S*)		**86** (*S*)	77 (R)
4[a,b]	Cl	**63** (*S*)	54 (*R*)	53 (*S*)	
5[a,b]	Br	**66** (*S*)		60 (*S*)	
6[a,c]	I	63 (*S*)		**70** (*S*)	
7[a]	C_2H_5	66 (*R*)		**72** (*R*)	
8[a]	$^nC_3H_7$	79 (*R*)		**88** (*R*)	
9[a]	$^nC_4H_9$	80 (*R*)		**89** (*R*)	
10[d]	$^nC_8H_{17}$	84 (*R*)	**80** (*S*)	**89** (*R*)	76 (S)
11[d]		64 (*R*)	66 (*S*)	**92** (*R*)	**87** (S)
12[e]	Me_3Si	46 (*R*)	44 (*S*)	88[a] (*R*)	
13[f]	Ph	**84** (*R*)		81 (*R*)	
14[d]	Ph	**97** (*R*)	**97** (*S*)	80 (*R*)	
15[g]		98 (*R*)			
16[d]		80 (*R*)		**93** (*R*)	
17[d]		88 (*R*)	86 (*S*)	**96** (*R*)	
18[d]		87 (*R*)	83 (*S*)	**94** (*R*)	**87** (*S*)
19[f]	Ph-O	**88** (*S*)	77 (*R*)	43 (*S*)	
20[f]	MeO	90 (*S*)			
21[f]	OMe	63 (*S*)	56 (*R*)		
22[f]		36 (*S*)			
23[d]		91 (*S*)	88 (*R*)		
24[b]	SO_2	40 (*S*)			
25[h]	PhS	61 (*S*)			
26[i]		**67** (*S*)		54 (*S*)	
27[d,j]	BnO	**77** (*S*)	70 (*R*)	41 (*S*)	
28[k]	EtO	67 (*S*)	52 (*R*)		

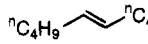
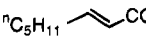
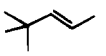
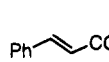
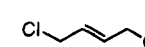
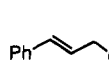
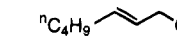
† The ee value obtained with the best ligand for a given substrate is printed in bold. The reactions were carried out in *t*-BuOH/H_2O at 0 °C with $K_3Fe(CN)_6$ as the cooxidant. All AD's with PHAL ligands were performed using the AD-mixes. AD's with PYR ligands were performed with 1.0 mol % of OsO_4 and 1.0 mol % of ligand. [a] See ref 37. [b] See ref 38. [c] See ref 39. [d] See refs 23a and 24. [e] Vinyl- and allylsilanes only give moderate enantioselectivities with phthalazine ligands, due to branching in close proximity to the double bond. Interestingly, DHQD-PHN and $(DHQD)_2PYR$ give better results in these cases, see ref 40. [f] See ref 41. [g] See ref 42. [h] See ref 43. [i] See ref 44. [j] See ref 45. [k] See ref 46.

Table 2. Asymmetric Dihydroxylation of 1,1-Disubstituted Olefins†

Entry	Olefin	PHAL DHQD	PHAL DHQ	(DHQD)$_2$PYR
1[a]		13		**25**
2[b]		**94** (*R*)	**93** (*S*)	69 (*R*)
3[c]		88 (*R*)		
4[c]		97 (*R*)		
5[c]		78 (*R*)		
6[b,d]		**78** (*R*)	**76** (*S*)	76 (*R*)
7[e]		69 (*R*)	75 (*S*)	
8[e]		30 (*R*)	39 (*S*)	
9[f]		91 (*R*)		
10[f]		31 (*R*)		

† The ee value obtained with the best ligand for a given substrate is printed in bold. The reactions were carried out in *t*-BuOH/H_2O at 0 °C with $K_3Fe(CN)_6$ as the cooxidant. All AD's with PHAL ligands were run using the AD-mixes. AD's with PYR ligands were performed with 1.0 mol % of OsO_4 and 1.0 mol % of ligand. [a] See ref 37. [b] See refs 23a and 24. [c] See ref 47. [d] See ref 45. [e] See ref 48. [f] See ref 28.

Table 3. Asymmetric Dihydroxylation of *trans*-1,2-Disubstituted Olefins†

Entry	Olefin	PHAL DHQD	PHAL DHQ
1[a]		72 (*R,R*)	
2[b]		97 (*R,R*)	93 (*S,S*)
3[b]		99 (*2S,3R*)	96 (*2R,3S*)
4[c,d]		95 (*R,R*)	
5[e]			97 (*S,S*)
6[b,c]		97 (*2S,3R*)	95 (*2R,3S*)
7[b,f]		99.8 (*R,R*)	> 99.5 (*S,S*)
8[g,h]		95 (*2S,3R*)	
9[g,h]		94 (*S,S*)	
10[g,h]		98 (*2S,3R*)	
11[g,h]		94 (*2S,3R*)	
12[i]		90 (*R,R*)	

† The reactions were carried out in the presence of 1 equiv of $MeSO_2NH_2$ in *t*-BuOH/H_2O (1:1) at 0 °C with AD-mix-α [(DHQ)$_2$PHAL] and AD-mix-β [(DHQD)$_2$PHAL], respectively. [a] See ref 37. [b] See ref 23a. [c] The reaction was performed at room temperature. [d] See ref 49. [e] See ref 50. [f] See ref 51. [g] See ref 39. [h] The reaction mixture was buffered with 3 equiv of $NaHCO_3$. [i] See ref 52.

all our previous ligands and the indolines **6**. Although it has been proposed that both alkaloids in these ligands act in concert,[30,35] a recent study has shown that they have independent functions,[8b] with only one alkaloid moiety being directly involved in the reaction with OsO_4 and the olefin (the "working alkaloid unit"). The function of the other, "bystander", alkaloid unit in combination with the heterocyclic spacer appears to be to set up a chiral binding pocket for the olefin[26] (see section I, Figure 3).

Kinetic measurements,[26] enantioselectivity studies, and molecular mechanics calculations[27] have shown that the binding pocket of the phthalazine ligands (**1**) is especially well suited to accommodate olefins with flat, aromatic substituents, making (DHQD)$_2$PHAL and (DHQ)$_2$PHAL the preferred ligands for these olefins (cf. data in Tables 1–5 concerning aromatic olefins). A recent study has revealed that increasing the size of the ring substituents on styrene disrupts the favorable stacking interactions within this binding pocket, leading to reduced enantioselectivities.[36]

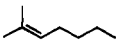
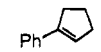
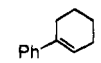
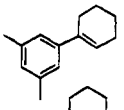
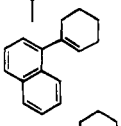
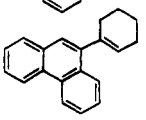
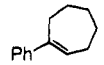
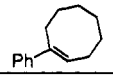
The phthalazine ligands **1** are also recommended for the 1,1- and 1,2-*trans*-disubstituted as well as the trisubstituted classes of olefins, as revealed by the data in Table 2 (entries 2 and 6) and Table 3. The diphenylpyrimidines **2** complement the phthalazines and they are the ligands of choice for the important class of monosubstituted terminal olefins, especially those with branching in the substituent (see Table 1, entries 1–3, 6–11, and 16–18). As demonstrated in Figure 6, the enantioselectivities with *n*-1-alkenes strongly depend on the chain length, and "saturation behavior" is observed. Thus, the ee initially increases with the number of carbon atoms (cf. propene to pentene) but then reaches a "ceiling", i.e., saturation value when the chain length is greater than 5. Although the pyrimidine ligands give the best selectivities with aliphatic olefins (Figure 6), the phthalazines perform better with olefins bearing aromatic substituents (Table 1, entries 13, 14, and 19, and Table 2, entry 2). Both PHAL and PYR derivatives are useful for tetrasubstituted olefins (see Table 6).

2.1.3. Limitations

Among the substrates that remain problematic are *cis*-olefins as they have provided no examples exceeding 90% ee, even when IND ligands are employed. Thus, *cis*-β-substituted styrenes yield products in the range of 70–80% ee (Table 7, entries 1–4), while aliphatic substrates give even lower selectivities (entry 5).[29]

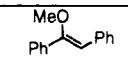
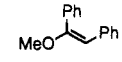
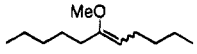
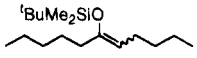
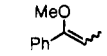
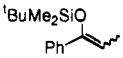
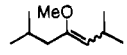
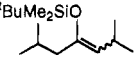
It should be pointed out, however, that certain cyclic *cis*-olefins give satisfactory results with the PYR ligands, even in those cases where IND ligands

Table 4. Asymmetric Dihydroxylation of Trisubstituted Olefins†

Entry	Olefin	PHAL DHQD	PHAL DHQ
1[a]		98 (*R*)	95 (*S*)
2[b,c]		97 (*R,R*)	
3[d]		52 (*1S,2R*)	
4[a]		99 (*R,R*)	97 (*S,S*)
5[e]		98 (*R,R*)	
6[e]		86 (*R,R*)	
7[e]		74 (*R,R*)	
8[f,g]		95 (*R,R*)	
9[f]		83 (*R,R*)	

† The reactions were carried out in the presence of 1 equiv of $MeSO_2NH_2$ in *t*-BuOH/H_2O (1:1) at 0 °C with AD-mix-α [$(DHQ)_2PHAL$] and AD-mix-β [$(DHQD)_2PHAL$], respectively. [a] See ref 23a. [b] See ref 36. [c] $(DHQD)_2PYR$ provides the diol in 90% ee with this substrate. [d] See ref 53. [e] See ref 54. [f] See ref 55. [g] The diol is obtained in 86% ee with $(DHQD)_2PYR$.

Table 5. Asymmetric Dihydroxylation of Enol Ethers Leading to α-Hydroxy Ketones†

Entry	Olefin	E/Z ratio	PHAL DHQD	PHAL DHQ
1		1/>99	99 (*R*)	98 (*S*)
2		>99/1	90 (*R*)	
3		4/96	95 (*R*)	96 (*S*)
4		25/75	89 (*R*)	86 (*S*)
5		33/67	85 (*R*)	84 (*S*)
6		1/>99	97 (*R*)	
7		6/94	91 (*R*)	93 (*S*)
8		12/88	79 (*R*)	

† The reactions were carried out in the presence of 1 equiv of $MeSO_2NH_2$ in *t*-BuOH/H_2O (1:1) at 0 °C with AD-mix-α [$(DHQ)_2PHAL$] and AD-mix-β [$(DHQD)_2PHAL$], respectively.[56]

fail (Table 8).[58] Interestingly, the dihydroquinine-based pyrimidine ligand, $(DHQ)_2PYR$, gives products with *higher* enantiomeric excesses than the corresponding dihydroquinidine ligand $(DHQD)_2PYR$, whereas the reverse is true for most other olefins (see Tables 1–6).

While most terminal olefins yield good results with PYR or PHAL ligands (Table 1), a few members of this olefin class cause problems. Thus, alkenes with a single, *small* substituent, e.g., allyl derivatives CH_2=$CHCH_2X$ [X = H, CH_3, OC(O)R, OR, OTs, halo], normally give <70% ee (Table 1, entries 1–7 and 24). However, the propensity of PHAL ligands (**1**) to "recognize" flat, aromatic surfaces can be utilized even here. Thus, aryl allyl ethers are excellent starting materials for chiral glycerin synthons[41] (Table 1, entries 19, 20, and 23), provided the aromatic group lacks substituents in the *ortho* positions (entries 21 and 22). These compounds are interesting C3 building blocks and some of them are intermediates in the synthesis of β-adrenergic blockers.[41a] In certain cases the use of other AD ligands can also lead to improved enantioselectivities for these difficult olefins. For instance, the modified "phthalazine" ligand **8** gives higher enantioselectivities than the original[38] (eq 1). However, **8** is less readily available, and it is therefore used only for certain problematic olefins, such as allyl bromide.

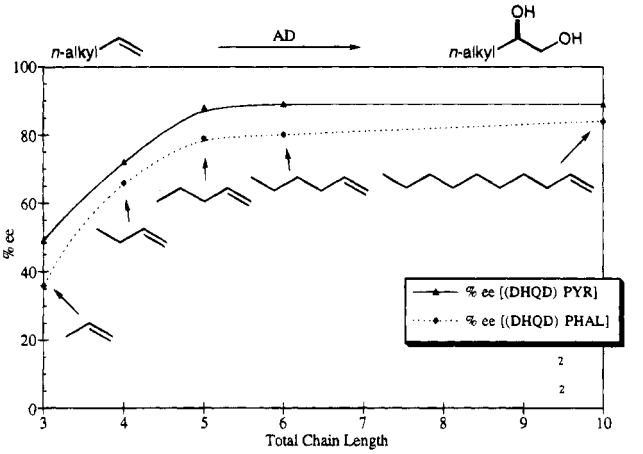
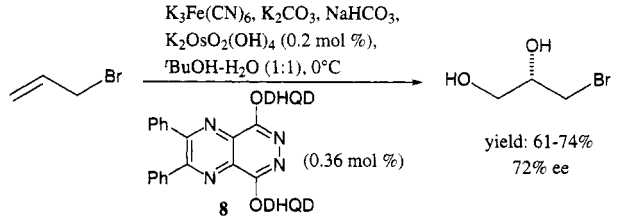
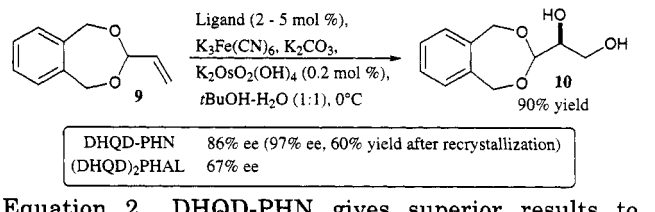


Figure 6. Dependence of the enantiomeric excess on the chain length of aliphatic *n*-alkenes.[37]



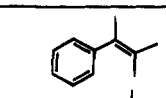
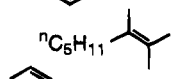
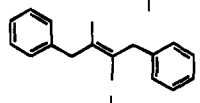
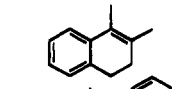
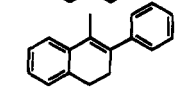
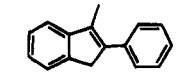
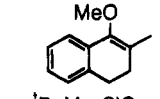
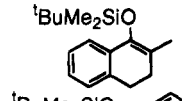
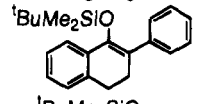
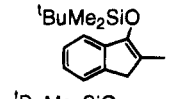
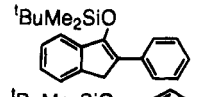
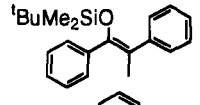
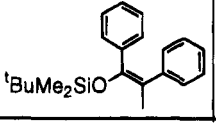
Equation 1. Asymmetric dihydroxylation of allyl bromide using the improved ligand **8**. The reaction mixture is buffered with 3 equiv of $NaHCO_3$ to prevent epoxide formation.[38]

In rare situations, the phenanthryl ether ligand **4** can provide a solution. Thus, DHQD-PHN gives glyceraldehyde synthon **10** with much higher enantioselectivity than phthalazine or pyrimidine ligands[44] (eq 2). Glyceraldehyde acetal **10** is an intermediate



Equation 2. DHQD-PHN gives superior results to $(DHQD)_2PHAL$ with acrolein acetal **9**.[44]

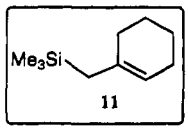
Table 6. Asymmetric Dihydroxylation of Tetrasubstituted Olefins, Including Enol Ethers[57,‡]

Entry	Olefin	PHAL		PYR		isolated yield (%)
		DHQD	DHQ	DHQD	DHQ	
1		39 *(R)*		**47** *(R)*		80-82
2		20 *(R)*		**22** *(R)*		51-55
3		29 *(R,R)*		**31** *(R,R)*		85-87
4		**59** *(1R,2S)*		56 *(1R,2S)*		23-24
5		83 *(R,R)*	85 *(S,S)*	**85** *(R,R)*	**89** *(S,S)*	29-31
6		75 *(R,R)*		**82** *(R,R)*		16-19
7		**64** *(S)*	60 *(R)*	41 *(S)*	**62** *(R)*	79-95[†]
8		**67** *(S)*	**65** *(R)*	6 *(R)*	37 *(R)*	89-92[†]
9		93 *(R)*	95 *(S)*	**95** *(R)*	**97** *(S)*	94-98[†]
10		**85** *(S)*	**81** *(R)*	59 *(S)*	80 *(R)*	64-85[†]
11		**89** *(R)*		84 *(R)*		23-32[†]
12		75 *(R)*	**81** *(S)*	**79** *(R)*	79 *(S)*	15-22[†]
13		53 *(R)*	**63** *(S)*	**60** *(R)*	33 *(S)*	46-60[†]

[‡] The ee value obtained with the best ligand for a given substrate is printed in bold. The reactions were carried out with 1 mol % of OsO_4 and 5 mol % of the ligand in *t*-BuOH/H_2O (1:1) in the presence of 1 equiv of $MeSO_2NH_2$ (enol ethers) or 3 equiv (all carbon substituted olefins). The reaction temperature was 0 °C (enol ethers) or room temperature (tetrasubstituted alkenes). [†] The product is an α-hydroxy ketone.

in the enzyme-mediated synthesis of fructose and other sugars by Wong.[59]

We are aware of only a few cases where the original *p*-chlorobenzoate ligand **3** gives higher selectivities than the current generation of ligands. Thus, the AD of allyl silane **11** in the presence of 25 mol % of DHQD-CLB yields a diol of 48% ee, while only 35% ee and 13% ee are obtained in the presence of the corresponding phenanthryl ether (13 mol %) and phthalazine (10 mol %) ligands, respectively.[40a]



11

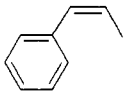
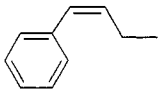
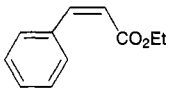
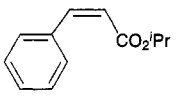
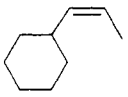
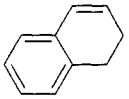
2.2. Reaction Conditions

This section is divided into four parts. The first part addresses the optimum reaction conditions for "standard AD substrates", i.e., terminal, 1,1-disubstituted, *trans*-1,2-disubstituted, and trisubstituted olefins. The second part provides the special reaction conditions that tetrasubstituted olefins require, and the third part deals with the AD of unreactive, electron-deficient olefins. In the fourth part, chemoselectivity aspects in the AD of sulfur-containing olefins are discussed.

2.2.1. Asymmetric Dihydroxylation of the "Standard Substrates"[23a]

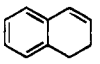
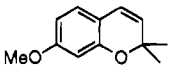
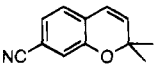
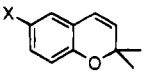
2.2.1.1. Choice of Solvent and Stoichiometric Additives. The catalytic asymmetric dihydroxyla-

Table 7. Enantioselectivities Obtained with *cis*-Olefins[29,†]

Entry	Olefin	% ee DHQD-IND	% ee DHQ-IND
1		72 *(1R, 2S)*	59 *(1S, 2R)*
2		72 *(1R, 2S)*	
3		78 *(2R, 3R)*	
4		80 *(2R, 3R)*	72 *(2S,3S)*
5		56 *(1R, 2S)*	44 *(1S,2R)*
6		16 *(1R, 2S)*	

† The AD reactions were carried out at 0 °C in 1:1 *t*-BuOH/H_2O in the presence of 2 mol % of ligand **6** (DHQD-IND or DHQ-IND), 0.2 mol % of OsO_4 and 1 equiv of $MeSO_2NH_2$.

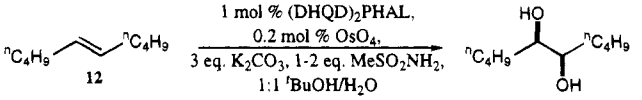
Table 8. The AD of Cyclic *cis*-Olefins[58,127,†]

Entry	*cis*-Olefin	DHQD-IND (%ee)	$(DHQD)_2PYR$ (%ee)
1		**16**	7
2		32	**67 (67)**
3			60
			
4	X = CN		58 (63)
5	Br		59 (74)
6	CF_3		66 (74)
7	Et		76 (84)

† The numbers in parentheses are the enantiomeric excesses obtained with the dihydroquinine based ligand. The reactions were performed at 0 °C in 1:1 *t*-BuOH/H_2O in the presence of 1 mol % of both ligand and OsO_4 as well as 3 equiv of $K_3Fe(CN)_6$ and K_2CO_3.

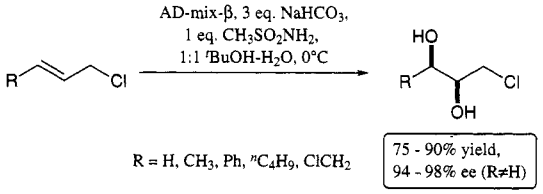
tion of olefins is one of the easiest metal-catalyzed reactions to perform. Water and oxygen pose no problems, since the reaction is actually performed in a solvent mixture containing 50% water, and is best carried out under heterogeneous conditions with 3 equiv of both $K_3Fe(CN)_6$ and K_2CO_3 in order to avoid the second catalytic cycle[20] (*vide supra*). Optimization studies have revealed that a 1:1 mixture of water and *tert*-butyl alcohol is the solvent system of choice, and less polar solvents can result in inferior enantioselectivities. Methyl *tert*-butyl ether has been successfully employed in an industrial application.[60] The olefin concentration in the *tert*-butyl alcohol/H_2O solvent mixture is usually 0.1 M.[23a]

Table 9. The Use of Sodium Peroxodisulfate as an Alternative Reoxidant[61]



Entry	Reoxidant	Temp.	reaction time	% ee	% yield
1	3 eq. $K_3Fe(CN)_6$	0°C	15.5 h	97	96
2	0.4 eq. $K_3Fe(CN)_6$, 1 eq. $Na_2S_2O_8$	0°C	15.5 h	97	97
3	0.2 eq. $K_3Fe(CN)_6$, 1 eq. $Na_2S_2O_8$	r.t.	6.5 h	94-95	100
4	1.5 eq. $Na_2S_2O_8$	r.t.	2 days	94-95	98

While the reaction is normally run under basic conditions (K_2CO_3, pH 12.2, aqueous layer), it is possible to buffer the system with 3 equiv of $NaHCO_3$ (pH 10.3, aqueous layer).[38,39] Buffering of the reaction mixture does not affect the ee, but it can have a beneficial effect on the yield when base-sensitive substrates are used or base-sensitive products are formed. Thus, the AD of allyl or cinnamyl halides (cf. eqs 1 and 3) should be performed under buffered conditions to minimize epoxide formation (see eq 1, the yield with allyl bromide as substrate is between 61 and 74% under buffered conditions; in the absence of $NaHCO_3$ only 40−50% of diol is obtained[38]). Unfortunately, the AD reaction does not turn over if K_2CO_3 is replaced entirely by $NaHCO_3$.



Equation 3. The AD of allylic halides gives better yields under buffered reaction conditions.[38,39]

Normally, the reaction is performed with 3 equiv of potassium ferricyanide as the reoxidant. The large quantity of salt (due to its high molecular weight, about 1 g of $K_3Fe(CN)_6$ is required per 1 mmol of olefin) may be disadvantageous for large-scale applications. In a study with *trans*-5-decene (**12**) as the substrate we found that ferricyanide can be largely replaced by sodium peroxodisulfate without an adverse effect on enantioselectivity or reaction rate[61a] (Table 9). Thus, at room temperature the reaction gives good results in the presence of only 0.2 mol % of $K_3Fe(CN)_6$ (0.066 g per 1 mmol of olefin) and 1 equiv of $Na_2S_2O_8$ (0.24 g per 1 mmol of olefin) with comparable reaction rates to the original conditions. However, complete replacement of ferricyanide resulted in much lower rates (entry 4). This use of peroxodisulfate was discovered independently by Bittman *et al.*[61b]

2.2.1.2. Concentration of OsO_4 and Ligand. Usually, the reaction is performed with very small amounts of the key reagents. Thus, only 0.2 mol % of Os reagent,[62] added to the reaction mixture either as OsO_4 or as the nonvolatile $K_2OsO_2(OH)_4$, and 1 mol % of ligand, i.e., PHAL or PYR ligands, are sufficient for most olefinic substrates.[23a] Interestingly, the enantioselectivity of the AD reaction has proven quite insensitive to variations in the relative

amounts of osmium and ligand. In some cases, the low ligand loading mentioned above can be dropped even further without much loss in the enantioselectivity. For example, stilbene still gives 96% ee when 1/100 of 1 mol % of $(DHQD)_2PHAL$ is used, as compared to the 99.8% ee obtained under normal conditions.[23a] Alternatively, it is possible to increase the amount of Os to 1 mol %, while maintaining the ligand concentration at the same level. This is useful for accelerating the reaction rate of relatively unreactive olefins (*vide infra*).

Additionally, the ligand can be recovered from the reaction mixture by extraction with dilute sulfuric acid and reused without purification.[63] This should prove important for very large-scale reactions and the procedure is described in section 2.2.1.4, below.

2.2.1.3. The "AD-Mixes". Terminal, 1,1-disubstituted and *trans*-1,2-disubstituted as well as trisubstituted olefins can be regarded as the "standard" substrates for the AD reaction. Since these substrates require very similar reaction conditions, it is possible to use a premix of all reactants [i.e., $K_2OsO_2(OH)_4$ as a nonvolatile OsO_4 source, $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$, K_2CO_3 and $K_3Fe(CN)_6$] for convenient dihydroxylations on a small scale. These "AD-mixes" can be readily prepared,[64] and they are also commercially available[34] as AD-mix-β [$(DHQD)_2PHAL$] and AD-mix-α [$(DHQ)_2PHAL$]. The currently recommended contents in 1 kg of AD-mix are as follows: $K_3Fe(CN)_6$, 699.6 g; K_2CO_3, 293.9; $(DHQD)_2$- or $(DHQ)_2$-PHAL, 5.52 g; and $K_2OsO_2(OH)_4$, 1.04 g.[64] [The ligand/Os molar ratio is 2.5:1.] The standard AD procedure calls for 1.4 g of this AD-mix per millimole of olefin.

Note that the above recipe corresponds to 0.4 mol % of Os with respect to the olefin in contrast to our original recommendations[23a,62] of 0.2 mol %. The adjustment was made to guarantee reproducible reaction times, since rate variations, caused by inhomogeneities in the AD-mix, had been observed with our original formulation. The higher concentration of Os has the additional advantage that it leads to shorter reaction times than those reported in our original paper,[23a] and it also means that less additional Os need be added to reach the 1 mol % level that some unreactive olefins require (*vide infra*).

2.2.1.4. Representative Procedures for the AD of the Standard Substrates.[23] The following points should be observed when choosing the optimum reaction conditions for the AD. First, 1 equiv of $MeSO_2NH_2$ should be employed for all substrates other than terminal alkenes to enhance hydrolysis of the osmate(VI) ester and hence the rate of catalytic turnover; no $MeSO_2NH_2$ should be added for monosubstituted or 1,1-disubstituted olefins except in special cases where turnover is noted to be very slow due to the presence of chelating functionality and/or steric problems in the substrate. Second, for small-scale reactions (<5 mmol) it is most convenient to use the AD-mixes, since only trace amounts of the key components are needed. However, for large-scale reactions it is more economical to add the reagents separately, and since the PYR or IND ligands are not available in premade mixes the latter procedure is necessary when their use is called for.

A representative procedure for the dihydroxylation of 1 mmol of olefin with AD-mix is given below. Under these conditions, 0.4 mol % of Os and 1 mol % of ligand, i.e. $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$, are used with respect to the alkene.

A 25-mL round-bottomed flask, equipped with a magnetic stirrer, is charged with 5 mL of *tert*-butyl alcohol, 5 mL of water, and 1.4 g of AD-mix-α or AD-mix-β.[65] [$MeSO_2NH_2$ (95 mg, 1 equiv) based on 1 mmol of olefin) should be added at this point for all 1,2-disubstituted, trisubstituted, and tetrasubstituted olefins.] The mixture is stirred at room temperature until both phases are clear, and then cooled to 0 °C, whereupon the inorganic salts partially precipitate. (For olefins which react sluggishly at 0 °C, e.g., ethyl cinnamate, the reaction should be performed at room temperature. Normally, this results in only a small loss in enantioselectively.) One mmol of olefin is added at once, and the heterogeneous slurry is stirred vigorously at 0 °C until TLC or GLC reveal the absence of the starting olefin (ca. 6 to 24 h). The reaction is quenched at 0 °C by addition of sodium sulfite (1.5 g) and then warmed to room temperature and stirred for 30−60 min. The reaction mixture is extracted several times with ethyl acetate or CH_2Cl_2 (when $MeSO_2NH_2$ is used, the combined organic layers should be washed with 2 N KOH to remove most of the sulfonamide) and then dried ($MgSO_4$) and concentrated to give a mixture of the crude diol and the ligand. Purification by flash chromatography (silica gel, EtOAc/hexane; the ligand does not elute under these conditions) gives the pure diol in typically excellent yield.

The following paragraph provides a representative procedure for the AD with separate addition of the reagents. This procedure is used typically on a large scale and/or when PYR[24] (**2**) or IND[29] (**6**) ligands are employed. Note that 2 mol % of the latter ligand is required for the AD of *cis*-olefins.

The ligand [i.e., PHAL ligands (7.8 mg, 1.0 mol %), or PYR ligands (8.8 mg, 1.0 mol %), or IND ligands (10.0 mg, 2 mol %)], $K_3Fe(CN)_6$ (990 mg, 3 mmol), K_2CO_3 (420 mg, 3 mmol), and OsO_4 (40 μL of a 0.1 M solution in toluene, 0.4 mol %) or $K_2OsO_2(OH)_4$ (1.4 mg, 0.004 mmol) are dissolved in a 1:1 mixture of water and *tert*-butyl alcohol (5 mL of each, 10 mL total) at room temperature. [$MeSO_2NH_2$ (95 mg, 1 equiv based on 1 mmol of olefin) should be added at this point for all 1,2-disubstituted and trisubstituted olefins.] The vigorously stirred mixture is then cooled to 0 °C and the olefin (1.0 mmol) is added in one portion. After complete consumption of the starting material (TLC or GLC), the reaction is worked up as described above (when $MeSO_2NH_2$ is used, the combined organic layers should be washed with 2 N KOH to remove most of the sulfonamide).

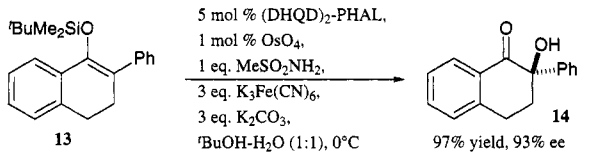
For large-scale preparations it is advisable to recover the ligand.[63] For the PHAL ligands this may be accomplished by extracting the combined organic layers with 3% aqueous H_2SO_4 saturated with K_2SO_4 (ca. 40 mL per 1 g of ligand), followed by a second extraction of the organic solution with saturated K_2-

SO_4 (ca. 40 mL per 1 g of ligand). The ligand enters the aqueous phase as the hydrogen sulfate salt and the solution can be reused directly for the subsequent AD reactions without further purification. Note, however, that the amount of K_2CO_3 in the subsequent AD reaction should be increased in order to neutralize excess H_2SO_4 and also to release the ligand salt as its free base. Additionally, the amount of water should be decreased by the volume of aqueous ligand solution added to the reaction mixture.

2.2.2. Asymmetric Dihydroxylation of Tetrasubstituted Olefins, Including Enol Ethers[57]

The hydrolysis of osmate esters derived from tetrasubstituted olefins is very slow, resulting in serious turnover problems. Consequently, the *catalytic* dihydroxylation of this class of olefins has been extremely rare.[13] However, recent studies have led to a much better process for this challenging class of substrates and the main improvements are as follows:

(1) $MeSO_2NH_2$ speeds up hydrolysis and hence catalytic turnover. One equivalent of this additive should be employed for the enol ethers, while 3 equivalents are required for the "all-carbon"-substituted cases. This sulfonamide effect can be dramatic as shown by the following example. In the presence of 1 equiv of $MeSO_2NH_2$, the AD of enol ether **13** was complete within 24 h at 0 °C, giving α-hydroxy ketone **14** in 97% isolated yield (eq 4). However, the reaction is incomplete even after 70 h in the absence of this additive, and the product is isolated in only 53% yield along with the starting material (44%).



Equation 4. The AD of enol ethers gives access to optically active α-hydroxy ketones.[57]

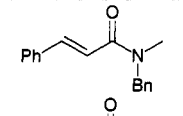
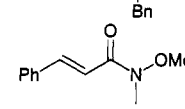
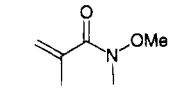
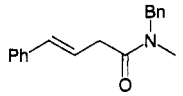
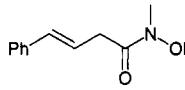
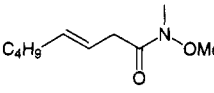
(2) The amount of OsO_4 should be increased to 1 mol % and the amount of ligand to 5 mol %.

(3) Whereas the more reactive enol ethers give satisfactory turnovers at 0 °C, the AD of the "all-carbon"-substituted olefins should be performed at room temperature. Under these conditions, most "all-carbon"-substituted cases give satisfactory reaction rates, except cyclic ones (Table 6, entries 4–6). The optimized procedure is as follows:

> The olefin is added in one portion to a mixture consisting of 3 equiv each of $K_3Fe(CN)_6$ and K_2CO_3, 1 mol % of OsO_4, 5 mol % of ligand (PHAL or PYR derivatives) and 1 molar equiv (for enol ethers) or 3 molar equiv (for all-carbon-substituted olefins) of $MeSO_2NH_2$ in 1:1 *tert*-butyl alcohol/water (5 mL of each per mmol of olefin) at 0 °C (for enol ethers) or at room temperature (for olefins). The reaction is monitored by TLC or GLC, and the workup is carried out as usual.

Under these conditions the AD of a number of tetrasubstituted olefins gives the corresponding diols in good yields and with good to excellent enantioselectivities when PHAL (**1**) or PYR (**2**) ligands are employed (see Table 6). This observation is somewhat surprising, since a belief had gradually evolved in our laboratory that nothing larger than a hydrogen would fit into the "southeast" quadrant of the catalytic site (see Figure 5 and discussion). The face selectivity of the AD on tetrasubstituted olefins can be predicted with our mnemonic device, and only one exception [Table 6, entry 8 with $(DHQD)_2PYR$] has been encountered so far. Thus, the olefinic substituent which is recognized as the smallest is placed in the southeast quadrant, as a hydrogen surrogate. The data for cyclic enol ethers show that the cyclic methylene is more suitable for this hindered quadrant than the OR group.

Table 10. The AD of Amides†

Entry	Olefin	%ee	Config.	Reaction Temp.	Yield, %
1		98	(2S, 3R)	r.t.	95
2		96	(2S, 3R)	r.t.	92
3		93	(2S)	0°C	81
4		98	(3R, 4R)	r.t.	97
5		98	(3R, 4R)	r.t.	81
6		96	(3R, 4R)	0°C	84

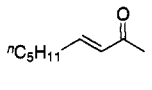
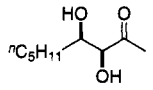
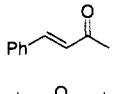
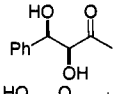
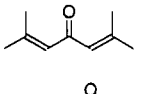
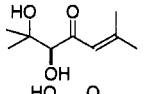
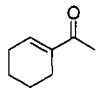
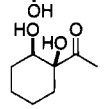
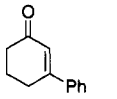
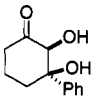
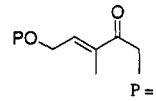
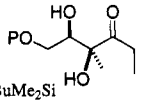
† Carried out in the presence of 1 mol % of OsO_4, 5 mol % of $(DHQD)_2PHAL$, and 1 equiv of $MeSO_2NH_2$ in 1:1 *t*-BuOH/H_2O.[66]

2.2.3. Asymmetric Dihydroxylation of Electron-Deficient Olefins[66,67]

Since OsO_4 is an electrophilic reagent, the rate of osmylation of electron-deficient olefins, such as α,β-unsaturated carbonyl compounds, can be very low. While unsaturated esters still give satisfactory reaction rates at room temperature under the standard AD conditions (i.e., 0.2–0.4 mol % OsO_4 and 1 mol % ligand), unsaturated amides, although more electron rich than the corresponding ester, react sluggishly, presumably due to osmate ester hydrolysis problems. However, a dramatic increase of the turnover rate can be achieved by increasing the amount of OsO_4 to 1 mol %. Thus, α,β-unsaturated amides can be dihydroxylated in the presence of 1 mol % OsO_4, 5 mol % ligand and 1 equiv of $MeSO_2NH_2$, to give the corresponding diols in good to excellent yields and enantiomeric excesses[66] (Table 10). The reaction is typically carried out as described for the tetrasubstituted olefins (section 2.2.2), except that 1 equiv of $MeSO_2NH_2$ is generally sufficient. A few representative examples for the AD of unsaturated amides are shown in Table 10.

Since *N*-methoxy-*N*-methyl amides (Weinreb amides) lead readily to aldehydes or ketones,[68] the products from the dihydroxylation of unsaturated Weinreb amides can be regarded as masked dihydroxy aldehydes or dihydroxy ketones.

Table 11. Asymmetric Dihydroxylation of Enones†

Entry	Substrate	Product	Yield	%ee
1			87	98
2			69	92
3			59	89
4			73	98
5			79	82
6††			61	99

P = ^{t}BuMe$_2$Si

† The reactions were performed in 1:1 *t*-BuOH/H_2O at 0 °C in the presence of 1 equiv of $MeSO_2NH_2$ using modified AD-mix-β [1 mol % of $K_2OsO_2(OH)_4$], buffered with 3 equiv of $NaHCO_3$. †† This particular reaction was carried out with regular AD-mix-β [0.4 mol % of $K_2OsO_2(OH)_4$], and it took 4 days at 0 °C (Marshall, J. A., personal communication).

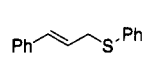
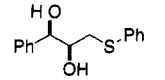
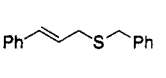
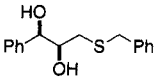
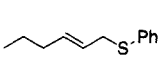
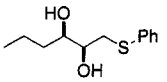
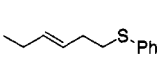
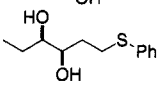
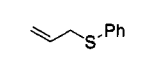
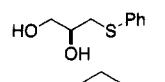
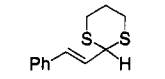
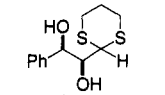
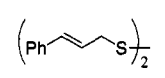
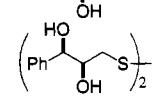
Even enones can be dihydroxylated with a fortified AD-mix, containing 1 mol % of $K_2OsO_2(OH)_4$ and 1 mol % of ligand **1**.[67] However, in order to prevent base-induced epimerization, the reaction mixture should be buffered with 3 equiv of $NaHCO_3$. In this way it is possible to obtain keto diols in good yields (Table 11). So far, this method has failed only with chalcone, which underwent epimerization and partial retro-aldol cleavage even under buffered conditions.

2.2.4. Chemoselectivity in the AD of Olefins Containing Sulfur[43]

In a recent study of the scope of the AD reaction, the chemoselectivity in the reaction of sulfur-containing olefins with OsO_4 was investigated.[43] Kaldor and Hammond had previously shown that an OsO_4/*N*-methylmorpholine *N*-oxide system is able to oxidize sulfides directly to sulfones,[69] although competitive dihydroxylation of a C−C double bond was also observed. Interestingly, however, the catalytic AD system displays very high chemoselectivity for the double bond in the presence of sulfur-containing functionality, and sulfoxide- or sulfone-containing side products were not detected. Thus, it is possible to dihydroxylate allylic and homoallylic sulfides (Table 12, entries 1−5), dithianes (entry 6, the reaction does not give satisfactory results with dithianes derived from 3-butenal and 3-methyl-3-butenal, probably due to insufficient activation of the double bond),[43b] and even disulfides (entry 7) to the corresponding diols in good yield and high enantiomeric excess.

The finding that sulfides, disulfides, and certain dithianes are unaffected under the AD conditions considerably broadens the scope of this reaction, since sulfur-containing functional groups are commonly used in organic synthesis.

Table 12. The AD of Sulfur-Containing Olefins[43]

Entry	Substrate	Product	Yield (%)	%ee
1			75	98
2			72	98
3			68	84
4			74	96
5			87	61
6			78	98
7			80	95†

† %de.

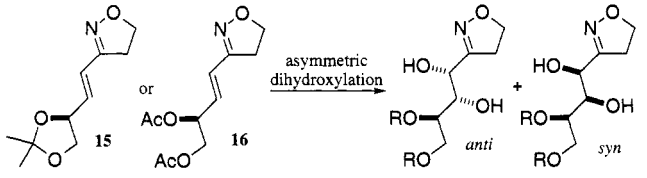
2.3. Double Diastereoselection and Kinetic Resolution

2.3.1. Double Diastereoselection

Given the high levels of enantioselectivity observed in the asymmetric dihydroxylation of prochiral olefins, we were optimistic that the AD would also be effective with chiral olefins. For a given case, a determination of the intrinsic diastereofacial selectivity of a chiral substrate is helpful in order to estimate the likelihood of success, especially in the "mismatched" pairing.[72] This is most easily accomplished by carrying out the osmylation in the absence of chiral ligand.[70] However, this control experiment may not be necessary for rigid cyclic olefins or for olefins bearing an allylic heteroatom as several accounts regarding the osmylation of such species have been published along with analyses for the observed diastereoselection.[71] A few examples of matched and mismatched double diastereoselection[72] in the asymmetric dihydroxylation of chiral olefins have been reported and are summarized in the following paragraphs.[73,74]

In his studies on the stereoselective synthesis of amino sugars, Wade investigated the asymmetric dihydroxylation of the 4,5-dihydroisoxazoles **15** and **16** shown in Table 13.[75] The reactions employing the phthalazine class of ligands displayed useful levels of matched and mismatched diastereoselectivity (entries 6−9). Thus, in the mismatched reactions (entries 7 and 9), the reagent was able to strongly override the intrinsic diastereofacial bias of the olefin substrate. It should be noted that these reactions use quantities of potassium osmate and ligand that exceed the amounts in our recommended procedure.[76] Since the reaction rate with AD-mix-α (entry 7) was very slow, it seems likely that turnover is being suppressed as a result of chelation by the dihydroisoxazole nitrogen at the osmate(VI) ester stage of the catalytic cycle. The added ligand and potas-

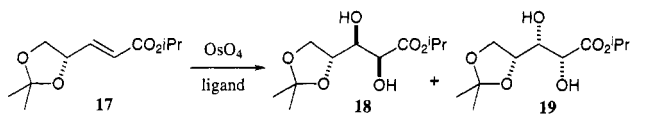
Table 13. Asymmetric Dihydroxylation of 4,5-Dihydroisoxazole Derivatives 15 and 16



Entry	Substrate	Ligand	Conditions	Anti/Syn	Yield,%
1	**15**	none	cat. achiral[a]	77 : 23	85
2	**16**	none	cat. achiral[a]	76 : 24	83
3	**15**	DHQD-MEQ	cat. chiral[a,b]	89 : 11	52
4	**15**	DHQD-MEQ	stoich. chiral[c]	78 : 22	48
5	**16**	DHQ-MEQ	cat. chiral[d]	52 : 48	66
6	**15**	$(DHQD)_2$-PHAL	cat. chiral[d]	96 : 4	53
7	**15**	$(DHQ)_2$-PHAL	cat. chiral[d,e]	11 : 89	62
8	**16**	$(DHQD)_2$-PHAL	cat. chiral[d]	98 : 2	82
9	**16**	$(DHQ)_2$-PHAL	cat. chiral[d]	5 : 95	85

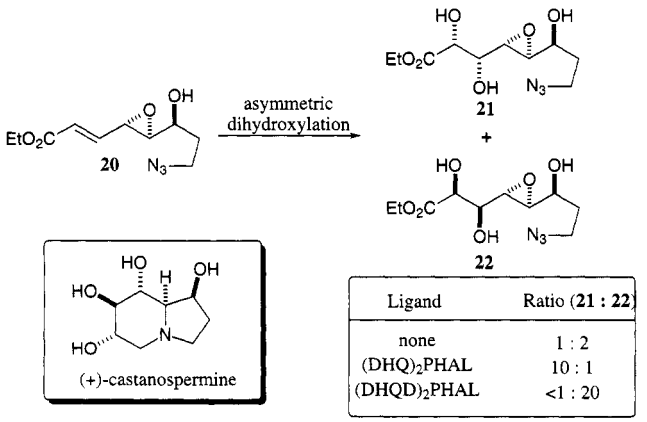
[a] 0.1 equiv of OsO_4, 3 equiv NMO, THF/water, 9:1, 20 °C. [b] 0.4 equiv of chiral aux. [c] 3 equiv of chiral aux, 1 equiv OsO_4, toluene, 20 °C. [d] 0.08 equiv of $K_2OsO_4{\cdot}2H_2O$, 3 equiv $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, 0.4 equiv of chiral aux, 1 equiv $MeSO_2NH_2$, *t*-BuOH/H_2O, 1:1, 20 °C. [e] Use of AD-mix-α under recommended conditions gave only 20% reaction after 22 h.

Table 14. Asymmetric Dihydroxylation of Olefin 17



Entry	Ligand (mol%)	Ratio (18 : 19)	Yield
1	quinuclidine (10)	2.6 : 1	85%
2	DHQD-CLB (10)	10 : 1	87%
3	DHQ-CLB (10)	1 : 10	85%
4	$(DHQD)_2$-PHAL (1)	39 : 1	84%
5	$(DHQ)_2$-PHAL (1)	1 : 1.3	52%
6	$(DHQD)_2$-PYR (5)	6.9 : 1	90%
7	$(DHQ)_2$-PYR (5)	1 : 4.1	86%
8	$(DHQD)_2$-PYR$(OMe)_3$ (5)	12 : 1	89%
9	$(DHQ)_2$-PYR$(OMe)_3$ (5)	1 : 7.0	90%

Scheme 8. Application of the AD for the Synthesis of (+)-Castanospermine[79]



Ligand	Ratio (**21** : **22**)
none	1 : 2
$(DHQ)_2$PHAL	10 : 1
$(DHQD)_2$PHAL	<1 : 20

sium osmate help alleviate this problem and allow the reaction to proceed at a reasonable rate.[76]

Morikawa and Sharpless carried out a similar set of experiments with the carbohydrate-derived olefin **17** shown in Table 14. These experiments were performed to assess the relative ability of several different ligands in the context of matching and mismatching in the asymmetric dihydroxylation reaction.[77,78] For this substrate, it was found that the phthalazine ligand $(DHQD)_2$PHAL was the ligand of choice for the matched reaction (entry 4). Whereas, in spite of their poor performance in the matched reactions, the pyrimidine derivatives $(DHQ)_2$PYR and $(DHQ)_2$PYR$(OMe)_3$ gave the best results in the mismatched examples (entries 7 and 9).

A mismatched double diastereoselective asymmetric dihydroxylation played a key role in a recently published synthesis of the polyhydroxylated indolizidine alkaloid castanospermine[79] (Scheme 8). In the asymmetric dihydroxylation of epoxy ester **20**,[79] Cha observed a 10:1 preference for the syn diastereomer **21** in reactions employing the $(DHQ)_2$PHAL ligand. A complete reversal of selectivity was observed in the matched case as the anti product **22** was the major product with >20:1 diastereoselectivity. The major product **21** from the mismatched reaction was subsequently converted to (+)-castanospermine in what is one of the most concise syntheses of this target to date.[81,82]

The asymmetric dihydroxylation was used to set the stereochemistry of the final two stereocenters of an advanced intermediate used in the preparation of squalestatin 1[83] (Scheme 9). Thus, the tetrahydrofuran derivative **23** was dihydroxylated in the presence of the DHQD-CLB ligand to provide diol **24** as a single diastereomer which was subsequently converted to the dioxabicyclo[3.2.1]octane derivative **25**, a late-stage precursor to squalestatin 1.

The asymmetric dihydroxylation of the following α,β-unsaturated ester derivatives has also been studied[84] (Table 15). The reactions of **26** and **27** using the DHQ-CLB ligand are matched since the diastereoselectivity is enhanced relative to the case without chiral ligand. Analogously, the reaction between ester **28** and OsO_4 using the DHQD-CLB also constitutes a matched pair. One notes, however, that in each mismatched example, the dihydroxylation reagent is unable to override the intrinsic diastereofacial preference of the ester.[85] It would be interesting to see how the new phthalazine and/or pyrimidine ligands would fare in these challenging mismatched cases.

The asymmetric dihydroxylation has also proven to be very useful for the synthesis of biologically active steroids having a vicinal diol in the side chain such as brassinosteroids,[86-92] potent plant growth regulators, ecdysteroid, an insect moulting hormone,[93] as well as active metabolites of vitamin D.[95] The AD has provided a direct method for the installation of the hydroxyl groups of the steroidal side chain with the correct relative and absolute configuration. This could not be accomplished in the absence of the chiral ligand.

Many brassinosteroid analogs were synthesized, and the (22*R*,23*R*)-diol (natural form) was found to be more active than the (22*S*,23*S*)-diol (unnatural form) by comparison of their biological activities[86] (Scheme 10). Previous work in this area had revealed that the natural stereochemistry of the steroidal side chain could not be accessed via normal dihydroxylation (i.e. without chiral ligand). Specifically, it was found that the nature of the substituent at C24 has a significant influence on the stereochemical course of the reaction. Steroids without a methyl group at C24 yielded a 7:3 mixture of the natural

Scheme 9. Asymmetric Dihydroxylation in the Synthesis of Squalestatin 1

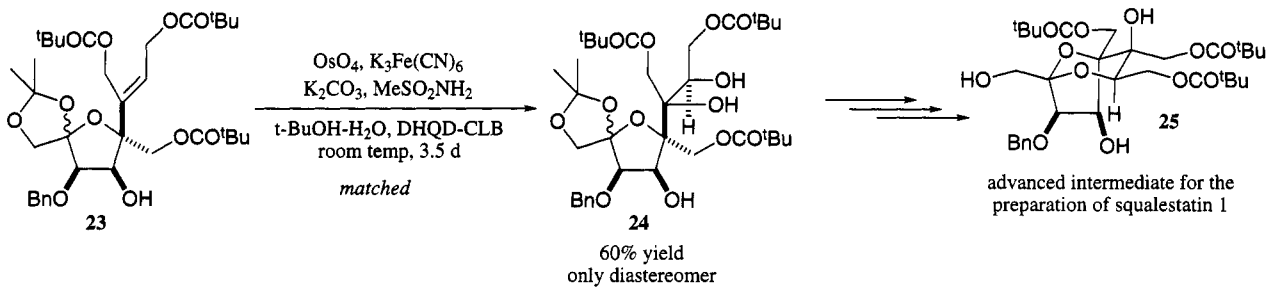
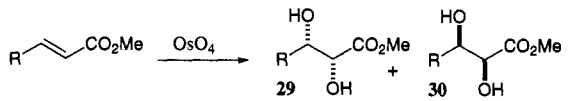
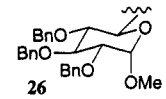
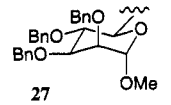
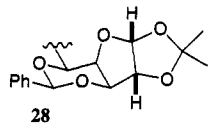
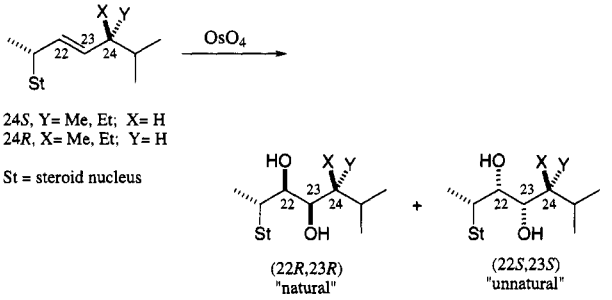


Table 15. Doubly Diastereoselective Dihydroxylations of Carbohydrate-Derived Olefins



R	Ligand	Ratio 29 : 30
 26	none	10.3 : 1
	DHQD-CLB	1.3 : 1
	DHQ-CLB	20.5 : 1
 27	none	7.4 : 1
	DHQD-CLB	3.4 : 1
	DHQ-CLB	15.9 : 1
 28	none	1 : 2.2
	DHQD-CLB	1 : 5.3
	DHQ-CLB	1 : 1.6

Scheme 10. Dihydroxylation of Steroidal Olefins



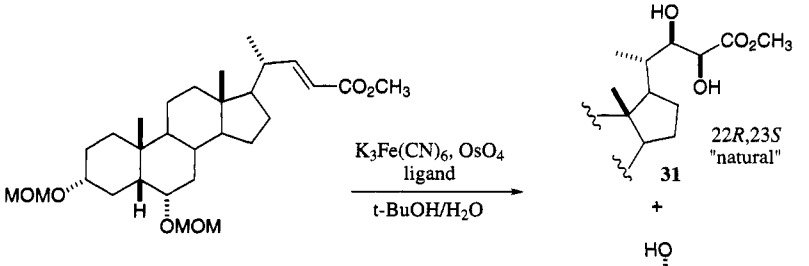
(22*R*,23*R*)- and the unnatural (22*S*,23*S*)-isomers while those with the (24*R*)-methyl group gave a 1:1 mixture of natural and unnatural isomers. Steroidal olefins containing (24*S*)-ethyl or (24*S*)-methyl groups also yielded diols with the unnatural (22*S*,23*S*) stereochemistry as major products.[87]

Cognizant of the difficulties presented by a C24 alkyl substituent, Zhou investigated the asymmetric dihydroxylation of a protected version of $\Delta^{22(23)}$-methyl hyodeoxycholate (Scheme 11). The reaction was found to be 4:1 selective in favor of the natural (22*R*,23*S*)-diol **31**. As was the case with the C24 alkyl derivatives, the reaction was 8:1 selective for the unnatural (22*S*,23*R*)-diol **32** in the absence of chiral ligand. The "natural" diastereomer **31** was then used for the preparation of several members of the brassinosteroid class.[88]

In a subsequent study, Zhou found that the natural diol stereochemistry could be obtained from steroidal olefins containing a C24 methyl group of either *R* or *S* configuration. The diol possessing the (22*R*,23*R*) configuration was the major product with each of the olefins (**33** and **34**) shown in Scheme 12. Steroidal olefins containing C24 ethyl groups, however, showed no diastereoselectivity in their AD reactions.[89]

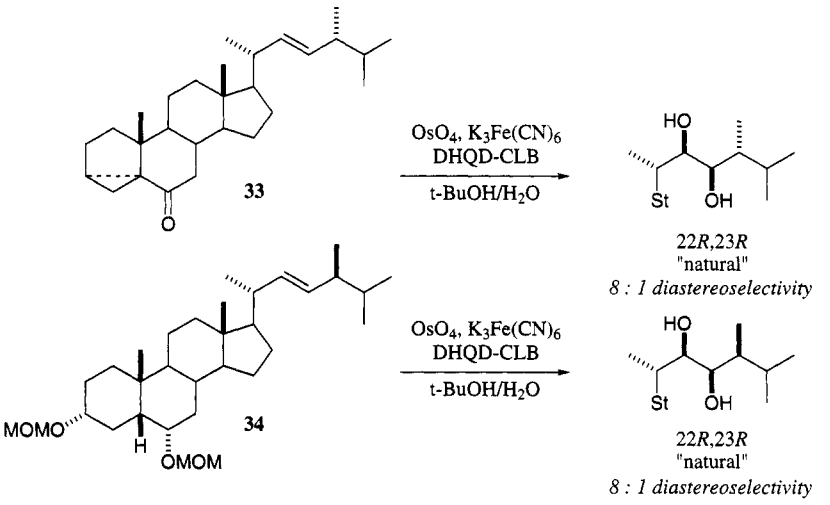
A short synthesis of 24-*epi*-brassinolide from brassicasterol was reported by Ikekawa.[90a] Significant effects of 24-*epi*-brassinolide on food production have been observed over the last several years in China[90b] (Scheme 13). For the synthesis of this compound, a key intermediate, 5α-ergost-2,22-en-6-one **35** was oxidized to tetrols **36** and **37** in a ratio of 1:1.6 in the absence of ligand.[90a] Kim then established that the diastereomer ratio could be shifted to 3.4:1 in favor of the natural (22*R*,23*R*) tetrol **36** by performing the reaction with DHQD-CLB using the NMO cooxidant system.[91] Subsequently, McMorris demonstrated that the ratio in favor of the natural diastereomer**36** could be increased to 9:1 through use of DHQD-CLB with the ferricyanide cooxidant system and that

Scheme 11. Asymmetric Dihydroxylation of $\Delta^{22(23)}$-Methyl Hyodeoxycholate

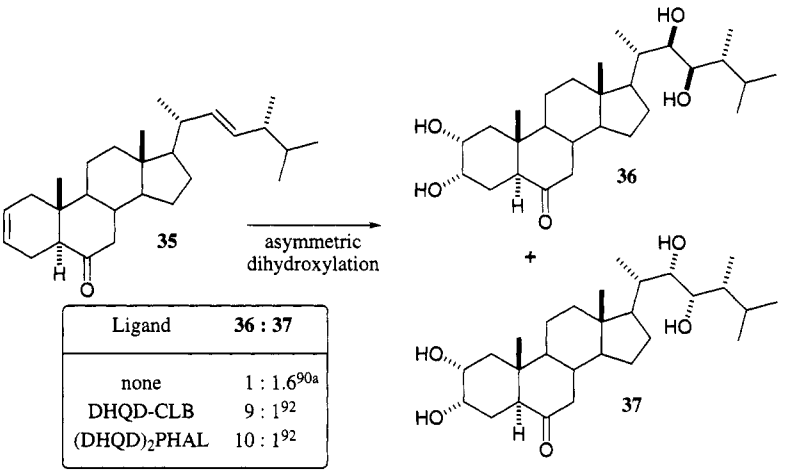


Ligand	31 : 32
none	1 : 8
DHQD-CLB	4 : 1

Scheme 12. Asymmetric Dihydroxylation of 24*S* and 24*R* Steroidal Olefins

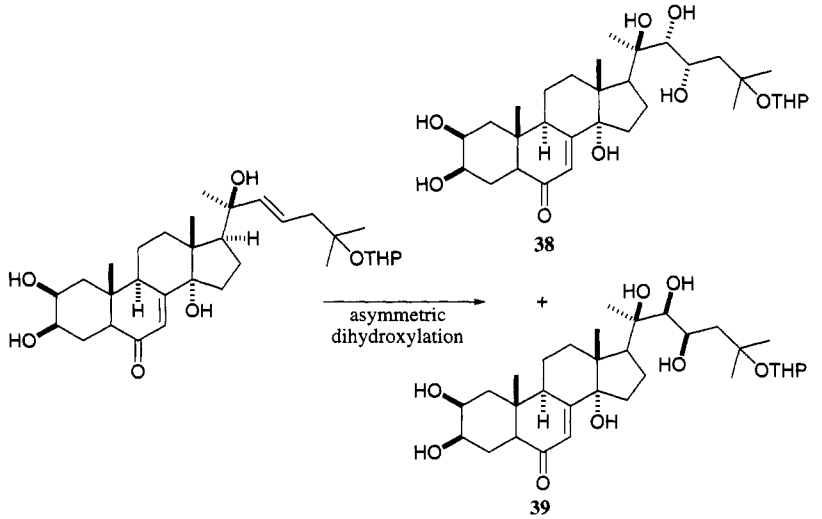


Scheme 13. Asymmetric Dihydroxylation of 5α-Ergost-2,22-en-6-one



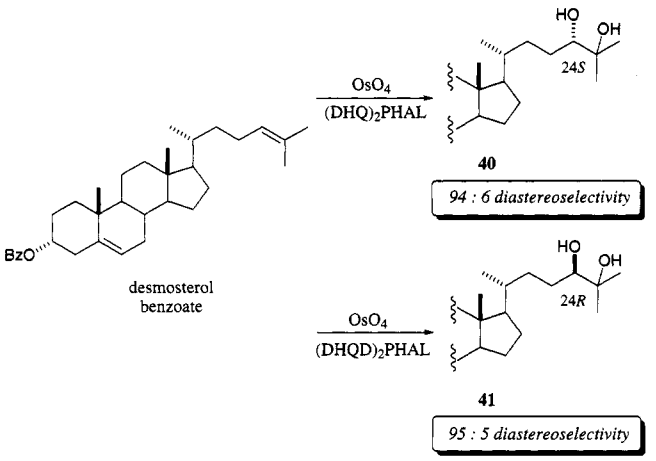
Ligand	36 : 37
none	1 : 1.6[90a]
DHQD-CLB	9 : 1[92]
$(DHQD)_2PHAL$	10 : 1[92]

Scheme 14. Asymmetric Dihydroxylation for Structure Elucidation of Gerardiasterone



Conditions	Yield	38 : 39
OsO_4, pyridine	85%	76 : 24
OsO_4, DHQ-CLB	80%	91 : 9
OsO_4, DHQD-CLB	87%	13 : 87

Scheme 15. Asymmetric Dihydroxylation of Desmosterol Benzoate

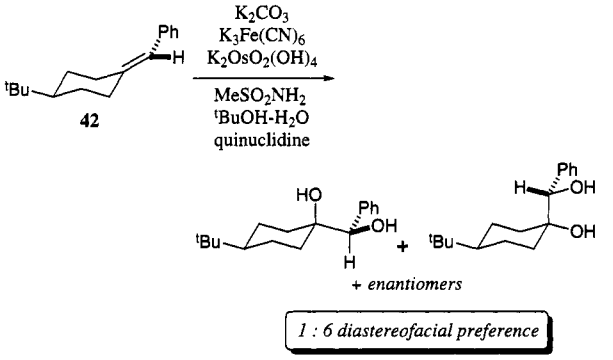


replacing DHQD-CLB with $(DHQD)_2PHAL$ gave an additional slight increase in the ratio (10:1) favoring the natural diastereomer **36**.[92]

In another application in the steroid area, Honda utilized a matched double diastereoselective asymmetric dihydroxylation to prove the absolute stereostructure of the C(19) side chain of the ecdysteroid, gerardiasterone (Scheme 14). Thus, experiments performed in the absence of a chiral ligand revealed the anti,syn diastereomer **38** to be intrinsically favored. The matched reaction with DHQ-CLB enhanced the selectivity to 91:9.[93] The major diastereomer **38** was found to be identical to gerardiasterone thus establishing the structure of the natural product. A good level of mismatched double diastereoselection was also observed as the all syn diastereomer **39** was found to be the major product of an 87:13 mixture with DHQD-CLB as the ligand.[94]

As a final example in the steroid area, Ikekawa has investigated the asymmetric dihydroxylation of desmosterol benzoate as a means of preparing an intermediate useful for the preparation of (24*R*)-24,25-dihydroxyvitamin D_3,[95] a compound effective for the treatment of osteoporosis[96] (Scheme 15). Thus, the asymmetric dihydroxylation of desmosterol benzoate using $(DHQ)_2PHAL$ as chiral ligand gave the (24*S*)-diol **40** as the major product of a 94:6 diastereomer mixture while the reaction with $(DHQD)_2PHAL$ provided the (24*R*)-diol **41** as the major product of a 95:5 mixture. The (24*R*)-diol is a potential precursor for the synthesis of (24*R*)-24,25-dihydroxyvitamin D_3.[95a] Lanosterol acetate bears an isopropylidene side chain like that in desmosterol benzoate and has been found to give the same high diastereoselectivity in both the matched and mismatched cases (24*R*:24*S* = 50:1 and 1:23) with AD-mix-β and AD-mix-α, respectively.[95b]

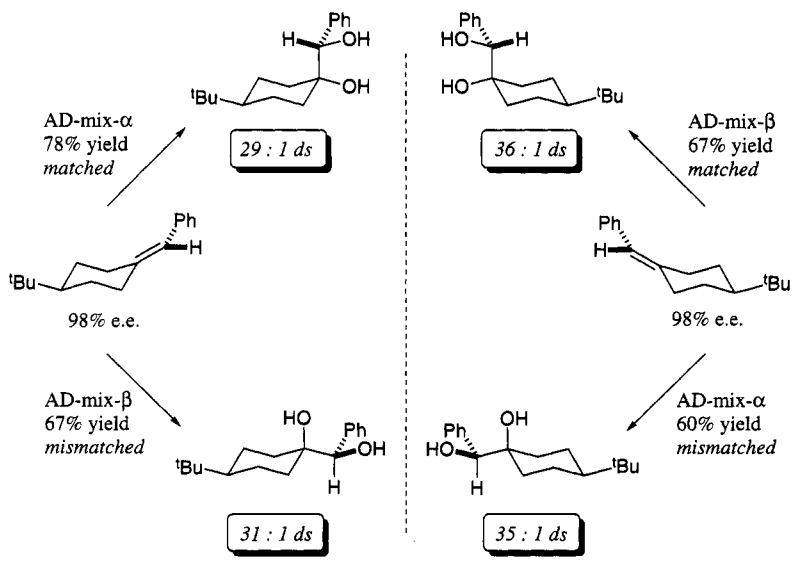
One of the more intriguing examples of double diastereoselection with the asymmetric dihydroxylation is shown below:[97]



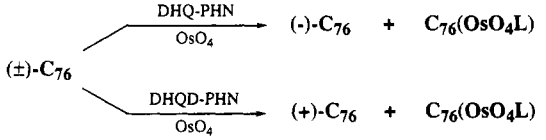
In these experiments, the osmium-catalyzed dihydroxylation in the absence of a chiral ligand displayed a 6:1 preference for equatorial dihydroxylation. In the double diastereoselective reactions of the enantiomerically pure olefins, the levels of diastereoselectivity in both the matched and mismatched reactions employing the $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ ligands were equal in magnitude and opposite in direction[98] (Scheme 16).

To date there have been several additional applications of the asymmetric dihydroxylation reaction in the double diastereoselective manifold. Among the reported examples are the preparation of intermediates for the synthesis of the immunosuppressant FK-506,[74a] the preparation of intermediates in the syntheses of mycalamide B,[99] insect juvenile hormone

Scheme 16. Double Diastereoselection in the AD of 4-*tert*-Butylbenzylidenecyclohexane



Scheme 17. Kinetic Resolution of C_{76} by Asymmetric Dihydroxylation



bisepoxide,[100] and the preparation of modified pyrimidine nucleobases.[101]

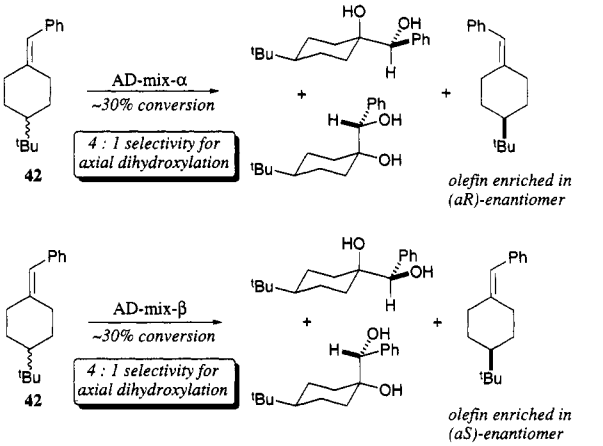
2.3.2. Kinetic Resolution

Several applications of the asymmetric dihydroxylation for the kinetic resolution of chiral racemic olefins have appeared. In spite of the fact that the AD generally gives higher enantioselectivities than the AE, the asymmetric dihydroxylation has not achieved the high levels of kinetic resolution efficiency observed with the asymmetric epoxidation (AE).[102,103] The generally superior chiral discrimination for the AD over the AE and the known effectiveness of the AE in kinetic resolution applications lead one to expect that the AD will exhibit excellent kinetic resolution discrimination when presented with a racemic chiral olefin. To date, however, with a few notable exceptions, the AD has generally proven to be ineffective for kinetic resolutions.

At present, we have no explanation for this difference between the AE and AD. Nevertheless, the coordination of the alkoxy group of the allylic alcohol to titanium in the AE greatly limits the possible transition state geometries for the AE. The absence of such a "restricting tether" in the AD process would seem to be implicated in the unusually small rate differences seen between enantiomers in the later process.

In what is to date the most interesting demonstration of kinetic resolution using the AD, Hawkins has resolved the enantiomers of C_{76}, thus preparing the first known example of an enantiomerically pure allotrope of an element[104] (Scheme 17). An obvious potential problem facing the use of the AD in a resolution of C_{76} is that the molecule contains 30 different types of double bonds, each of which is capable of dihydroxylation, thus raising the specter of enantiomeric discriminations that could oppose one another. It was noted from *ab initio* calculations that two of the 30 double bond types were pyramidalized to a greater extent (i.e. possessed greater curvature) than all the others. Osmylation occurred preferentially at one of these two sites thus making the resolution possible.[105]

Scheme 19. Kinetic Resolution of Olefin 42 via Asymmetric Dihydroxylation



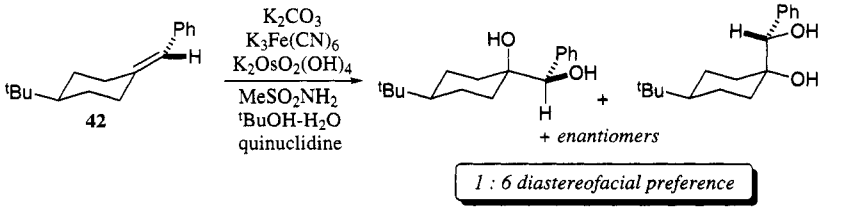
The major dihydroxylation product in each case arises from preferential axial dihydroxylation; a result opposite to that observed in the absence of the chiral ligand!

The Sharpless group has also investigated the kinetic resolution of racemic olefins with an axial chirality element. In these experiments, it was found that the resolution proceeded by dihydroxylation through an unexpected manifold.[97] For example, when the dihydroxylation of olefins **42** and **43** was performed in the absence of a chiral ligand, it was found in each case that equatorial dihydroxylation was favored for each substrate (Scheme 18).

In the kinetic resolution experiments, however, it was found that the fastest forming diol in each case was that arising from axial dihydroxylation (Scheme 19). Since the resolution itself is a double asymmetric process, the dihydroxylation that makes the resolution possible is a mismatched double asymmetric reaction.[172,106] The results of these experiments are summarized in Table 16.

In addition to those mentioned above, several additional olefin classes were investigated as potential substrates for kinetic resolution experiments.

Scheme 18. Intrinsic Diastereoselection in the Dihydroxylation of Exocyclic Olefins 42 and 43



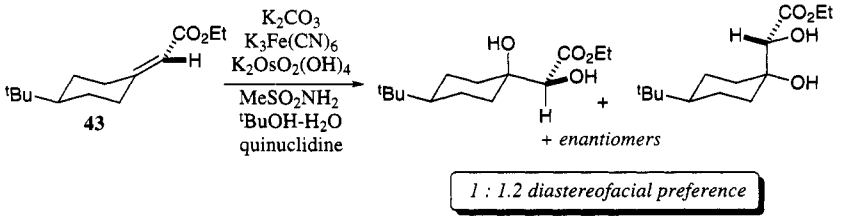
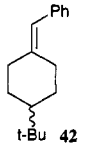
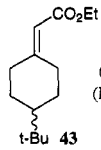


Table 16. Summary of Kinetic Resolution Experiments with Exocyclic Olefins 42 and 43

Olefin	Ligand	k_{rel}	Recovered Olefin
	$(DHQ)_2PHAL$	5.0	*(aR)*
	$(DHQD)_2PHAL$	9.7	*(aS)*
	$(DHQ)_2PHAL$	26.5	*(aR)*
	$(DHQD)_2PHAL$	32.0	*(aS)*

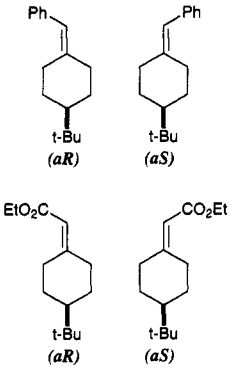
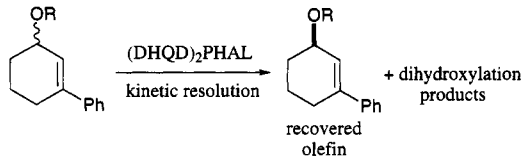
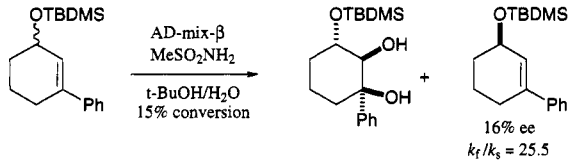


Table 17. Relative Rate Data from Kinetic Resolution Experiments with 3-Substituted Cyclohexenol Derivatives



R	k_f/k_s
H	5.6
Me	10.0
TBDMS	25.5
Bz	6.5

These investigations focused exclusively on allylic alcohol derivatives and the following trends emerged from these experiments. First, racemic acyclic allylic alcohols and their protected derivatives were generally poor substrates for kinetic resolution via the asymmetric dihydroxylation. Second, variously substituted cyclopentenols and cyclohexenols were investigated with the latter showing greater rate differences (i.e. higher k_f/k_s ratios). Third, within the cyclohexenol substrate class, 3-substituted derivatives were superior to 2-substituted derivatives with phenyl being the optimal substituent for the 3-position.[107,108,109] For example, the kinetic resolution of the TBDMS ether of 3-phenyl-2-cyclohexen-1-ol was allowed to proceed to 15% conversion using $(DHQD)_2$-PHAL as chiral ligand. Analysis of the recovered



starting material revealed the *R*-isomer to be present in 16% enantiomeric excess thus giving a k_f/k_s for the resolution process of 25.5.[109,110] Shown in Table 17 are kinetic resolution data obtained from a series of experiments utilizing 3-phenyl-substituted cyclohexenol derivatives as substrates where k_f/k_s is the ratio of rate constants for the dihydroxylation of each of the enantiomers.

Lohray has also investigated the utility of the asymmetric dihydroxylation reaction in kinetic resolution applications with studies on racemic allylic acetates. Several reaction variables including substrate to catalyst ratio, reaction temperature, and olefin substitution patterns were systematically investigated. Each of the reactions was carried out using the bis(dihydroquinidinyl) terephthalate $(DHQD)_2$-TP as the chiral ligand. Best results were obtained with 1-acetoxy-1-cyclohexyl-3-phenyl-2-propene (e.g. entries 4 and 5).[111] These data are summarized in Table 18.[112]

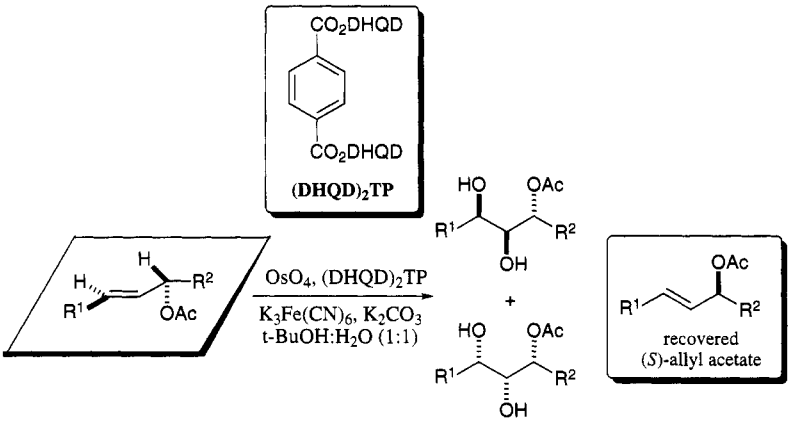
Recently, a comparative study of the relative efficiency of the $(DHQD)_2PHAL$, $(DHQD)_2TP$, and DHQD-CLB ligands for the kinetic resolution of 1-acetoxy-1-cyclohexyl-3-phenyl-2-propene was reported.[33] Each of the resolutions was carried out to ~60% conversion. This is most conveniently accomplished by simply limiting the amount of cooxidant and running the reaction until there is no Fe(III) present in the reaction mixture.[113] The enantiomeric excesses were then determined by chiral HPLC and the relative rates calculated using the Kagan equation.[109,110] These data are presented in Table 19.

In summary, the performance of the AD reaction in kinetic resolution applications is generally poor. This is surprising given the high levels of enantiofacial selectivity observed with prochiral olefins. At present we do not have an explanation for the poor performance of the AD in kinetic resolutions, and it appears unlikely that the AD will ever approach the effectiveness of the AE in kinetic resolution applications.[114] On the other hand, the scope of the AD is enormous compared to that for the AE, which works only for allylic alcohols. Therefore, one can imagine that the kinetic resolution version of the AD will often prove useful as a fast route to a chiral olefin and/or for establishing absolute configurations.

2.4. Asymmetric Dihydroxylation of Polyunsaturated Substrates

Polyunsaturated olefins have considerable synthetic potential, since they are highly functionalized compounds and each sp^2 center may in principle be prochiral. Thus, the face-selective manipulation of the double bonds in these substrates yields valuable chiral building blocks. The AD reaction has several virtues which make it especially useful for this kind of strategy, the most important being exquisite selectivity coupled with great reliability. Thus, the AD stereospecifically adds two hydroxyl groups in suprafacial fashion across each double bond and the *enantiofacial* selectivity of the initial dihydroxylation step can be confidently predicted based on the mnemonic device (see section 1). The *diastereofacial* selectivity of the subsequent dihydroxylation steps may also be controlled by the choice of the appropriate ligand. The reaction can be directed to effect either poly-dihydroxylation or regioselective monodihydroxylation of polyenes, leading to valuable polyols or ene diols, respectively. Most importantly, the regioselectivity of the dihydroxylation of unsymmetrical polyenes can generally be predicted based on a simple set of rules (*vide infra*).

Table 18. Kinetic Resolution of *sec*-Allylic Acetates via AD with $(DHQD)_2TP$



Entry	R^1	R^2	Substrate/ Catalyst	Conversion (%)	%ee (Config.) of recovered	S (k_f/k_s)
1	Me	c-C_6H_{11}	100	60	47 (*S*)	6.7
2			250	83	98 (*S*)	12.0
3			500	75	84 (*S*)	9.5
4	Ph	c-C_6H_{11}	500	60	88 (*S*)	24.5
5			100	70	98 (*S*)	25.0
6	Ph	Me	500	40	25 (*S*)	6.4
7			500	80	82 (*S*)	7.6
8			500	90	98 (*S*)	8.8
9	Me	n-C_8H_{17}	250	70	61 (*S*)	6.8
10			250	88	>98 (*S*)	9.7
11	Ph	Ph	250	70	15 (*R*)	4.8
12			250	92	33 (*R*)	3.0

Table 19. Kinetic Resolution of 1-Acetoxy-1-cyclohexyl-3-phenyl-2-propene

Ligand	ee at 60% conv.	k_{rel}
$(DHQD)_2PHAL$	38%	2.3
$(DHQD)_2TP$	70%	7.4
DHQD-CLB	81%	8.0

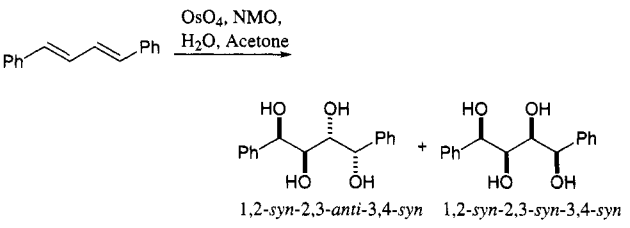
2.4.1. Formation of Polyols from Conjugated and Nonconjugated Polyenes

The exhaustive dihydroxylation of polyenes can be performed either in a single step by employing the homogeneous *N*-methylmorpholine *N*-oxide (NMO) process[115] or stepwise by carrying out sequential mono-dihydroxylations using the heterogeneous ferricyanide conditions.[51]

Treatment of conjugated dienes or trienes with catalytic amounts of OsO_4 in the presence of NMO as the stoichiometric reoxidant results in almost exclusive formation of tetrols and hexols, respectively, as shown for a diene case in Scheme 20.

The poly-dihydroxylation in the NMO reaction, as opposed to the single dihydroxylation in the ferricyanide system,[116a] is thought to result from the participation of the second catalytic cycle oxidant, the trioxoosmium(VIII) glycolate (Scheme 2). Extensive control experiments established that the 1,2-dihydroxy 3-ene class of ene diols is uniquely reactive toward further oxidation in the NMO-based catalytic osmylation system, thus explaining the propensity for exhaustive dihydroxylation[116b] (cf. relative rates for entries 1 and 5, Table 20a).

Scheme 20. Diastereoselective Bis-dihydroxylation of Conjugated Dienes[115]

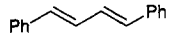
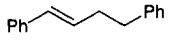
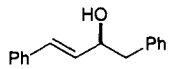
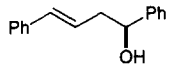
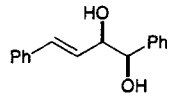
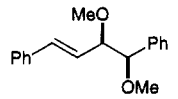
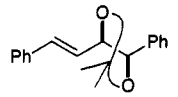


No ligand present:	16	:	1
DHQD-CLB present:	6	:	1

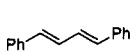
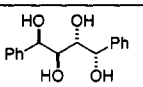
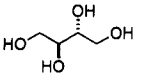
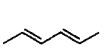
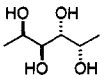
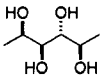
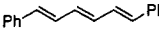
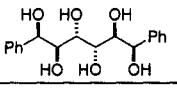
Further experiments, not shown in Table 20a, revealed that, in the absence of ligand, stoichiometric osmium tetraoxide reacts much faster with the parent diene than with the ene diol intermediate, which is consonant with the fact that the ferricyanide AD process stops at the ene diol stage. Hence, the culprit in these exhausitve dihydroxylations of conjugated polyenes appears to be the trioxoosmium(VIII) glycolate complexes which are present in the NMO system, but not the ferricyanide or the stoichiometric OsO_4 systems. Our current hypothesis is that the trioxoosmium(VIII) glycolate can attain favorable, transition state hydrogen bonding interactions between its oxo ligand(s) and the ene diol hydroxyls, interactions which either do not exist or are less favorable with free OsO_4.[116c] These interactions cannot occur if the two hydroxyl groups of the ene diol are protected, leading to lower reaction rates for these substrates (Table 20a, compare entry 5 with entries 6 and 7). This hypothesis of stabilizing

Table 20

a. Relative Rates of Reaction in NMO-Based Catalytic Osmylations (no ligand present)[116b]

Entry	Substrate	Relative Rate
1		1.0
2		4.0
3		5.2
4		6.0
5		9.2
6		0.4
7		0.3

b. Diastereoselective Formation of Polyols (no ligand present)[115]

Entry	Substrate	Major Product	Ratio (2,3-anti/2,3-syn)	% Yield
1			16 : 1	87
2			5 : 1	80
3			10 : 1	72
4			2 : 1	95
5			7 : 4 : 1†	95

† Ratio (2,3-*anti*-4,5-*anti*)/(2,3-*anti*-4,5-*syn*)/(2,3-*syn*-4,5-*syn*). All product polyols are racemic.

hydrogen-bonding interactions accounts for the tendency for each new dihydroxylation event to occur adjacent to the previous site of attack, and from the opposite face, leading to 1,2-*syn*-2,3-*anti*-3,4-*syn* tetrols and 1,2-*syn*-2,3-*anti*-3,4-*syn*-4,5-*anti*-5,6-*syn* hexols (Table 20b) with conjugated dienes and trienes, respectively. Unfortunately, the selectivity drops considerably when the starting material has four or more double bonds, not a surprising outcome given the increasing opportunities for nonadjacent oxidation in extended conjugated polyenes.

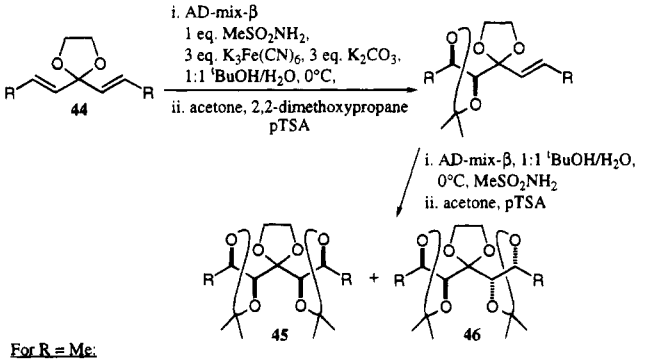
It should be noted that the intrinsic diastereofacial preference described above mismatches the selectivity imposed on the system by a cinchona ligand, since the ligand-mediated reaction would require attack of the two double bonds of a *trans,trans* diene from the same face. However, the induction by the ligand is too weak to overcome the strong anti diastereoselectivity exhibited by the trioxoosmium(VIII) glycolate oxidant with ene diols and merely results in reduced 2,3-*anti* to 2,3-*syn* ratios in the presence of the chiral ligand (DHQD-CLB, Scheme 20).

Since the unselective second cycle is avoided under the heterogeneous ferricyanide conditions,[116a,117] it is possible to obtain satisfactory enantio- and diastereoselectivities by performing a *stepwise* poly-dihydroxylation.[51] The diol obtained from a mono-dihydroxylation can then be used as a stereochemical template for exhaustive dihydroxylation (i.e. a "zip-dihydroxylation") of the remaining double bonds using the NMO oxidant system. Each successive dihydroxylation event will occur from the olefin diastereoface that is *anti* to its nearest hydroxyl neighbor. The great *anti* diastereoselectivity for dihydroxylation of ene diols in the NMO system is unique and should be synthetically useful.[116d]

Alternatively, a polyene can be exhaustively dihydroxylated by performing one AD reaction at a time and protecting the intermediate diols as, for example, acetonides. This procedure enables better control of the diastereofacial selectivity of the subsequent dihydroxylation steps as well as simplifying the isolation of the final product.

2.4.1.1. Asymmetric Dihydroxylation of Divinyl Ketals. A stepwise dihydroxylation strategy has been employed in the enantio- and diastereoselective preparation of protected keto tetrols **45** and **46** derived from diene ketals **44**[118] (Scheme 21 and Table

Scheme 21. Enantio- and Diastereoselective Exhaustive Dihydroxylation of Divinyl Ketals[118]



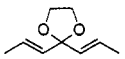
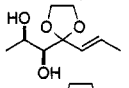
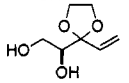
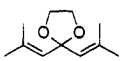
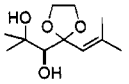
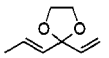
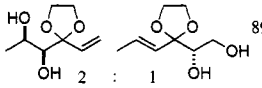
For R = Me:			
AD-mix-α [(DHQ)$_2$PHAL]	4.0	:	1.0
AD-mix-β [(DHQD)$_2$PHAL]	1.0	:	3.5

21). As discussed in the previous section, dihydroxylations employing the ferricyanide oxidant system stop at the ene diol stage, presumably due to electronic deactivation of the remaining olefin.

Ketal-protected divinyl ketones **44** are readily available from the corresponding saturated ketones by ketalization followed by α,α′-dibromination and bis-dehydrobromination.[119] Treatment with 1 equiv of AD-mix results in selective mono-dihydroxylation with high enantioselectivity in most cases (Table 21).

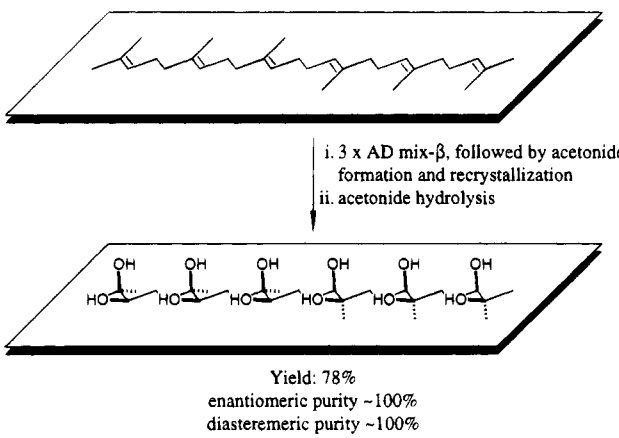
One of the strong points of this reaction sequence is that it not only provides control over the absolute configuration (in the first AD reaction), but also over the relative stereochemistry (in the second dihydroxylation reaction). Thus, depending on the choice

Table 21. The Mono-dihydroxylation of Protected Divinyl Ketones[118,†]

Entry	Substrate	Products	%ee with $(DHQD)_2PHAL$	%ee with $(DHQD)_2PYR$
1			93	72
2			47	60
3			77	
4			89/63	

† The AD reactions were performed under standard conditions in *t*-BuOH/H_2O employing 1 equiv of AD-mix and 1 equiv of $MeSO_2NH_2$. (No $MeSO_2NH_2$ was used in entry 2.)

Scheme 22. Exhaustive Dihydroxylation of Squalene[51]



Yield: 78%
enantiomeric purity ~100%
diasteremeric purity ~100%

of the ligand, either diastereomer **45** [with $(DHQ)_2$-PHAL] or diastereomer **46** [with $(DHQD)_2PHAL$] may be obtained as the main product.

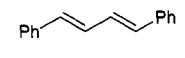
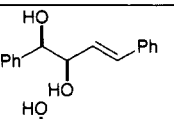
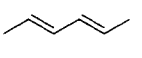
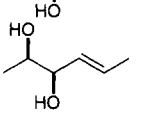
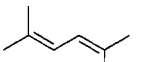
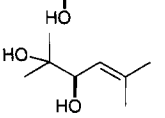
The stepwise poly-dihydroxylation strategy has been taken to the extreme with the enantio- and diastereoselective, exhaustive dihydroxylation of squalene[51] (Scheme 22). The dodecaol was obtained as essentially a pure enantiomer of a single diastereomer in 78% yield.

The high overall yield and stereoisomeric purity requires that each of the six dihydroxylation events, of which the first one is enantioselective and the remaining ones are diastereoselective, occurs with at least 96% ee or de, respectively, and an average chemical yield of 98%.

2.4.2. Selective Mono-dihydroxylation of Polyenes

As mentioned earlier, under the heterogeneous ferricyanide conditions, the asymmetric dihydroxylation may be controlled to selectively produce ene diols from conjugated polyenes[116a,117] (Tables 22 and 23), since the second cycle, trioxoosmium(VIII) glycolate oxidants are never produced in this system. The latter oxidants cause the rapid perhydroxylation of conjugated polyenes which is an unavoidable feature of the NMO-based system (*vide supra*). In the ferricyanide system, which involves free OsO_4, the preferential osmylation of the polyene starting

Table 22. Mono-dihydroxylation of Symmetrical Conjugated Dienes[116a]

Entry	Substrate	Product	% yield	% ee
1			84	99
2			78	93
3			94	93

material over the ene-diol product is most likely due to the electron-withdrawing, and therefore deactivating properties of the two OH groups of the latter. In the NMO system, the favorable H-bonding effects provided by these same OH groups to the trioxoosmium(VIII) glycolate oxidant are thought to overwhelm their inherent electronic deactivating effects.

Polyenes with isolated double bonds may also be mono-dihydroxylated,[74c,116a,117,120-124] but the yields tend to be lower if the double bonds are electronically and sterically very similar, no doubt a result of competitive poly-dihydroxylation.

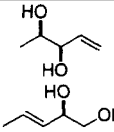
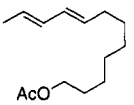
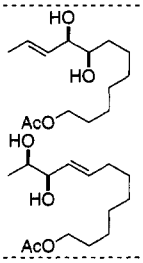
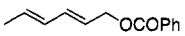
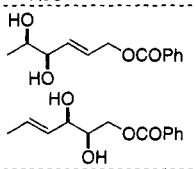
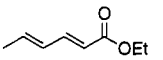
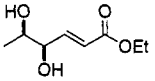
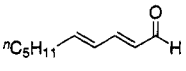
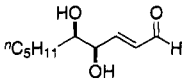
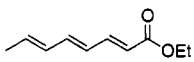
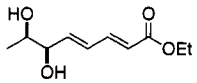
2.4.2.1. Regioselectivity. The regioselectivity of the mono-dihydroxylation of a polyene is determined both by electronic and by steric effects. Recently, it was shown that the rate constants of the dihydroxylation of isolated double bonds are much larger with *trans*-1,2-disubstituted and trisubstituted olefins than with *cis*-1,2-disubstituted and terminal alkenes.[125] Similar trends are also observed with polyenes, and the factors governing the regioselectivity are discussed in more detail in the following paragraphs.

Electronic factors greatly influence the regioselectivity, and the osmylation of unsymmetrical polyenes preferentially occurs at the more electron-rich double bond. This is true for conjugated polyenes (Table 23) as well as substrates with isolated double bonds (Table 24).

Steric effects may play a decisive role in systems with electronically very similar double bonds, and generally the sterically most accessible site is osmylated preferentially (Table 25).

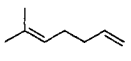
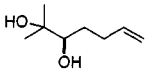
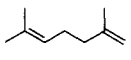
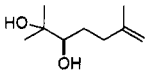
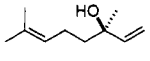
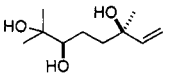
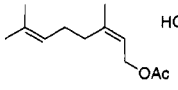
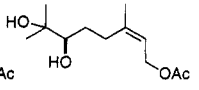
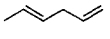
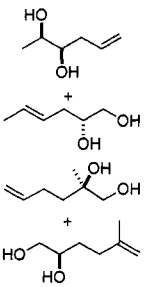
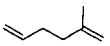
The osmylation of methyl farnesoate **47** (Table 25, entry 4) proceeded with the highest preference for the 10,11-double bond when carried out in the presence of $(DHQD)_2PHAL$, affording the 10,11- and 6,7-diols in a 20:1 ratio[121] [9:1 in the presence of $(DHQ)_2PHAL$]. In contrast, only a 3:1 selectivity was obtained in the absence of the ligand. The higher sensitivity of the OsO_4 ligand system for steric effects may be due to the greater steric demand of a transition state complex involving both OsO_4 and ligand. A similar enhancement of the positional selectivity by the ligand has been noticed in the mono-dihydroxylation of squalene[120] (Scheme 23). In the absence of a ligand, a 1:1:1 mixture of the three regioisomeric diols **48**, **49**, and **50**, along with polyols, was obtained. However, a slight preference for the less hindered double bonds was observed when the reaction was carried out in the presence of 5 mol % of $(DHQD)_2PHAL$, affording the diols **48**, **49**, and **50** in a 2.4:1.8:1.0 ratio.

Table 23. Regioselective Mono-dihydroxylation of Conjugated Dienes and Trienes[116a,117,†]

Entry	Substrate	Products	Ratio	%ee	% yield
1			3 : 1	90 : 72	48
2			2 : 1	95 : 94	82
3			17 : 1	98 : 91	
4				92	78
5				94	50
6				95	93

† The AD reactions were performed under standard conditions[23a] using $(DHQD)_2PHAL$ and 0.2–1.0 mol % of OsO_4.

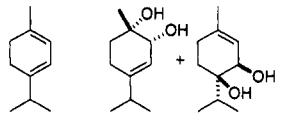
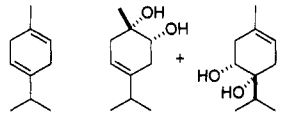
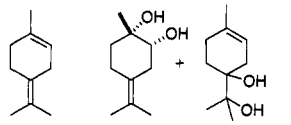
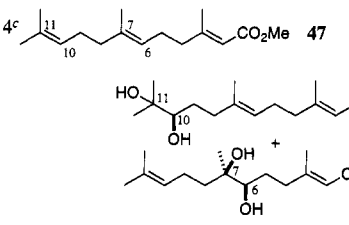
Table 24. Regioselective Mono-dihydroxylation of Dienes with Isolated Double Bonds†

Entry	Substrate	Products	Ratio	% ee	% yield
1[a]				98	73
2[a]				98	70
3[b]				94[c]	77
4[d]				97	94
5[a]			13 : 1	94	56
6[a]			5 : 1	74	42

† The AD reactions were performed under standard conditions[23a] using $(DHQD)_2PHAL$ and 0.2–1.0 mol % of OsO_4. [a] See ref 116a. [b] See ref 122. [c] % de. [d] See ref 126.

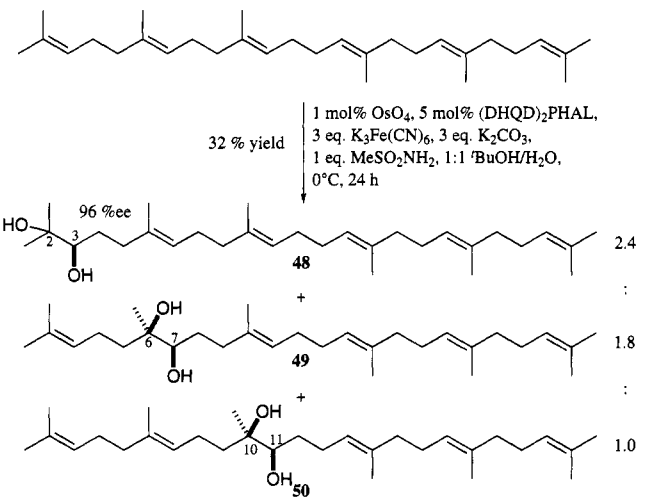
The geometry of the double bond also has an important influence on its reactivity toward OsO_4 in the presence of the PHAL and PYR ligands. The *cis*-double bond(s) of a *cis,trans*-polyene will not be attacked to an appreciable extent during asymmetric dihydroxylation of the *trans*-double bond(s) with these ligands[116a,117] (Table 26).

Table 25. The Influence of Steric Effects on the Regioselectivity†

Entry	Substrate	Products	Ratio	% ee[a]	% yield
1[b]			8 : 1	86	78
2[b]			> 20 : 1	96	84
3[b]			5 : 1	92	80
4[c]		**47**	20 : 1	98	40

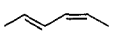
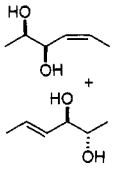
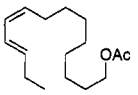
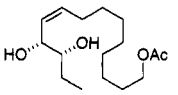
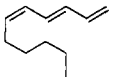
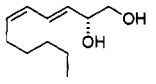
† The AD reactions were performed under standard conditions[23a] using $(DHQD)_2PHAL$ and 0.2–1.0 mol % of OsO_4. [a] % ee of the major product. [b] See ref 117. [c] See ref 121.

Scheme 23. Regioselective Mono-dihydroxylation of Squalene[120]



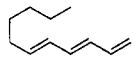
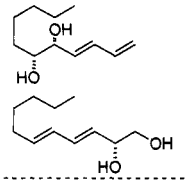
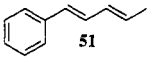
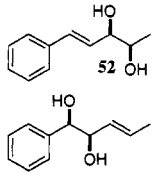
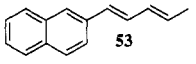
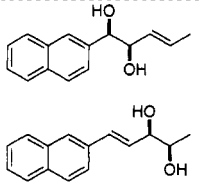
Another selectivity-determining factor is the preservation of conjugation in trienes and in dienes which are conjugated with aromatic groups. The examples in Table 27 (entries 1 and 2) demonstrate that generally one of the terminal double bonds of a conjugated system is attacked in order to maintain a maximum degree of conjugation.[117] This effect is probably also partially responsible for the selective attack of the double bond farthest away from the carbonyl group of the polyunsaturated carbonyl compounds in Table 23 (entries 4, 5, and 6).

Table 26. Selective Mono-dihydroxylation of *cis,trans*-Dienes and Trienes†

Entry	Substrate	Products	Ratio	% ee	% yield
1[a]			15 : 1	98	88
2[b]			93	93	82
3[b]			84	84	48

† The AD reactions were performed under standard conditions[23a] using $(DHQD)_2PHAL$ and 0.2−1.0 mol % of OsO_4. [a] See ref 116a. [b] See ref 117.

Table 27. The Selective Mono-dihydroxylation of Highly Conjugated Systems[117,†]

Entry	Substrate	Products	Ratio	% ee	% yield
1			6 : 1		60
2	 51	 52	4 : 1	92	68
3	 53		4 : 1	98	87

† The AD reactions were performed under standard conditions[23a] using $(DHQD)_2PHAL$ and 0.2−1.0 mol % of OsO_4.

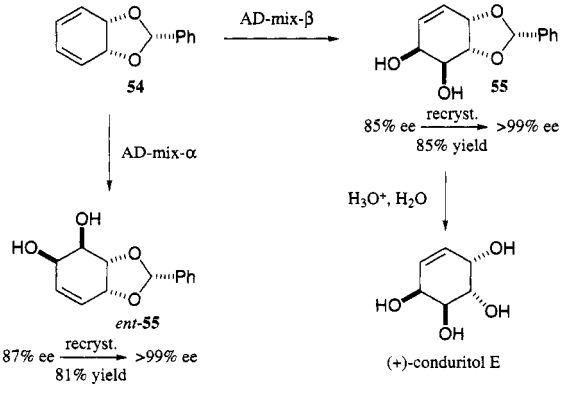
Interestingly, however, 1-(2-naphthyl)penta-1,3-diene (**53**) reacts mainly at its internal double bond in the presence of the phthalazine ligand (Table 27, entry 3), leading to disruption of conjugation. In contrast, the phenyl analog **51** (entry 2) reacts in a "normal" fashion to give mainly ene diol **52**, thereby maintaining a maximum degree of conjugation. The preference for the internal double bond in the naphthalene system may be due to especially favorable stacking interactions between the naphthyl group and the binding pocket of the phthalazine ligand[26,27] (cf. section 1, Figure 3). Molecular mechanics simulations indicate that such stacking is not as feasible in the transition state involving the external double bond. Apparently, a phenyl group does not provide enough "binding energy" to compensate the energy loss caused by interruption of conjugation and/or the conjugation is worth less in the naphthyl case. This finding parallels the earlier observation that 2-vinylnaphthalene has a five times larger saturation rate constant than styrene in the presence of $(DHQD)_2PHAL$.[26]

2.4.3. Asymmetric Dihydroxylation of Cyclic Polyenes

2.4.3.1. Small Ring Dienes. Recently, the asymmetric dihydroxylation of cyclic dienes was investigated,[117,127] since the products may provide useful synthetic building blocks and precursors for a number of biologically active compounds, such as sugar analogs, inositols, conduritols, etc. Unfortunately, most cyclopentadienes and other 6- to 8-membered ring dienes are poor substrates for the AD reaction, probably a result of the *cis* geometry of the double bonds (Table 28). As shown in Tables 28 and 29, the phthalazine ligand gives the best results with most substrates, and the enantiomeric excesses of the products are normally between 30 and 60% ee. Certain substituents lead to improved selectivities, and aromatic groups have an especially beneficial influence. Thus, an almost enantiomerically pure ene diol was obtained in the AD of phenylcyclopentadiene (Table 28, entry 3).

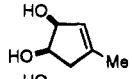
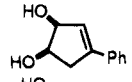
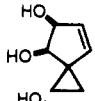
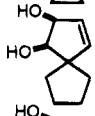
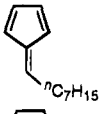
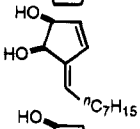
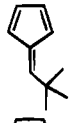
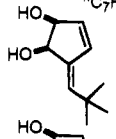
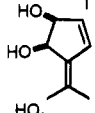
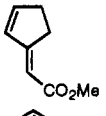
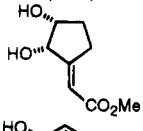
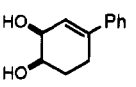
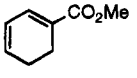
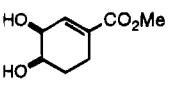
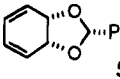
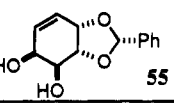
Interestingly, the asymmetric dihydroxylation of benzylidene-protected *cis*-cyclohexa-3,5-diene-1,2-diol (**54**) (Table 28, entry 13) proceeds in a highly enantioselective manner, providing the *exo*-diols **55** and *ent*-**55** (both in about 85% ee) with AD-mix-α and AD-mix-β, respectively. The improved enantiomeric excess compared to that of 1,3-cyclohexadiene (Table 28, entry 10) may be due to the increased steric bulk on one side of the *cis*-double bond thereby resulting in better enantioselection. Ene diol **55** is the penultimate intermediate in a recent synthesis of conduritol E[128] (Scheme 24), and simple recrystallization from $CCl_4-CH_2Cl_2$ raises its enantiopurity to >99% ee. It is important to note that all of the configurational assignments in this reference[128] are reversed due to a comparison with an incorrect literature assignment. The authors have corrected their assignment,[128b] and they now agree with the outcome predicted by the AD mnemonic device. In fact, it was our inability to fit their results to the mnemonic which led us to question their original assignments.

Scheme 24. Asymmetric Synthesis of Conduritol E[128]



2.4.3.2. Asymmetric Dihydroxylation of Mid-sized and Large-Ring Polyenes. As expected, even if they are tied into a ring, *trans* double bonds are dihydroxylated with considerably higher enan-

Table 28. Asymmetric Dihydroxylation of 5- and 6-Membered Ring Dienes and Trienes†

Entry	Substrate	Product	$(DHQD)_2PHAL$ %ee	$(DHQD)_2PYR$ %ee	DHQD-IND %ee
1[a]			38 (37)	7 (15)	29 (39)
2[a]			56 (14)	8 (10)	31 (8)
3[a]			99 (50)	97 (6)	95 (15)
4[a]			53 (38)	55 (34)	50 (36)
5[a]			70 (71)	70	73
6[a]			80 (60)		
7[a]			83 (58)		61 (61)
8[a]			30 (50)		
9[a]			47 (80)		
10[a]			37 (97)	23 (88)	24 (82)
11[a]			91 (42)	10 (57)	
12[a]			31 (84)		
13[b]	 **54**	 **55**	85 (85)		

† The numbers in parentheses are isolated yields. The absolute configurations were assigned tentatively based on the mnemonic device. The AD reaction was carried out at 0 °C in the presence of 5 mol % of the ligand and 1 equiv of $MeSO_2NH_2$. [a] See ref 127. [b] The dihydroxylation was carried out at 0 °C with AD-mix-β in the presence of 1 equiv of $MeSO_2NH_2$, and it occurred from the sterically less hindered face and anti to the adjacent oxygen substituent (cf. Scheme 24). The product was isolated as the diacetate; subsequent $LiAlH_4$ reduction and recrystallization gave the *optically pure* diol in an overall yield between 55 and 65%; see ref 128. The absolute configuration of entries 10, 12, and 13 have been established, the rest are tentatively assigned based on the mnemonic device.

tioselectivities than *cis* double bonds. A recent study[117] has revealed that the pyrimidines **2** are the ligands of choice, and the results are summarized in Table 30.

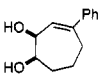
The remaining double bonds can be dihydroxylated in a highly diastereoselective fashion[117] (Table 31), and the intrinsic diastereofacial preference (cf. data obtained with quinuclidine) can either be enhanced [matched pair, $(DHQ)_2PYR$] or almost completely reversed [mismatched pair, $(DHQD)_2PYR$] depending on the choice of ligand. The pyrimidines **2** are again the optimal ligands for this application.

2.4.4. Asymmetric Dihydroxylation of Enynes[129]

Although it is possible for OsO_4 to oxidize triple bonds to 1,2-diketones,[10,130] they have a much lower reactivity than do double bonds. Consequently, the asymmetric dihydroxylation of enynes occurs exclusively at the double bond, affording yne diols in excellent yields. However, since triple bonds are among the sterically least demanding functional groups, the enantioselectivities obtained with enynes (Table 32) are generally lower than with the corresponding saturated olefins. As expected, *trans*-olefins give enantioselectivities in the 90% ee range, while *cis*-olefins are much poorer substrates. The results shown in Table 32 demonstrate that the phthalazines are the ligands of choice for this class of substrates.

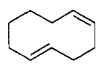
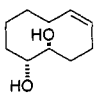
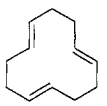
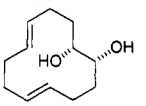
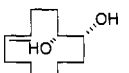
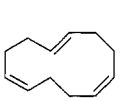
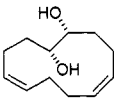
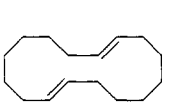
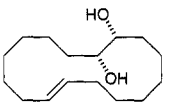
This methodology has been employed in the synthesis of optically active furfuryl alcohols and hy-

Table 29. Asymmetric Dihydroxylation of 7- and 8-Membered Ring Dienes and Trienes[127,†]

Entry	Substrate	Product	(DHQD)$_2$PHAL % ee	(DHQD)$_2$PYR % ee	DHQD-IND % ee
1			30 (37)	21 (37)	1 (28)
2			41 (46)		
3			16 (36)	24 (36)	11 (36)
4			5 (29)		

† The numbers in parentheses are isolated yields. The absolute configurations were assigned tentatively based on the mnemonic device. The AD reaction was carried out at 0 °C in the presence of 5 mol % of the ligand and 1 equiv of $MeSO_2NH_2$.

Table 30. Asymmetric Dihydroxylation of Cyclic Polyenes[117,†]

Entry	Substrate	Product	(DHQD)$_2$PYR % ee	(DHQD)$_2$PHAL % ee
1			**94**	51
2			**95**[a]	65
3			**88**[a]	69
4			**89**[a]	22
5			**92**	50

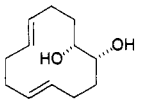
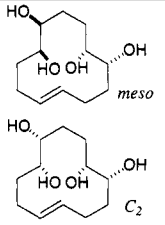
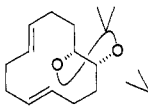
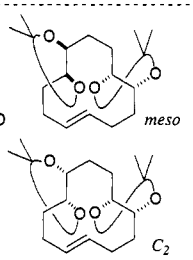
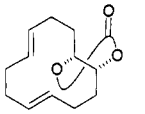
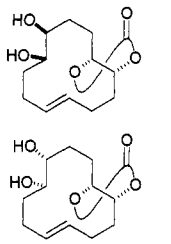
† The reactions were carried out in the presence of 1 mol % of OsO_4 and 1 mol % of the ligand. [a] The ee was determined at low conversion.

droxybutenolides.[131] Thus, hydromagnesiation of yne-diol **56** gives the corresponding Grignard reagent **57** in good yield. Furfuryl alcohols **58** are formed upon acylation of the organometallic reagent with a nitrile and subsequent acid-mediated hydrolysis, resulting in cyclization and aromatization (Scheme 25, path A). Hydroxybutenolide **59** is accessible in a sequence involving carboxylation of the Grignard reagent with CO_2, followed by hydrolysis (path B).

2.5. Influence of Acidic Hydrogens in the Substrate on Rates, Chemoselectivity, and Stereoselectivity

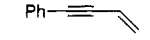
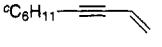
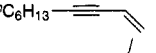
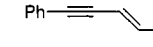
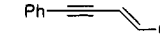
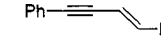
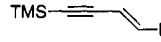
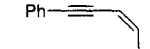
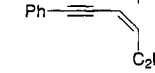
Several groups have reported the ability of certain functional groups to affect the stereoselectivity of the osmium-mediated dihydroxylation process.[132] Sul-

Table 31. Influence of the Ligand on the Diastereofacial Selectivity of the Second Dihydroxylation[117,†]

Entry	Substrate	Products	Ligand: Quinuclidine	Ligand: (DHQ)$_2$PYR	Ligand: (DHQD)$_2$PYR
1		 meso : C_2	97 : 3	99.7 : 0.3	25 : 75
2		 meso : C_2	89 : 11	99 : 1	11 : 89
3			74 : 26	99 : 1	4.5 : 95.5

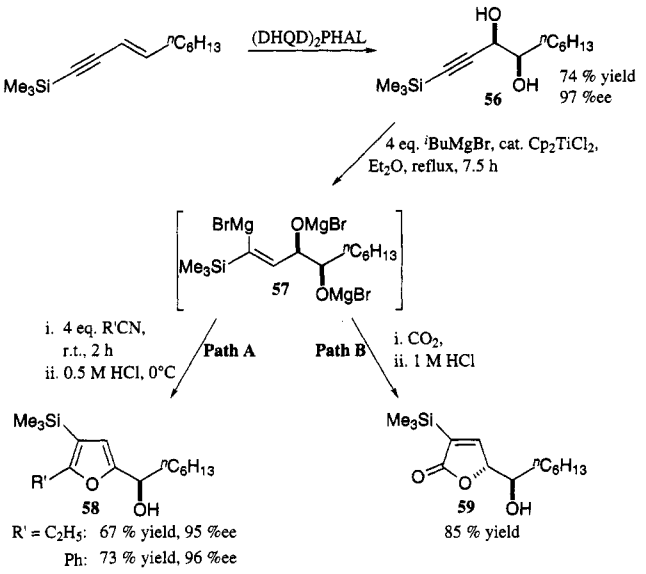
† The dihydroxylation reactions were performed under the ferricyanide conditions using 1 mol % of quinuclidine, 1 mol % of (DHQ)$_2$PYR, and 5 mol % of (DHQD)$_2$PYR, respectively. The diol in entry 2 is protected as the acetonide, and in entry 3 as the carbonate.

Table 32. Asymmetric Dihydroxylation of Enynes[129,†]

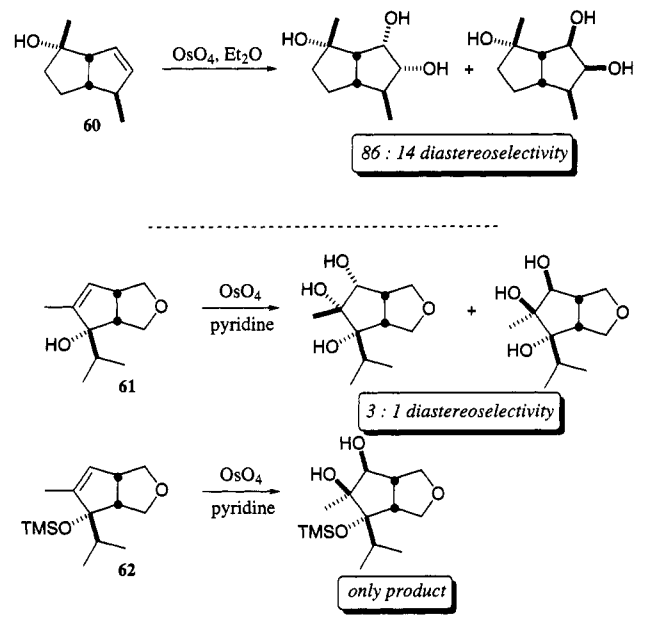
Entry	Substrate	% yield[a]	Ligand: DHQD-PHN % ee	Ligand: (DHQD)$_2$PHAL % ee
1		91	53	**73**
2		67	44	**72**
3		76	38	**54**
4		91	48	**79**
5		98	73	
6		94[b]	90	
7		67	97	
8		66	94	
9		82	29	
10		94[b]	54	

† The reactions were performed in 1:1 *t*-BuOH/H_2O at 0 °C in the presence of 0.2 mol % of OsO_4 and 1 mol % of the ligand using $K_3Fe(CN)_6$ as the reoxidant. [a] Isolated yield of yne diol from the AD with DHQD-PHN. [b] The reaction was performed on a mixture of geometric isomers of 1-phenyl-3-hexen-1-yne (*cis/trans* 25:75).

Scheme 25. Synthesis of Optically Active Furfuryl Alcohols and Butenolides from Enynes[131]



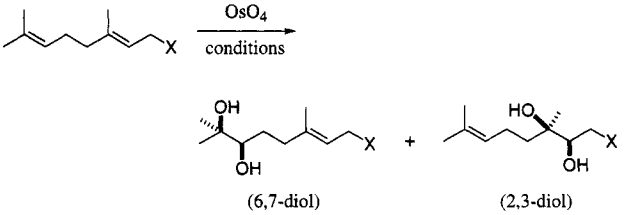
Scheme 26. Hydroxyl-Directed Osmylations



foxides,[133] sulfoximines,[134] nitro groups,[135] as well as carbamates and acetates,[136] have been implicated in directing the stereochemical course of the dihydroxylation.[137] In contrast, functional groups with acidic hydrogens have received little notice regarding their directing effects on the osmylation event. We are aware of two citations for possible hydroxyl-directed dihydroxylations.[138,139] There are no doubt other examples which we have missed, but the main point is that the hydroxyl-directing effect which is ubiquitous in olefinic alcohol epoxidations is almost unknown in osmylations of the same substrate class. In the first example, the bicyclic system **60**, having a free hydroxyl group, was dihydroxylated from the concave face with 86:14 diastereoselectivity (Scheme 26).[138] Similarly, allylic alcohol **61** showed a 3:1 preference for dihydroxylation from the concave face while the corresponding silyl ether **62** was dihydroxylated exclusively from the convex face.[139,140]

In the remainder of this section, we will present data which suggest that functional groups bearing

Table 33. OsO_4-Catalyzed Dihydroxylation of Geraniol and Derivatives



Entry	X[a]	condition[b]	6,7-diol/ 2,3-diol
1	OH	A , B	80 : 20
2	OMe	A, B	>98 : 2
3	OAc	A	>99 : 1
4	NHMs	B	67 : 33
5	NHTs	B	60 : 40
6	NHNs	B	60 : 40

[a] Ms = methanesulfonyl, Ts = *p*-toluenesulfonyl, Ns = *p*-nitrobenzenesulfonyl. [b] Conditions: (A) 5% OsO_4, 3 equiv of $K_3Fe(CN)_6$, 1 equiv of $MeSO_2NH_2$, 3 equiv K_2CO_3, 1:1 (v/v) *t*-BuOH/H_2O, RT; (B) 1 equiv of OsO_4, PhMe, RT.

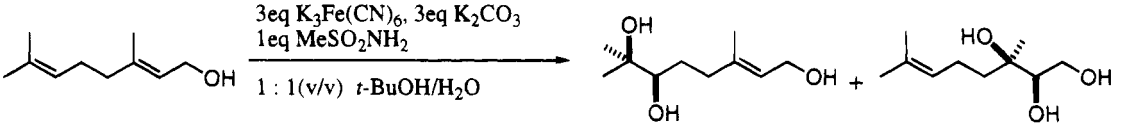
acidic hydrogen atoms (e.g., OH, NHTs, NHMs, NHTf), particularly when they occupy the allylic position, can influence the regio- and stereochemical course of the osmium-mediated dihydroxylation as well as exert significant rate enhancements when compared to electronically similar substrates.

2.5.1. Influence on Regioselectivity

To probe the effect exerted by allylic hydroxyl groups and other functional groups with acidic hydrogens on the regioselectivity of the osmium-mediated dihydroxylation, a series of experiments were performed with geraniol derivatives[141] (Table 33). Under both stoichiometric and catalytic conditions, dihydroxylation of geraniol gives an 80:20 mixture favoring the 1,6,7-triol. Dihydroxylation of the corresponding methyl ether and acetate derivatives resulted in almost exclusive oxidation at the remote double bond. On the basis of the electron-withdrawing effect of the allylic substituents, a preference for dihydroxylation at the remote double bond was anticipated. However, the increased propensity for dihydroxylation of the proximal double bond in underivatized geraniol suggests an attractive interaction between the hydroxyl group and OsO_4 (possibly a hydrogen bond) which partially offsets the electronic deactivation.[142] Even higher selectivity was observed for oxidation of the proximal double bond of sulfonamido derivatives of geranylamine, this in spite of both more unfavorable electronic and steric influences for the sulfonamido substituents vis-á-vis the hydroxyl substituent. The increase in selectivity relative to geraniol may be due to the increased acidity of the sulfonamido protons relative to a hydroxyl proton. The increased acidity may enhance the strength of the hydrogen bond thus enhancing allylic selectivity.

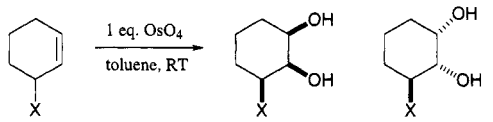
The magnitude of this hydroxyl-directing effect may be influenced by performing the dihydroxylation in the presence of ligand. For example, the dihydroxylation of geraniol in the presence of quinuclidine suppressed oxidation of the 2,3 double bond giving the 1,6,7-triol as the major product of a 9:1 mixture

Scheme 27. Dihydroxylation of Geraniol in the Presence of Ligand



5 mol % OsO_4, **NO ligand**, RT 4 : 1
1 mol % OsO_4, 5% quinuclidine, RT 9 : 1
1 mol % OsO_4, 5% $(DHQD)_2$-PHAL, 0 °C ≥49 : 1 (1,6,7: 89% yield, 94% ee)

Table 34. Dihydroxylation of 1-Substituted 2-Cyclohexenes



Entry	X	syn/anti
1	OH	1 : 3.3
2	NHTs	1 : 2.5
3	NHTf	1.1 : 1
4	N(Me)Tf	0 : 1

(Scheme 27). This ratio increased to ≥49:1 when performed with $(DHQD)_2$PHAL.

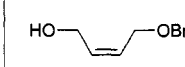
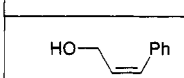
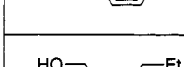
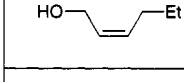
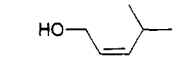
2.5.2. Influence on Stereoselectivity

Functional groups in the allylic (or homoallylic) position bearing acidic hydrogens can also have a marked influence on the stereoselectivity of the dihydroxylation reaction. For example, the diastereofacial selectivity in the dihydroxylation of 1-substituted 2-cyclohexenes was found to be dramatically influenced by the acidity of the allylic substituent in agreement with the proposed hydrogen bonding interaction between OsO_4 and the allylic substituent (Table 34).[143] An increase of syn vs anti attack was observed as the allylic substituent was changed from hydroxyl to *p*-toluenesulfonamido to trifluoromethanesulfonamido (entries 1−3). Complete anti selectivity was observed in the absence of an acidic hydrogen (entry 4).

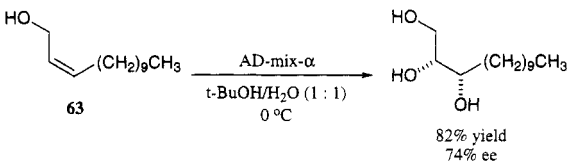
More recently, it was found that free hydroxyl groups have a beneficial effect on the enantioselectivities observed in the asymmetric dihydroxylation of *cis*-allylic and -homoallylic alcohols, especially when using the phthalazine ligands, $(DHQD)_2$PHAL and $(DHQ)_2$PHAL.[144] This result was rather surprising given that previous investigations had shown this ligand class to be very poor for the asymmetric dihydroxylation of simple hydrocarbon *cis*-olefins, especially those bearing alkyl groups at each terminus.[145] In addition, previous studies with *trans*-allylic alcohols had suggested that a free allylic hydroxyl has a slight deleterious effect on enantioselectivity.[141] The asymmetric dihydroxylations of *cis*-allylic and homoallylic alcohols were performed using the phthalazine ligands under standard conditions (i.e. t-BuOH/H_2O 1:1, 0 °C). For some substrates, the enantioselectivities were comparable to those obtained using the IND ligand class.[145] These data are summarized in Table 35.

In a subsequent experiment, it was found that the asymmetric dihydroxylation of the C_{13} allylic alcohol

Table 35. Enantiomeric Excesses Obtained in the AD of *cis*-Allylic and -Homoallylic Alcohols with Various Chiral Ligands

Substrate	$(DHQD)_2$-PHAL	$(DHQ)_2$-PHAL	DHQD-IND
	64 (*2S,3R*)	57 (*2R,3S*)	31 (*2S,3R*)
	71 (2S,3R)	73 (2R ,3S)	72 (*2S,3R*)
	74 (*2S,3R*)	64 (*2R,3S*)	51 (*2S,3R*)
	64 (*2S,3R*)	--	--
	54 (*3S,4R*)	45 (*3R,4S*)	--

63 with AD-mix-α proceeded in 74% ee.[146] Thus,

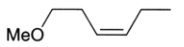
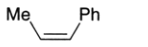


when compared to *cis*-2-hexen-1-ol, an increase in enantioselectivity of 10% is realized when the terminal *n*-propyl substituent is replaced by *n*-decyl (cf. *cis*-2-hexen-1-ol gave 64% ee with $(DHQ)_2$PHAL, see Table 35).

Hydrogen bonding of the free hydroxyl to an oxo group on osmium may account for the enhanced enantioselection observed with this special class of *cis*-olefins. The final entry in Table 35 also appears to support this hypothesis. Although the enantioselectivity observed with this substrate was modest [54% ee with $(DHQD)_2$PHAL], it is nonetheless surprising given that the environment near the olefin unit is nearly symmetric.[147] The catalyst is somehow able to differentiate the two ends of the olefin even though the hydroxyl group is fairly remote from the reaction center.

To further test the hypothesis regarding the beneficial effects of a free, proximate hydroxyl group, asymmetric dihydroxylation experiments were performed on the corresponding methyl ethers. The data obtained from these experiments are summarized in Table 36. When compared to the corresponding alcohols in Table 35, a dramatic drop in enantioselectivity is evident in each case.

Table 36. AD Data of Methyl Ether Derivatives and *cis*-β-Methylstyrene with $(DHQD)_2PHAL$

Substrate	% ee	Major Product
	23	(2*S*,3*R*)
	13	(2*S*,3*R*)
	0	---
	35[13]	(1*R*,2*S*)

An attractive feature of this methodology is that the crude triol products tend to be crystalline, presenting the opportunity for enantiomeric enrichment. For example, the enantiomeric purity of the triol obtained from *cis*-2-hexen-1-ol increased from 74% to 96% after a single recrystallization.[144]

2.5.3. Influence on Rates

To further examine the notion that a hydrogen bond may be responsible for the enhanced enantioselection observed in the asymmetric dihydroxylation of *cis*-allylic alcohols, the rates of formation of the osmium(VI) glycolate of α-substituted styrene derivatives were measured using stopped flow methods under pseudo first-order conditions.[148] Calculation of the ceiling rate constants for each of the substrates provided the data shown in Figure 7.

Since the addition of OsO_4 to olefins is known to be a mildly electrophilic process,[10] one would expect the reaction rates for the hydroxyl- and methoxyl-substituted cases to be slower than that for the parent α-methylstyrene. The rate data bear this out for the methyl ether, however, when compared to α-methylstyrene, the compound with an allylic hydroxyl group is, by some mechanism [perhaps a hydrogen bond to an osmium oxo ligand (Os=O)], almost able to overcome the deactivating effect of the allylic oxygen. Finally, it is worth noting that ee and rate-enhancing effects for an acidic functional group seem to require that it reside in the NW quadrant of the AD mnemonic device (cf. section 1, Figure 5). In contrast, earlier results[26,141,149] indicate that the presence of such a group in the NE and, perhaps also, the SW quadrants has a deleterious effect on the AD process. More specific suggestions for the role of these putative hydrogen bonding effects are discussed elsewhere.[26,27b]

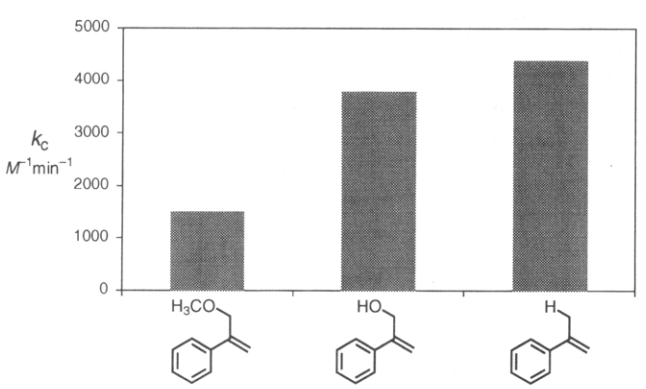


Figure 7. Saturation rates with $(DHQD)_2PHAL$ in *t*-BuOH at 25 °C.

2.5.4. Summary

The data presented in this section reveal that an allylic hydroxyl group, or other allylic functional groups with acidic hydrogens, can exert an influence on the regio- and stereochemistry of dihydroxylation as well as enhance the reaction rate in comparison to other functional groups of similar electronic demand. Although the magnitude of the effect may be small when compared to effects seen in other functional group directed reactions, there are instances, as in the asymmetric dihydroxylation of *cis*-allylic alcohols, where the effect is of sufficient magnitude to be synthetically useful.

3. Synthetic Applications for 1,2-Diols

The chemistry of carbohydrates and polyols is as old as the field of organic chemistry. Consequently there is a wealth of chemical knowledge on this class of compounds and many transformations which were originally developed for carbohydrates are also applicable to diols derived from the AD of olefins. Polyols play an important role not only in biological systems, they have also found frequent use as starting materials for the enantiospecific synthesis of natural products and drugs[150] ("The Chiron Approach"). However, the AD reaction offers some important advantages over the use of sugars as chiral building blocks in enantioselective synthesis. First, the AD, catalytic in both OsO_4 and the chiral auxiliary, provides either enantiomer of the product with almost equal efficiency. Second, the AD is not limited to a certain number of standard starting materials (e.g. carbohydrates, tartrates, etc.), since virtually any olefin can be regarded as a substrate. Thus, the synthetic strategy is left almost entirely to the imagination of the chemist and not restricted by the availability of certain starting materials. Third, most enantiospecific syntheses from the chiral pool require an elaborate protecting group strategy. This does not necessarily apply to syntheses involving the AD, since the diol can be carried through the synthesis "masked" as an olefin, ready to be released at any point.

This section is intended to concentrate specifically on chemical transformations of diols prepared by the AD reaction and their application in the synthesis of natural products and biologically active compounds as well as chiral building blocks and auxiliaries. In most instances, diols are not the final products and their synthetic elaboration requires some further transformations. Commonly, these involve the selective manipulation of one of the two OH groups either by protecting it or by converting it into a leaving group, suitable for displacement by a nucleophile.

In the first section of this chapter, some recent methods for the differentiation and manipulation of the hydroxyl groups of a diol are reviewed. The second section describes the preparation of chiral

building blocks using the AD reaction. The AD has also been used for the preparation of chiral auxiliaries for other asymmetric transformations. These applications are discussed in the third section.

3.1. Methods for the Differentiation of the Hydroxyl Groups of a Diol

3.1.1. Selective Arenesulfonylation

Selective manipulations of diols may be based upon steric effects, which render one hydroxyl group more reactive than the other.[151,152] Additionally, electronic effects, which manifest themselves in different acidities of the OH groups, influence the reactivity.[153,154]

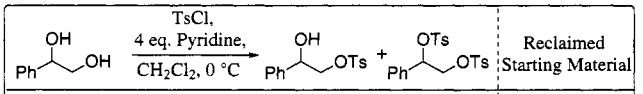
The primary OH group of a diol derived from a terminal olefin can be readily converted into a sulfonate leaving group by reaction with arenesulfonyl chlorides in the presence of a tertiary amine. Although *p*-toluenesulfonates are used in most cases due to their inexpensiveness, better results in the subsequent nucleophilic displacement step are often obtained with *p*-nitrobenzenesulfonates (nosylates) due to their considerably higher reactivity as a leaving group.[155] The formation of the bis-sulfonate as a side product can be minimized by using only a small excess of sulfonylating reagent (Table 37). However, lowering the reagent amount will also result in an increased amount of the starting material left over and commonly one has to settle for a compromise.

The regioselectivity of the sulfonylation can be enhanced further by using sterically more encumbered reagents. Thus, 2,4,6-trimethylbenzenesulfonyl chloride (**64**) or the corresponding 2,4,6-triisopropyl derivative **65** are the reagents of choice for diols with very small steric differences (Table 38).[157]

Frequently, hydroxy sulfonates are only intermediates on the way to chiral epoxides and the sequence olefin → diol → monosulfonate → epoxide has been applied in a number of natural product and drug syntheses.[158] However, for this strategy to be successful it is important to realize a high regioselectivity in the initial sulfonylation step, since the cyclization of the regioisomeric sulfonates **66** and **67** leads to opposite enantiomers (Scheme 28) and consequently a loss in optical purity.

An example for the usefulness of the olefin → diol → monosulfonate → epoxide reaction sequence is shown in Scheme 29. Glyceraldehyde synthon **10** can be obtained in good enantiomeric excess by the

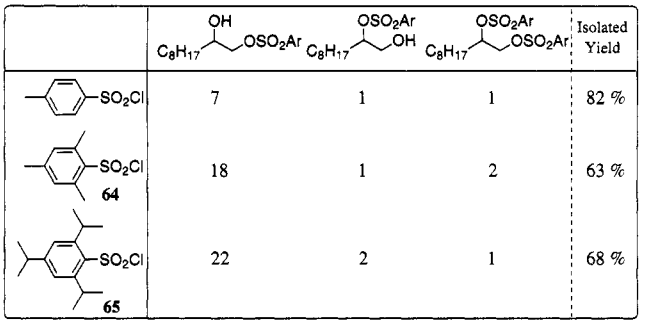
Table 37. The Formation of Mono- and Bistosylates in the Reaction of Phenylethylene Glycol with Varying Amounts of *p*-Toluenesulfonyl Chloride[156,†]



			Reclaimed Starting Material
1.3 eq. TsCl	5.4	1	0 %
1.0 eq. TsCl	18	1	23 %
0.5 eq. TsCl	> 49	1	40 %

† The initial diol concentration was 0.4 M. The product ratios were determined by ^{1}H NMR analysis of the crude product.

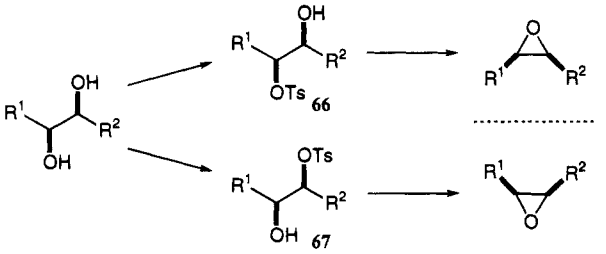
Table 38. Selective Arenesulfonylation with Various Arenesulfonyl Chlorides[156,†]



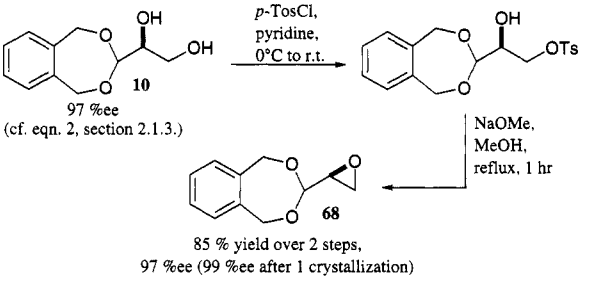
				Isolated Yield
SO2Cl	7	1	1	82 %
SO2Cl (64)	18	1	2	63 %
SO2Cl (65)	22	2	1	68 %

† The reactions were performed in CH_2Cl_2 at 0 °C in the presence of 2 equiv of pyridine and 1.1 equiv of the sulfonyl chloride. The initial diol concentration was between 0.35 and 0.4 M. The ratios were determined by weighing the isolated products.

Scheme 28. Potential Racemization during the Formation of Epoxides via Hydroxytosylates



Scheme 29. Synthesis of Glycidaldehyde Building Block 68[44]

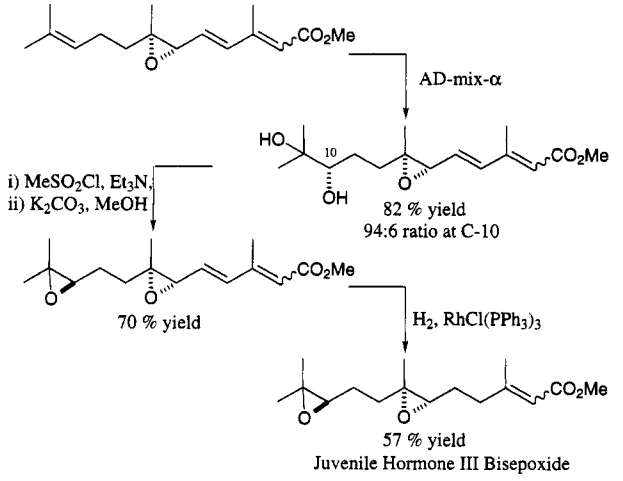


dihydroxylation of the corresponding acrolein acetal (eq 2) and one recrystallization from benzene.[44,159] Monotosylation and treatment with sodium methoxide gives the glycidaldehyde building block **68**. This compound has several advantages over other glycidaldehyde synthons,[160] since it is readily available in enantiomerically pure form, crystalline and stable at ambient temperature. Additionally, the deprotection of the aldehyde function can be carried out under neutral conditions by catalytic hydrogenolysis.

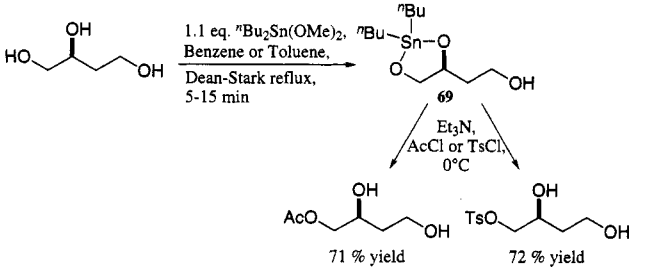
Tertiary hydroxyl groups can be readily differentiated from primary or secondary hydroxyl groups due to the former's low nucleophilicity. Mesyl chloride is the reagent of choice in such cases as it is relatively reactive and inexpensive. An AD, mesylation, and cyclization sequence represents the key steps in recent syntheses of juvenile hormone III bisepoxide[161] (Scheme 30) and also 2,3-oxidosqualene.[124]

High selectivities can also be obtained by way of stannylene acetals of diols (Scheme 31).[162] Thus, **69** preferentially reacted at the least hindered oxygen center without affecting the primary OH group at the

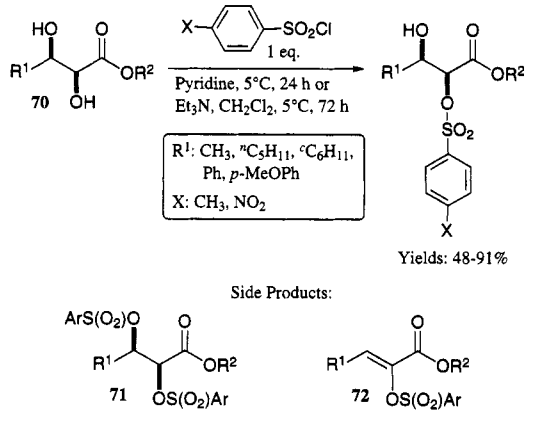
Scheme 30. Synthesis of Juvenile III Bisepoxide by an AD–Mesylation–Cyclization Sequence[161]



Scheme 31. Highly Selective Acetylation and Tosylation of Polyols via Stannylene Acetals[163]



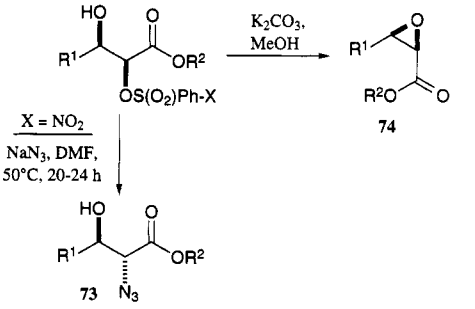
Scheme 32. Regioselective Arenesulfonylation of Dihydroxy Esters[153]



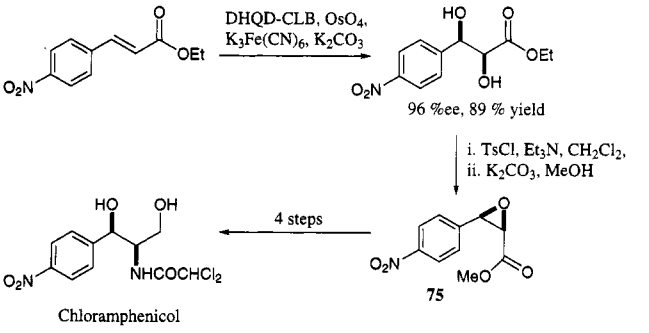
other terminus.[163] Peracylation, a common problem in the reactions of polyhydroxylated compounds, was almost completely eliminated. Recently, Ley *et al.* published a simplified "one-pot" procedure, which allows the preparation of the tin acetal by reaction of the diol with dibutyltin dimethoxide in benzene under Dean–Stark conditions and its subsequent benzylation, acylation, or sulfonylation in the same solvent.[163]

In certain cases modest differences in acidity can be the origin of selectivity. Thus, α,β-dihydroxy esters **70** are selectively sulfonylated at the α-OH group with either tosyl chloride or nosyl chloride[153,154] (Scheme 32). The formation of α,β-bissulfonates **71** and α-(sulfonyloxy)-α,β-unsaturated esters **72** as side products (the latter arising by elimination of the former) can be minimized by performing the reaction

Scheme 33. Some Synthetic Transformations with α-(Sulfonyloxy)-β-hydroxy Esters[153]



Scheme 34. Asymmetric Synthesis of Chloramphenicol[164]



at a low concentration, typically between 0.2–0.3 M in diol ester.

In most cases *p*-nitrobenzenesulfonyl chloride gives superior yields (57–91%) to tosyl chloride[153] (48–76%), and it also leads to more reactive products.[155] Thus, the better leaving group character of the nosyl group has been utilized in the preparation of α-azido carboxylic acids **73** (Scheme 33), precursors for α-amino acids.[153,155e,f] Also glycidic esters **74** are accessible by this method.

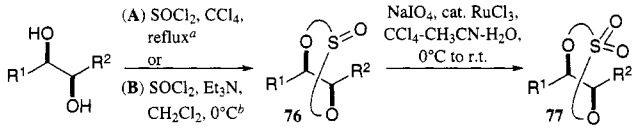
Rao *et al.* prepared glycidic ester **75** by this method and converted it into the broad-spectrum antibiotic chloramphenicol[164] (Scheme 34).

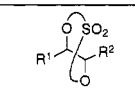
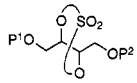
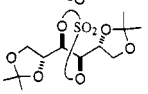
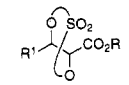
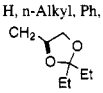
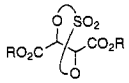
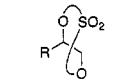
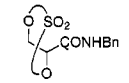
3.1.2. Cyclic Sulfites and Sulfates as Epoxide-like Synthons[165,166]

Optically active epoxides play an important role in synthetic organic chemistry[158] as they constitute electrophilic, chiral building blocks with an "unnatural" 1,2-functional group relationship.[167] Additionally, elimination processes in small rings can be stereoelectronically disfavored in certain situations,[168] thereby rendering epoxides more useful than their acyclic equivalents. Many of these beneficial properties of epoxides are shared by cyclic sulfates and sulfites, with the sometimes useful distinction that cyclic sulfates are more reactive than oxiranes.[165] Consequently, these compounds can be regarded as synthetic equivalents of epoxides and a number of useful synthetic examples have appeared in the literature over the years.[166]

3.1.2.1. Preparation of Cyclic Sulfites and Sulfates. Whereas the reaction of diols with $SOCl_2$ in the presence of an amine base gives the cyclic *sulfites* **76** directly in good yields,[165] the analogous reaction with SO_2Cl_2 usually results in low yields of the corresponding *sulfates* **77**. However, cyclic sul-

Table 39. Preparation of Cyclic Sulfites 76 and Sulfates 77 from Diols†



Entry	Product	Method	Yield
1[a,c]	 R¹, R² = n-Alkyl, Ph	A	~ 90 %
2[d]	 P¹= CH_2Ph, P²= $SiMe_2{}^tBu$		93 %
3[b]		B	94 %
4[a,b]	 R¹ = H, n-Alkyl, Ph, c-C_6H_{11}, 	A B	88-97 % 95 %
5[a]	 R = Me, Et, ^iPr	A	63 - 93 %
6[a,b,e]	 R = n-Alkyl, c-C_6H_{11}, CH_2Ph $CH_2OSiMe_2{}^tBu$	A B	> 90 % 87 %
7[a]		A	64 %

† Procedure (A) is normally used in the "one-pot" preparation of cyclic sulfates via the sulfites,[165] while procedure (B) is more suitable for acid-sensitive substrates or when sulfites are the desired products.[169] [a] See ref 165. [b] See ref 169. [c] See ref 170. [d] See ref 171. [e] See ref 172.

fates are readily available by the oxidation of cyclic sulfites (Table 39).

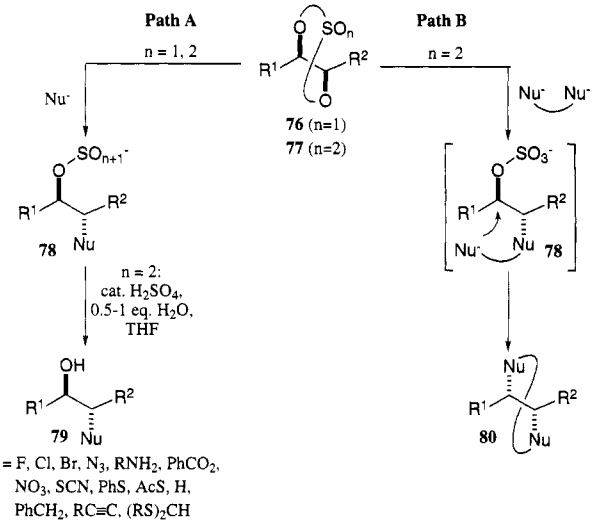
Originally, stoichiometric quantities of reagents like potassium permanganate[173] and RuO_4[174] were used for the oxidation of cyclic sulfites. However, better yields and cost considerations make the catalytic "one-pot" process, developed by Gao and Sharpless,[165] more economical (Table 39). This new procedure employs $NaIO_4$ as the stoichiometric reoxidant for RuO_4, of which catalytic quantities are sufficient. Thus, a solution of the diol in CCl_4 is refluxed with $SOCl_2$ to prepare the corresponding sulfite **76** (Table 39, conditions A). Although this reaction is fast even at room temperature, refluxing is desired to expel the HCl that is formed in the reaction, since it would cause side reactions in the subsequent oxidation step. For certain unreactive diols it may be necessary to add a small amount of DMF to promote the reaction with $SOCl_2$.[170] The crude cyclic sulfite is then oxidized in the same reaction vessel, following addition of acetonitrile and water as additional solvent components, in the presence of a slight excess of $NaIO_4$ and catalytic amounts of $RuCl_3{\cdot}3H_2O$ (ca. 0.1−1 mol %). Aqueous workup and purification by filtration through a small pad of silica gel gives the pure cyclic sulfate **77** in normally excellent yields.

Slight modifications of the above procedure are required for acid-sensitive substrates. In these cases the reaction with $SOCl_2$ should be performed in the presence of a tertiary amine base to neutralize the HCl formed[169] (Table 39, conditions B). The crude cyclic sulfite (isolated from the reaction mixture by an aqueous workup, since tertiary amines inhibit the oxidation catalysis) is subjected to oxidation as described above.

Table 39 demonstrates the broad scope of the method and even acid-sensitive functionality is tolerated, provided a proton scavenger is present during the formation of the sulfite.[169]

3.1.2.2. The Chemistry of Cyclic Sulfites and Sulfates.[166] Analogous to epoxides, cyclic sulfates and sulfites can be opened by attack of a nucleophile at either carbon center (Scheme 35). The product,

Scheme 35. Some Representative Reactions of Cyclic Sulfites 76 and Sulfates 77[165,166]



however, is not an alcohol, but a sulfate monoester (**78**, $n = 2$) in the case of cyclic sulfates as substrates. These sulfate monoesters allow some interesting transformations, which make the chemistry of cyclic sulfates more versatile than that of epoxides.

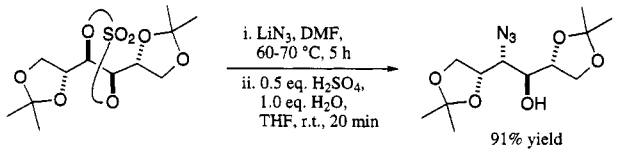
Naturally, hydrolysis of the sulfate monoesters (Scheme 35, path A) leads to hydroxyl compounds **79** that parallel those obtained from oxiranes.[165] However, the sulfate in **78** ($n = 2$) can also function as a leaving group, leading to disubstitution products **80**[165] (Scheme 35, path B).

a. Monosubstitution of Cyclic Sulfites and Sulfates (Path A). As shown in Scheme 35 cyclic sulfites and especially sulfates react with a variety of nucleophiles and a few examples are Cl^- (LiCl),[177] Br^- (NH_4Br),[177] F^- ($Et_4NF{\cdot}2H_2O$, n-Bu_4NF),[165,175] N_3^- (LiN_3, NaN_3),[165,169,172,175,176,178] RNH_2,[172,180] $PhCO_2^-$ ($PhCO_2NH_4$),[165,169,175] ROH (intramolecular, *vide infra*),[179] NO_3^- (Bu_4NNO_3),[165] SCN^- (NH_4SCN),[165,177] PhS^- (PhSNa),[183] AcS^-,[184] H^- ($NaBH_3CN$, $NaBH_4$),[165] $PhCH_2^-$ ($PhCH_2MgBr$, Li_2CuCl_4),[165] $RC{\equiv}C^-$ ($RC{\equiv}CSiMe_3$ + MeLi),[181] $(RS)_2CH^-$ (with 1,4-cyclic sulfates).[182]

The hydrolysis of sulfate monoesters **78** ($n = 2$) to β-hydroxyl compounds **79** is carried out by treatment with a catalytic amount of sulfuric acid and 0.5−1.0 equiv of water in THF.[169] These conditions are sufficiently mild to tolerate even acid-sensitive functionalities, such as acetonide and silyloxy groups (Scheme 36).

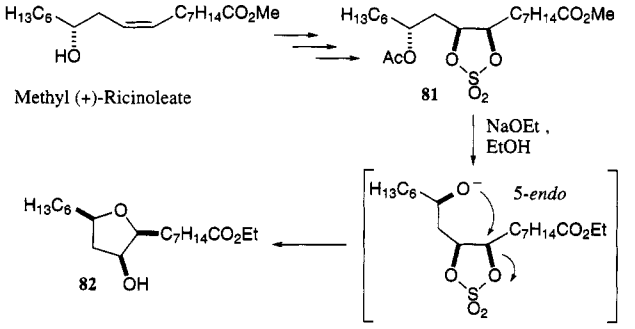
It is well known that nucleophilic 5-*endo* cyclizations of hydroxy epoxides are disfavored for steric and

Scheme 36. Nucleophilic Opening and Hydrolysis in the Presence of Acid-Sensitive Functionality[169]



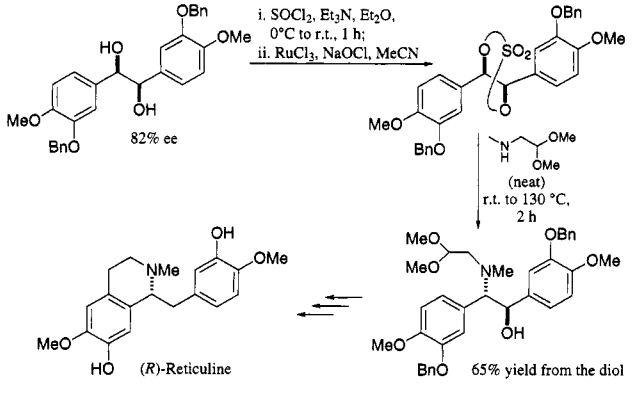
stereoelectronic reasons.[185] Interestingly, this does not apply for hydroxy cyclic sulfates, since the attacking oxygen, carbon, and leaving oxygen can be collinear without imposing too much strain on the system. Thus, 5-*endo* opening of the hydroxy cyclic sulfate, formed *in situ* by saponification of the acetate **81**, leads to optically active tetrahydrofuran **82** with inversion of configuration at the reacting center[179] (Scheme 37).

Scheme 37. Formation of Tetrahydrofurans by 5-*endo* Opening of Cyclic Sulfates[179]



Nucleophilic opening of cyclic sulfates by amines provides β-hydroxy amines in analogy to epoxide opening. This transformation has been employed in a recent synthesis of the morphine precursor (*R*)-reticuline[180] (Scheme 38).

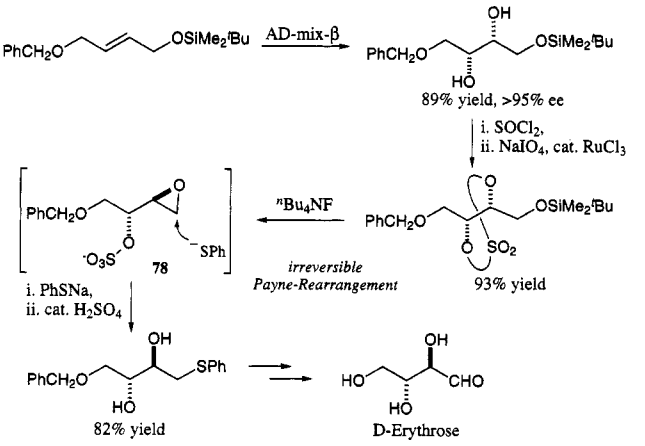
Scheme 38. Asymmetric Synthesis of (*R*)-Reticuline[180]



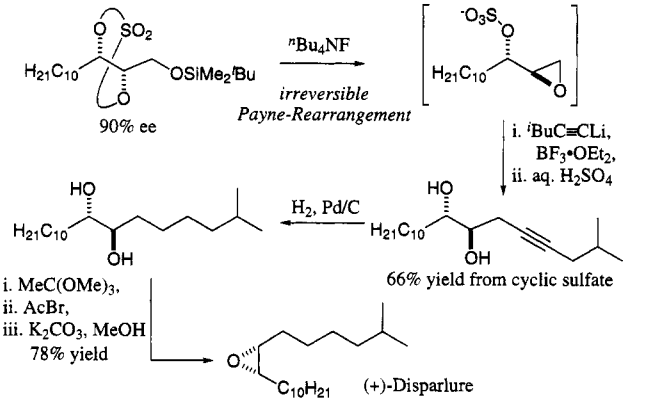
The sulfate group in intermediate **78** ($n = 2$) (see Scheme 35) formed as the initial product of the nucleophilic opening of a cyclic sulfate may function as an *in situ* protecting group for the β-hydroxyl substituent. Thus, the nucleophilicity of this masked OH group is completely eliminated, a feature that causes Payne-type rearrangements to be irreversible[171,186] (Scheme 39). This behavior was utilized in a recent synthesis of erythrose.[171]

An irreversible Payne rearrangement was also the key step in a very efficient asymmetric synthesis of

Scheme 39. Synthesis of D-Erythrose via an Irreversible Payne Rearrangement[171]



Scheme 40. Asymmetric Synthesis of (+)-Disparlure Employing an Irreversible Payne Rearrangement[186]



(+)-disparlure, the sex attractant pheromone of the female gypsy moth[186] (Scheme 40).

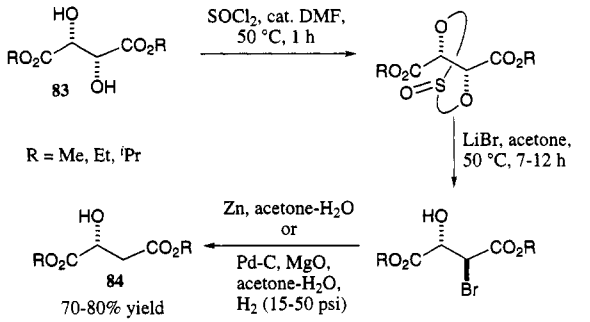
Cyclic sulfites **76** react in a similar fashion as the sulfates **77**,[166,176-178] and an additional hydrolysis step of the initial product is not necessary. However, in contrast to the S(VI) esters, cyclic sulfites are *kinetically labile at the sulfur center* which may lead to unwanted side reactions, e.g. hydrolysis. Additionally, cyclic sulfites are much less reactive at the carbon centers than cyclic sulfates and they tend to give good results only with good nucleophiles such as bromide, thiocyanate, and azide in polar aprotic solvents.[177,178]

The cyclic sulfite chemistry provides ready access to enantiomerically pure β-lactams[178] and a practical synthesis of the unnatural D-enantiomer of malic acid (**84**), starting from L-tartaric acid (**83**), has appeared recently[177] (Scheme 41).

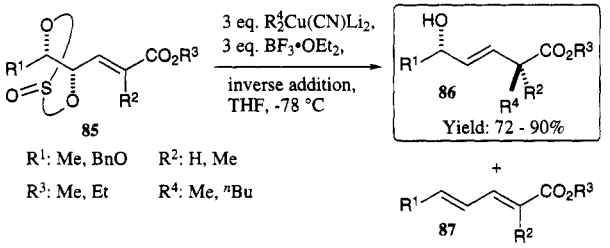
In analogy to the chemistry of epoxides, cyclic sulfites **85** derived from γ,δ-dihydroxy α,β-enoates can be opened in S_N2' fashion with organocuprate reagents,[187] leading to allylic alcohols **86** (Scheme 42). The 1,3-chirality transfer is almost complete and reductive elimination, giving rise to dienoates **87** as side products, can be suppressed by adding the cuprate reagent to the substrate (inverse addition).

This methodology has been employed in the synthesis of the carpenter bee sex pheromone (**88**) (Scheme 43).

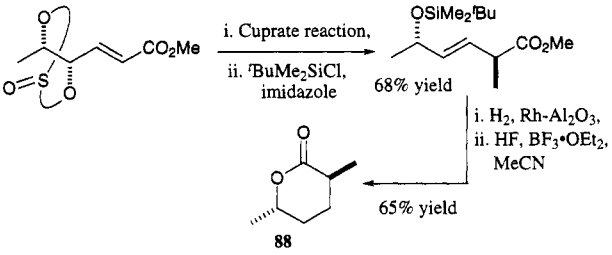
Scheme 41. Preparation of D-Malate Esters from L-Tartrate Esters[177]



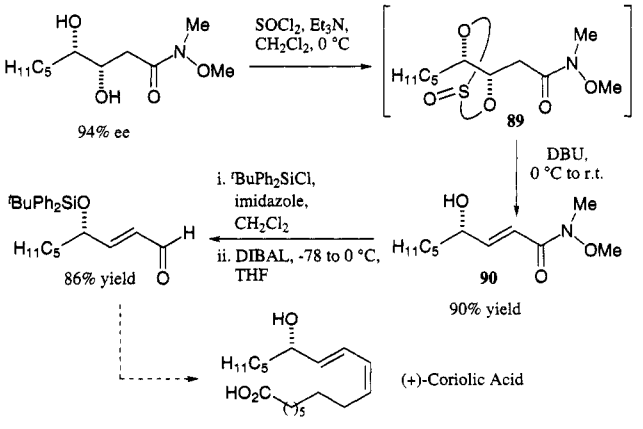
Scheme 42. Reaction of Cyclic Sulfites with Organocopper Reagents[187]



Scheme 43. Asymmetric Synthesis of the Carpenter Bee Pheromone (88) by Diastereoselective S_N2' Opening of a Cyclic Sulfate[187]



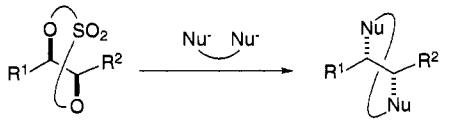
Scheme 44. Formal Synthesis of (+)-Coriolic Acid[188]



As with epoxides, β-elimination provides allylic alcohols and the reaction becomes quite facile in the presence of an activating carbonyl group. Thus, a recent formal synthesis of (+)-coriolic acid makes use of the base-induced elimination of cyclic sulfite **89**, to produce allylic alcohol **90** as a synthetic intermediate[188] (Scheme 44).

b. Disubstitution of Cyclic Sulfates (Scheme 35, Path B). Unlike the β-hydroxyl group, generated in

Table 40. Double Displacement of Cyclic Sulfates



Entry	Bis-Nucleophile and conditions	Product
1[a]	DME, reflux, then hydrolysis of the resulting imidazoline	
2[b]		
3[c]	$K_2CS_3•H_2O$, 18-crown-6, THF	
4[d]	NaH, DME	

[a] See ref 170. [b] See ref 184. [c] See ref 189. [d] See ref 165.

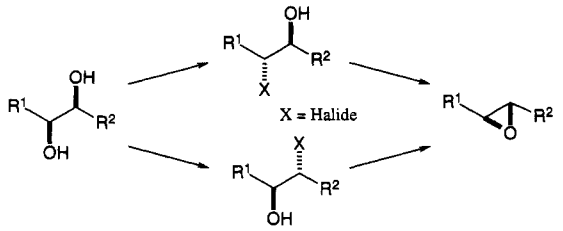
nucleophilic openings of epoxides, the β-sulfate in **78** still is a leaving group that can be displaced by a nucleophile in a second step. This allows an overall substitution of *both* OH groups of diols and considerably enhances their synthetic usefulness. However, since a SO_4^{2-} dianion is a much worse leaving group than a $ROSO_3^-$ anion (cf. the pK_a values of H_2SO_4, $pK_a \ll 0$, and $HOSO_3^-$, $pK_a = +1.92$) the second displacement is much less facile than the first and has so far only succeeded in an intramolecular fashion. A variety of optically active products are available by this methodology as shown in Table 40.

3.1.3. Conversion of Diols into Halohydrin Esters and Epoxides

Despite the synthetic versatility of epoxides, there are very few methods available for the direct enantioselective epoxidation of olefins.[4,6,190] The titanium tartrate catalyzed asymmetric epoxidation (AE) is restricted to allylic and homoallylic alcohols only,[6] while chiral manganese salen complexes give good results mainly with *cis*-olefins.[4,190f-l] Other methods use *stoichiometric* amounts of chiral reagents and/or suffer from low enantioselectivities.[190] Thus, there is no general epoxidation process available yet that parallels the osmium-catalyzed asymmetric dihydroxylation in scope.

Consequently, methods for the stereospecific conversion of diols into epoxides are of immense interest. However, cyclodehydration sequences via monotosylates may result in partial racemization, since the overall process proceeds with inversion of configuration at only one carbon center (cf. Scheme 28). These problems are avoided in epoxidation procedures that involve two inversions and, therefore, net retention of configuration (Scheme 45). Such reactions may proceed via halohydrin intermediates which are formed from the diol with inversion of configuration. Since the subsequent base-mediated cyclization leads to a second inversion, the epoxide is formed with

Scheme 45. Stereochemical Outcome of the Formation of Epoxides via Halohydrins[50]



overall retention.[50] The advantage of this strategy is that the regioselectivity of the halohydrin formation is inconsequential, since both regioisomers produce the same epoxide upon cyclization (Scheme 45).

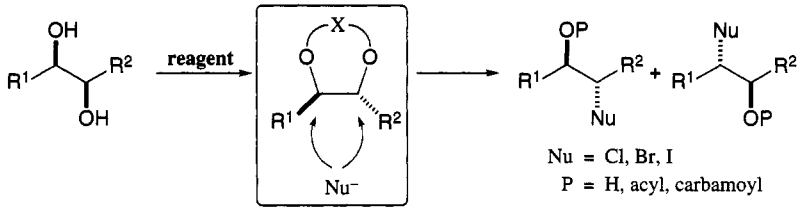
Most commonly, a diol is activated toward nucleophilic attack via a reactive, *cyclic* intermediate. This has the advantage that bis-functionalization of the diol cannot occur. A variety of methods employ this strategy and some of them are shown in Table 41.

The majority of these processes utilize the high reactivity of 1,3-dioxolan-2-ylium cations **91** toward nucleophiles. These reactive species can either be formed *in situ* from the diol and a reagent such as HBr in acetic acid[153,193] (entry c), α-acetoxyisobutyryl bromide[194] (entry d), acetylsalicyloyl bromide[195] (entry e), *N*-(dichloromethylene)-*N*,*N*-dimethylammonium chloride[201] (Viehe's salt, entry i), or stepwise via stable, cyclic intermediates such as orthoesters[50,192,196-199] (entries b, f, and g), benzylidene acetals[200] (entry h), thiocarbonates[202] (entry j), or 2-(*N*,*N*-dimethylamino)-1,3-dioxolanes[191] (entry a). Methods involving cyclic acyloxonium cations **93**, formed by reaction of a diol with HBr/acetic acid (Scheme 46, path A) or via cyclic orthoesters **92** (path B), have frequently been used in conjunction with the AD reaction, since they require inexpensive reagents.

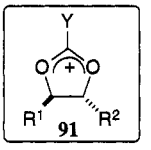
3.1.3.1. Preparation of Bromohydrin Acetates from Diols Using HBr–Acetic Acid (Scheme 46, Path A). The reaction of a diol with 30% by weight HBr in acetic acid is stereospecific and yields acetoxy bromides with inversion at the halide-bearing center.[153,193] Thus, (*S*)-(+)-propylene glycol reacted with HBr/HOAc to give a 94:6 mixture of regioisomeric bromo acetates (Scheme 47), which upon treatment with base afforded (*S*)-(−)-propene oxide in good overall yield.[193]

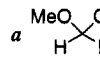
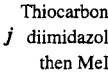
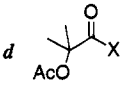
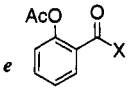
In the case of diol esters **94** the yields range from 72 to 96% and the halide is normally introduced in the α-position to the carbonyl group, leading to **95**[153] (Scheme 48, path A). However, a phenyl group (i.e. **94**, R^1 = Ph) exerts a stronger directing influence than a carbonyl group, resulting in α-acetoxy-β-bromo-β-phenyl esters (**96**, R^1 = Ph) (path B).

Table 41. Reagents for the Manipulation of 1,2-Diols via Cyclic Intermediates



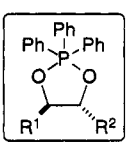
Reagents which lead to 1,3-dioxolan-2-ylium cations as intermediates:



Y =	H	CH_3	Ph	Me_2N	MeS
Reagents	*a* 	*c* HBr/HOAc	*g* $PhC(OMe)_3$, AcBr	*i* 	*j* Thiocarbonyl diimidazole, then MeI
	b $HC(OEt)_3$, then PCl_5	*d* 	*h* PhCHO, NBS		
		e 			
		f $MeC(OMe)_3$, Me_3SiX, or AcX			

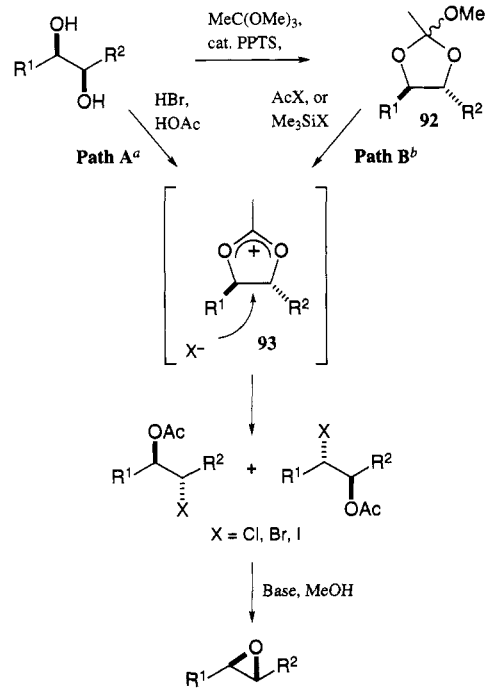
Reagents which give dioxaphospholane intermediates:[k]

$PPh_3/(PhCO_2)_2$, or $PPh_3/RO_2C\text{-}N{=}N\text{-}CO_2R$, or $PPh_3/CCl_4/K_2CO_3$, or $Ph_3P(OR)_2$



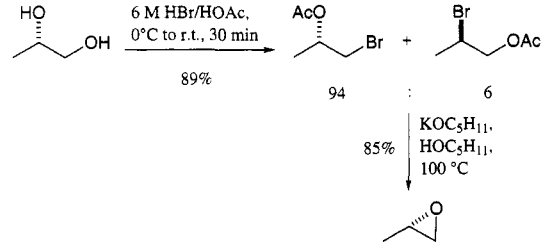
[a] See ref 191. [b] See ref 192. [c] See refs 153 and 193. [d] See ref 194. [e] See ref 195. [f] See refs 50 and 196–198. [g] See ref 199. [h] See ref 200. [i] See ref 201. [j] See ref 202. [k] See refs 203–205.

Scheme 46. Formation of Acetoxy Halides and Epoxides via Cyclic Acetoxonium Ions

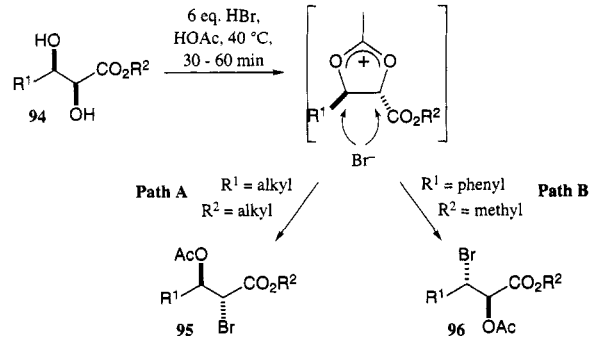


[a] See refs 153 and 193. [b] See refs 50 and 196–198.

Scheme 47. Preparation of (*S*)-(−)-1,2-Epoxypropane[193]



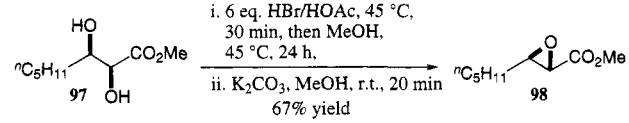
Scheme 48. Regioselective Formation of Acetoxy Bromides from Diol Esters[153]



The α-bromo-β-hydroxy ester derived from **97** gave glycidic ester **98** upon treatment with base[153] (K_2CO_3 in MeOH) (Scheme 49).

3.1.3.2. Preparation of Halohydrin Esters and Epoxides from Diols via Cyclic Orthoesters (Scheme 46, Path B). Naturally, the HBr/acetic acid procedure is only applicable to acid-stable compounds, and in certain cases partial racemization can occur, due to opening of the intermediate 1,3-dioxolan-2-ylium ion with formation of an acyclic carbocation. Thus, enantiopure (*R*)-(−)-1-phenylethane-1,2-diol gave (*R*)-(+)-styrene oxide in only 88% ee

Scheme 49. Preparation of Glycidic Esters from α,β-Dihydroxy Esters[153,a]



[a] Note that the intermediate bromohydrin acetate is saponified *in situ* by addition of MeOH to prevent β-elimination.

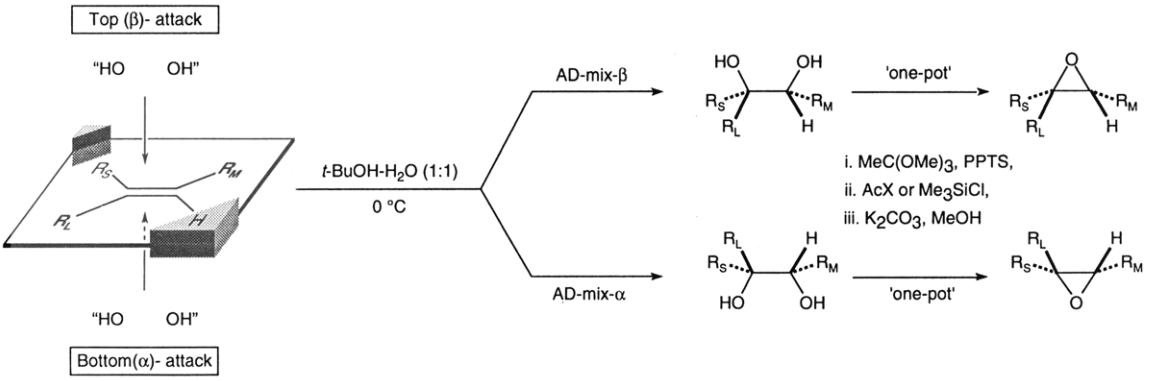
upon treatment with HBr/acetic acid and subsequent cyclization.[193]

In many cases it is advisable, therefore, to use more neutral and milder conditions for the preparation of acyloxy halides and epoxides. In 1958, Baganz and Domaschke reported that cyclic orthoformates yield halohydrin formates upon treatment with neat acetyl chloride or bromide.[196] Although their method required vigorous reaction conditions, later work by other groups showed that the same transformation could be achieved under milder conditions. Reagents, such as trityl chloride,[197] Me_3SiCl[198] or PCl_5,[192] have also been employed in place of acetyl halides to effect the same type of transformation.

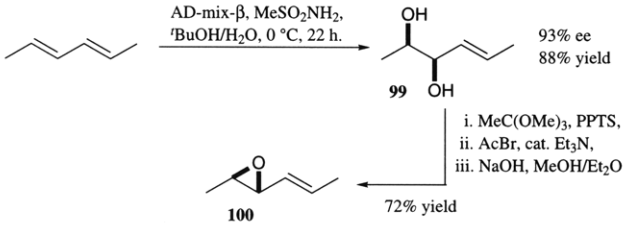
In a recent study, the scope and limitations of the reaction of cyclic orthoacetates, derived from chiral diols, with acetyl halides or Me_3SiCl have been investigated.[50] It was found that the formation of the cyclic orthoester intermediate, its opening, and the subsequent base-mediated cyclization to the epoxide can be carried out in one reaction vessel. This has led to the development of a convenient "one-pot" procedure for the conversion of diols into acetoxy halides or epoxides. Thus, the asymmetric epoxidation of olefins can now be realized in only two steps (Scheme 50).

Depending on the type of substrate, two different methods for the formation of acetoxy halides have been developed. In most cases, a solution of the diol in CH_2Cl_2 is treated at room temperature with a slight excess of trimethyl orthoacetate in the presence of a catalytic amount of a mild acid (ca. 1 mol % of pyridinium *p*-toluenesulfonate or *p*-toluenesulfonic acid) to effect transesterification. In rare cases warming to ca. 40 °C may be necessary to achieve complete reaction. The solution is then evaporated to remove most of the methanol formed during the reaction (a small amount of MeOH is actually beneficial for the next step), and the residue is taken up in a solvent, usually CH_2Cl_2 (MeCN or C_6H_6 have also been used). The acetoxy halide is formed upon addition of Me_3SiCl, acetyl chloride, or acetyl bromide (the latter reagent usually gives the best results). While this reaction is normally performed at room temperature, reduced temperatures (−20 to 0 °C) may be advisable for very sensitive substrates or if high regioselectivities in the nucleophilic opening of the acetoxonium ion are required. The reaction mixture may be buffered with up to 0.1 equivalents of triethylamine so that even acid sensitive substrates give good results (Table 42, entries 3 and 5). After completion of the reaction, the volatiles are evaporated to yield virtually pure acetoxy halides. These are dissolved in MeOH and treated with base [K_2CO_3 or Amberlite IRA 410 (OH^-)] to effect cyclization to the corresponding epoxides, which are typi-

Scheme 50. Asymmetric Epoxidation of Olefins in Two Steps[50]



Scheme 51. Formation of Hexadiene Oxide[206]



cally isolated in ca. 90% yield. For very volatile epoxides, e.g. **100**, the cyclization may be carried out with solid NaOH in diethyl ether in the presence of 1.5 equiv of MeOH[206] (Scheme 51).

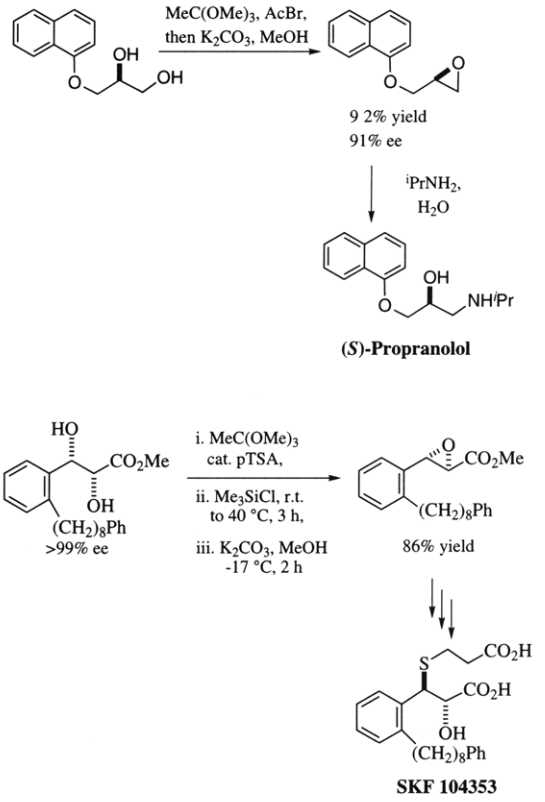
The other procedure for formation of epoxides is even easier to perform and best suited for activated diols, i.e. benzylic diols[50] (Table 42, entries 1 and 2). In these cases acetoxy halides are formed directly by adding trimethyl orthoacetate and Me_3SiCl to a solution of the diol in CH_2Cl_2. The reaction is worked up by evaporating the volatiles to give almost pure chlorohydrin acetates. These may be cyclized as described above.

As illustrated by the examples in Table 42, the reaction is of broad scope and even acid-sensitive substrates give good results. It should be pointed out that no racemization was observed even with (+)-(*S*)-1-phenylethane-1,2-diol (entry 1), in contrast to the HBr−acetic acid reaction (*vide supra*). The special features of the procedure can be summarized as follows.[50] Depending on the choice of the reagent, chlorohydrins (with Me_3SiCl or AcCl), bromohydrins (AcBr), and even iodohydrins (AcCl−NaI in MeCN) may be prepared. The halide is introduced in a highly regioselective fashion, i.e. at the least hindered position (entry 6), and/or away from an inductively electron-withdrawing functional group (entries 3, 4, and 7), or in the benzylic position (entries 1, 2, and 8). Only a few limitations are known. Thus, sterically crowded diols derived from trisubstituted olefins normally give unsatisfactory results. However, these diols are excellent substrates for the formation of epoxides via mesylates (*vide supra*). Partial racemization may occur with electronically activated diols, e.g. 1-(*p*-methoxyphenyl)ethane-1,2-diol.[207]

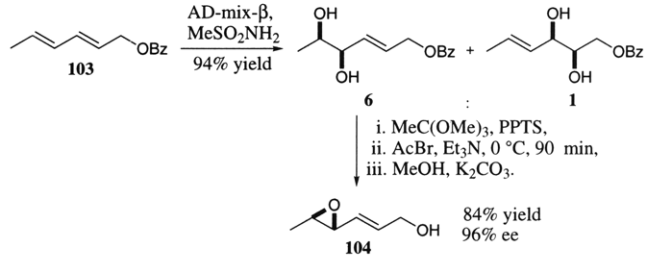
The asymmetric dihydroxylation−epoxidation sequence has found recent application in the syntheses of the β-blocker (*S*)-propranolol[41a] and the leukotriene antagonist SKF 104353[50] (Scheme 52).

The regioselective AD and epoxidation of dienes gives access to vinyl epoxides,[206,208] which are interesting chiral building blocks (Scheme 53, see also Scheme 51).

Scheme 52. Preparation of (*S*)-Propranolol[41a] and SKF 104353[50] by Way of Chiral Epoxides

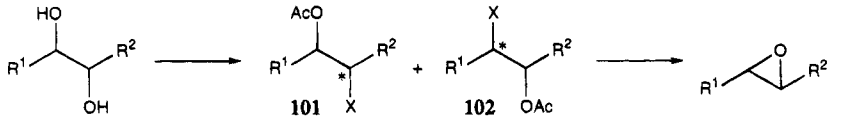


Scheme 53. Regioselective Dihydroxylation of 2,4-Hexadienyl Benzoate (103)[117] and Conversion into the Corresponding Vinyl Epoxide 104[208]

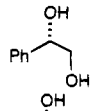
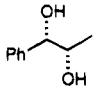
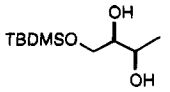
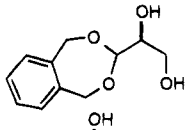
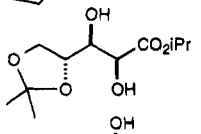
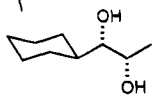
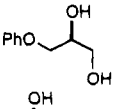
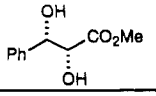


Also acyloxy halides are useful synthetic intermediates as demonstrated by a recent synthesis of the C13 phenylisoserine side chain of taxol[199,209] (Scheme 54). This new synthesis may be the most practical for the large-scale preparation of phenylisoserine derivatives, since it is free of chromatographic sepa-

Table 42. One-Pot Synthesis of Epoxides[50,†]

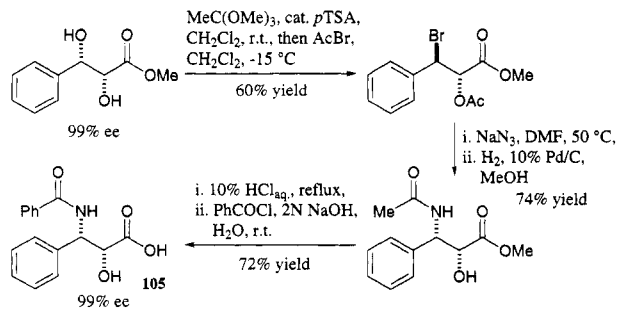


* = inverted configuration

Entry	diol	% ee[a]	Ratio of acetoxy halides **101 : 102**[b] (X)	% Yield of epoxide[c]
1		97	< 4 : 96 (Cl)	84[d]
2		97	0 : 100 (Cl)	92
3		59	85 : 15 (Br)	83[e,f]
4		96	100 : 0 (Br)	98[d,g]
5		100[h]	100 : 0 (Br)	(77)[e,i]
6		97[j]	86 : 14 (Cl) 88 : 12 (Br) 87 : 13 (I)	89 91 (50)[k]
7		89	100 : 0 (Br)	97[d]
8		99	14 : 86 (Br)	82[l]

† For the diols in entries 1 and 2 the reactions were performed according to the procedure for activated diols (i.e. direct mixing of the diol, $MeC(OMe)_3$, and Me_3SiCl). All other diols were converted into epoxides using the three step procedure for unactivated diols. [a] The enantiomeric excesses were determined by HPLC or GC analysis of the free diols or the bis-MTPA esters. [b] Determined by integration of the ^1H NMR spectra of the crude products. [c] Isolated yields. [d] The enantiomeric excess of the epoxide was found to be identical within the experimental error to that of the diol by HPLC analysis. [e] The preparation of the acetoxy bromides was performed at 0 °C in the presence of 10 mol % of Et_3N. [f] Methanolysis of the acetoxy bromide was performed with Amberlite IRA 410 (OH^-) as base, since K_2CO_3 gave inferior yields due to partial cleavage of the silyl ether. [g] The preparation of the acetoxy bromide was performed in the presence of 2 mol % of Et_3N. [h] The diol was prepared from D-Glyceraldehyde acetonide. [i] Yield of the acetoxy bromide. This compound decomposed on treatment with K_2CO_3, presumably due to β-elimination of acetate. [j] Prepared by hydrogenation of the diol in entry 2. [k] Yield of acetoxy iodide. [l] Treatment of the pure acetoxy bromide of type **102** with K_2CO_3 in methanol provided the epoxide in entry 8 in 91% yield.

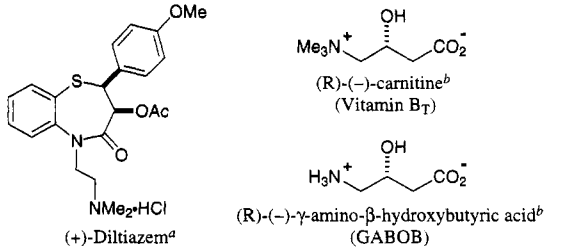
Scheme 54. Large-Scale Synthesis of the Taxol Side Chain[209]



N-Benzoyl-(2*R*,3*S*)-3-phenylisoserine
(C13 Taxol side chain)

rations and requires only minimal extraction processes; all intermediates and the final product are readily purified by recrystallization. In this manner more than 100 g of the enantiomerically pure taxol side chain (**105**) was prepared.[209]

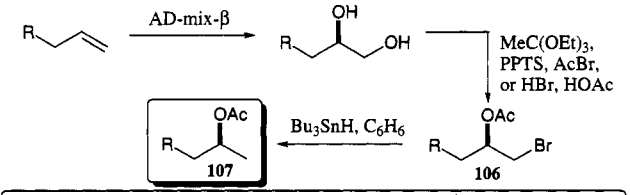
Scheme 55. Some Biologically Active Compounds Which Have Been Synthesized with the Orthoester Methodology

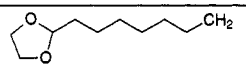
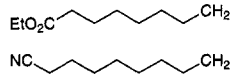
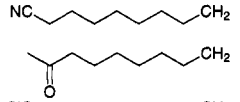
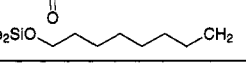


[a] See ref 198d. [b] See ref 38a.

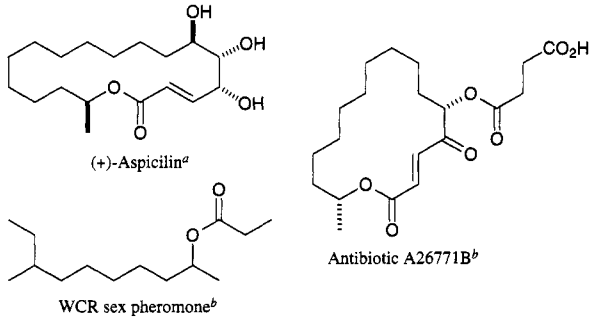
Other biologically active compounds, such as (+)-diltiazem,[198d] (*R*)-(−)-γ-amino-β-hydroxybutyric acid,[38a] and (*R*)-(−)-carnitine,[38a] have also been synthesized using the orthoacetate methodology (Scheme 55).

Table 43. Preparation of Enantiomerically Enriched Methyl Carbinols[123]



Entry	R	AD Reaction: yield (%ee)	Acetoxy bromide: yield	Reduction: % yield
1		93 (89)	58	57
2		96 (90)	96	74
3		94 (87)	83	89
4		99 (86)	90	80
5		92 (84)	85	77

Scheme 56. Some Targets Prepared by Deoxygenation of Terminal Diols



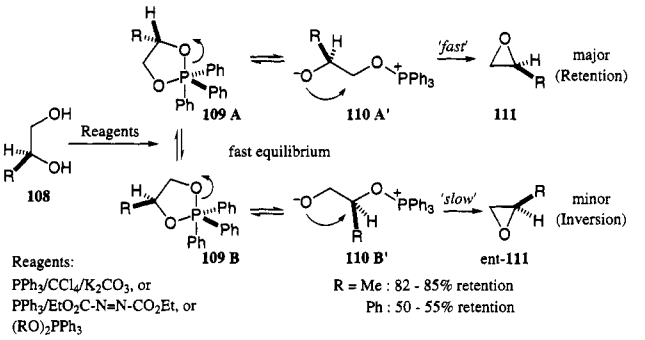
[a] See ref 74c. [b] See ref 123.

Another application has been for the preparation of enantiomerically pure methyl carbinol acetates **107** (Table 43).[123] Thus, the AD reaction of terminal olefins gives the corresponding diols in good enantiomeric excess and the optical purity can be enhanced further by recrystallization. Subsequent reaction via the cyclic orthoacetate of the diols gives acetoxy bromides **106** in good yield, even when an acid-sensitive functionality is present. As expected, the bromide is introduced at the terminus and its reductive removal with Bu_3SnH leads to acetates of methyl carbinols **107**.

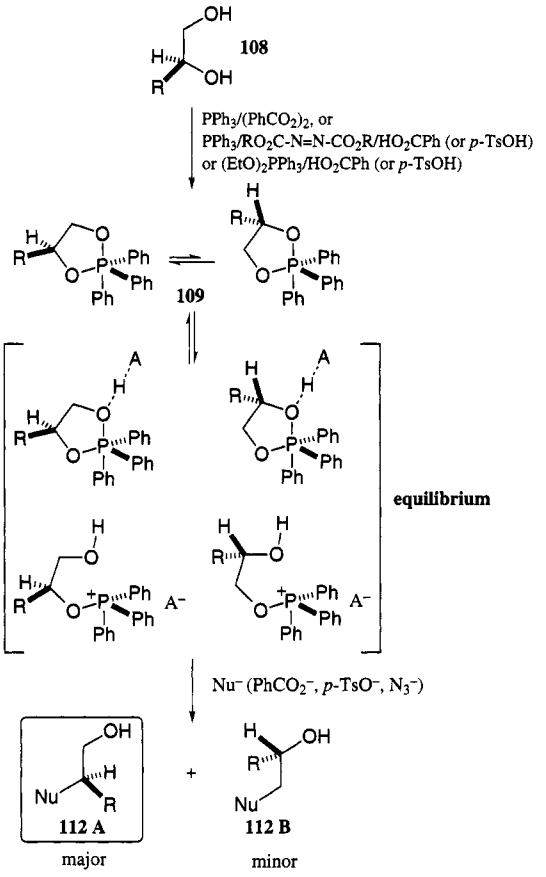
Keinan *et al.* employed this strategy in syntheses of the macrolides (+)-aspicillin[74c] and antibiotic A26771B as well as the four possible stereoisomers of the western corn rootworm (WCR) sex pheromone[123] (Scheme 56).

3.1.3.3. Cyclodehydration and Monosubstitution of Diols via 1,3,2λ⁵-Dioxaphospholanes. Cyclodehydration of diols to epoxides can be effected in one step by treatment with phosphorus-based reagents such as dialkoxytriphenylphosphoranes, $PPh_3/CCl_4/K_2CO_3$, or $PPh_3/RO_2CN{=}NCO_2R$.[203] The initially formed intermediate, a dioxaphospholane **109**, may exist in two isomeric forms **A** and **B** which lead to regioisomeric betaines **110A′** and **B′** (Scheme 57). Intramolecular substitution of triphenylphosphine oxide results in the formation of the epoxide **111**. However, as in the case of epoxidation via tosylates (*vide supra*), partial racemization usually occurs,

Scheme 57. One-Step Cyclodehydration of Diols[203]



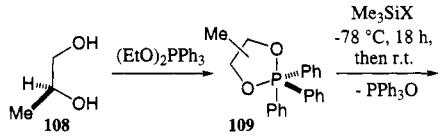
Scheme 58. Regioselective and Stereospecific Monosubstitution of Unsymmetrical 1,2-Diols via Dioxaphospholanes[204]

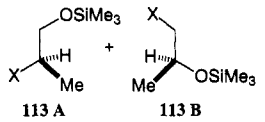


since the two regioisomers **A′** and **B′** give opposite enantiomers, i.e. **111** and *ent*-**111**, upon cyclization. Thus, (*S*)-(+)-propane-1,2-diol (**108**, R = Me) afforded the corresponding epoxide with ca. 82−85% retention of configuration, while activated diols, e.g. (*S*)-(+)-phenylethane-1,2-diol (**108**, R = Ph), lead to complete racemization (Scheme 57). The fact that the configuration of the stereogenic carbon center is retained during cyclodehydration indicates that the collapse of betaine **110A′** is faster than that of betaine **B′**.

If a dioxaphospholane **109** is reacted with a nucleophile in the presence of an acid, i.e. $PhCO_2H$, HOTs, or NaN_3/HOTs in MeCN, the corresponding benzoates, tosylates, and azides **112** (Nu = $PhCO_2$, TsO, N_3), respectively, are obtained with essentially complete inversion of the chiral carbon center[204] (Scheme 58). Interestingly, the nucleophile is introduced at the more hindered carbon, leading to the

Table 44. Regioselective and Stereospecific Functionalization of (S)-1,2-Propanediol with Trimethylsilyl Reagents[205]





Me3SiX	113 A : B	% Yield[a]
SPh	17 : 1	70
Br	5 : 1	77
I	8 : 1	60
Cl	1.6 : 1	61
CN	1.9 : 1	60
N_3[b]	>99 : <1	85

[a] Isolated yields. [b] 25 °C, 1 h.

formation of **112A**, which may be due to activation of the dioxaphospholane **109** by complexation of an acid (i.e. $PhCO_2H$ or *p*-TSA) at the most basic apical oxygen of the complex which is also sterically least hindered. This may lead to an increased electron deficiency of the equatorial oxygen atom and consequently the carbon atom attached to it, thereby activating it for nucleophilic displacement.[204]

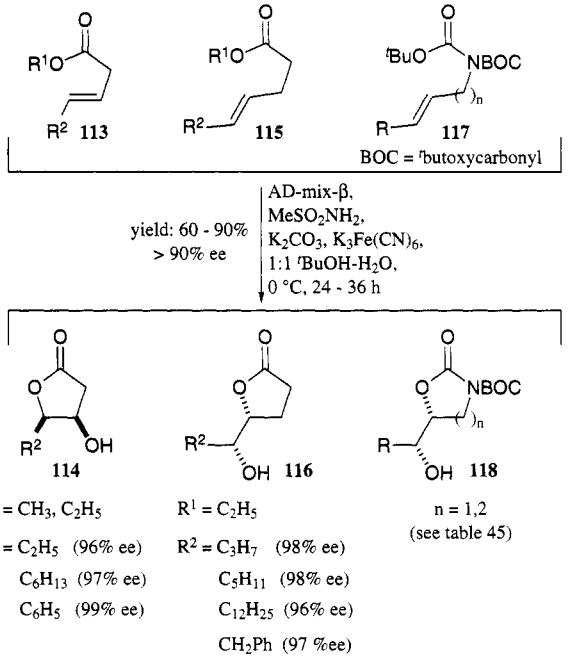
Analogous chemistry has been observed with trimethylsilyl reagents instead of acids, again resulting in preferential substitution at the more hindered carbon with nearly complete inversion of configuration[205] (Table 44). Trimethylsilyl halides give rise to silyl ethers of halohydrins **113** (X = Cl, Br, I), while Me_3SiN_3, Me_3SiCN, and Me_3SiSPh afford the corresponding (trimethylsilyl)oxy azides **113** ($X = N_3$), cyanides (X = CN), and thioethers (X = SPh), respectively.

3.1.4. Differentiation of the Hydroxyl Groups by Selective, Intramolecular Trapping

In the previous chapters the differentiation of hydroxyl groups based on steric or electronic grounds was discussed. Another strategy to achieve this goal is to effect cyclization involving only one of the two OH groups. This approach may be adopted with AD substrates that contain a carbonyl group at an appropriate distance from the double bond. Under kinetic conditions, 5-membered rings are favored over 6-membered rings (Scheme 59), and cyclization normally occurs spontaneously during the AD reaction of olefinic substrates that contain ester or carbamate functionality.

3.1.4.1. Formation of γ-Lactones During the Asymmetric Dihydroxylation of β,γ- and γ,δ-Unsaturated Esters. Functionalized γ-lactones are important synthetic building blocks for a number of natural products, precursors for HIV-1 protease inhibitors and other biologically active compounds.

Scheme 59. Differentiation of Hydroxyl Groups by Kinetically Controlled Cyclization[114,210,211]



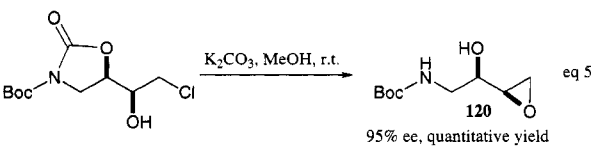
These building blocks are obtained in excellent yield and enantiomeric purity by asymmetric dihydroxylation of β,γ- or γ,δ-unsaturated esters **113** and **115**, respectively, under the $K_3Fe(CN)_6/K_2CO_3$ conditions[210] (Scheme 59).

Muricatacin, an acetogenin derivative that shows some cytotoxicity toward human tumor cells, is readily accessible by this strategy[210] (Scheme 59, compound **116**, $R^2 = C_{12}H_{25}$).

In recent elegant syntheses of solamin and reticulatacin the lactonization was employed to enable regioselective monotosylation of diol intermediate **119** as a key step[212] (Scheme 60).

3.1.4.2. Formation of Cyclic Carbamates during the Asymmetric Dihydroxylation of BOC-Protected Allylic and Homoallylic Amines. Diols derived from *N,N*-di(*tert*-butoxycarbonyl)allylic or homoallylic amines **117** also cyclize spontaneously to cyclic carbamates **118** during the AD reaction, thereby differentiating the two hydroxyl groups[211] (Table 45).

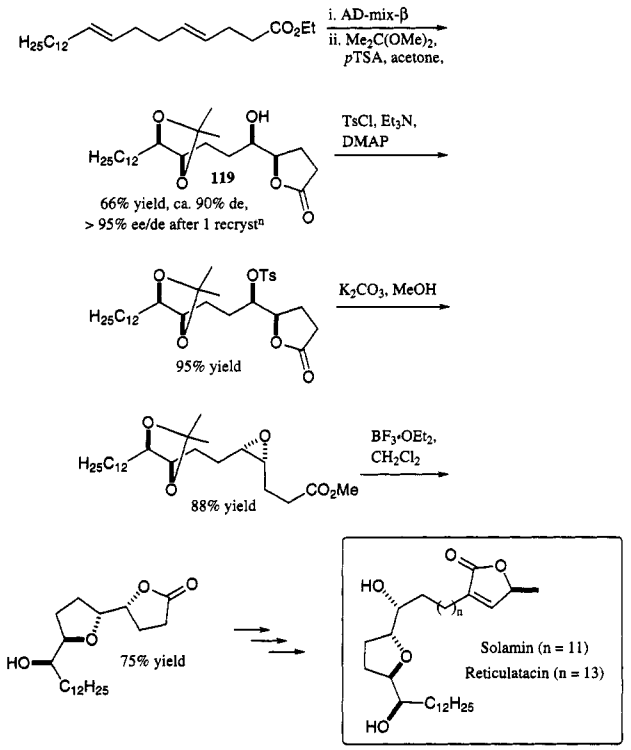
The cyclic portion of the protecting group can be selectively removed under basic conditions, enabling the synthesis of the highly functionalized chiral building block **120** (eq 5).



eq 5

3.1.4.3. Formation of Bicyclic Systems by Intramolecular Ketalization. The asymmetric dihydroxylation provides an efficient access to natural products with a 6,8-dioxabicyclo[3.2.1]octane skeleton. These bicyclic systems are formed by intramolecular ketalization of dihydroxy ketones, derived from unsaturated ketones or ketone equivalents. Thus, (+)-*exo*-brevicomin has recently been synthesized[214] by a sequence involving asymmetric dihy-

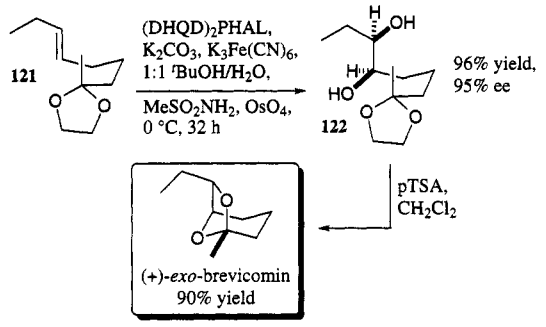
Scheme 60. Asymmetric Synthesis of Solamin and Reticulatacin[212]



droxylation of the protected unsaturated ketone **121** and subsequent acid-catalyzed transketalization of the resulting diol **122** (Scheme 61).

Other bicyclic natural products that have been prepared in similar fashion are the beetle aggregation pheromone (−)-frontalin[215] and 7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane,[216] a volatile component of the aroma of beer (Scheme 62).

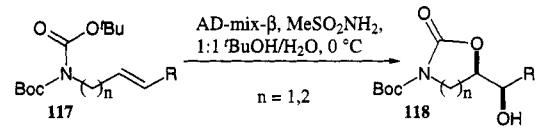
Scheme 61. Asymmetric Synthesis of (+)-*exo*-Brevicomin[214]

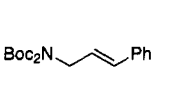
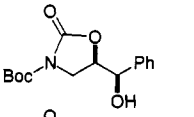
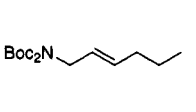
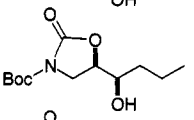
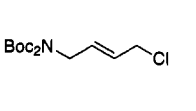
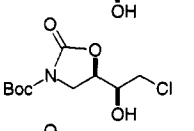
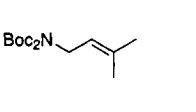
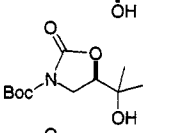
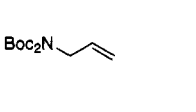
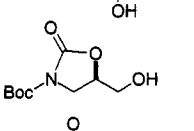
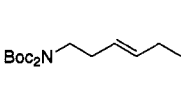
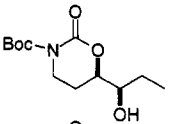
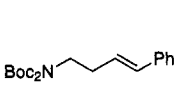
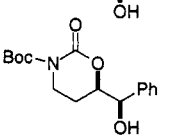


3.1.5. Miscellaneous Transformations

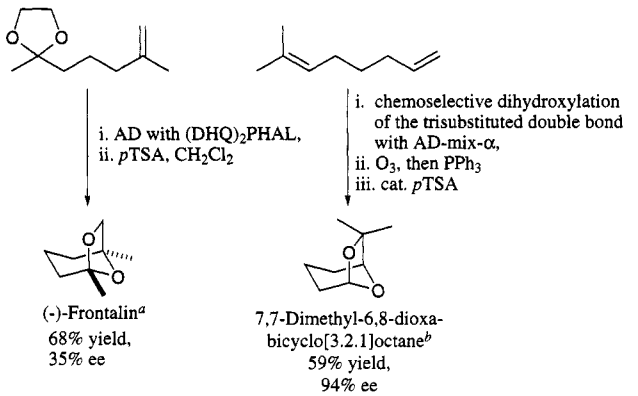
The hydroxyl groups of a diol can also be distinguished based on the proximity to certain functional groups, i.e. silyl groups or double bonds. Thus, Peterson elimination of dihydroxy silanes **124**, involving the OH group closest to the silicon, yield enantiomerically enriched secondary allylic alcohols **125**[40] (Scheme 63). It is also possible to make use of the electronic activation of the allylic position by a double bond for selective manipulations. Thus, the single dihydroxylation of diene **126** and conversion of both OH groups into leaving groups, e.g. carbamates, leads to the activated system **127**, which allows selective substitution of the allylic group by treatment with a nucleophile in the presence of a palladium(0) complex[217] (Scheme 63).

Table 45. Formation of N-Protected Cyclic Carbamates 118 in the AD Reaction of Allylic and Homoallylic Di(*tert*-butoxycarbonyl)amines 117[211]



Substrate	Product	% yield	% ee
		78	97
		80	90
		80	95
		44	47
		93	34
		73	89
		73	98

Scheme 62. Asymmetric Synthesis of (−)-Frontalin and 7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane

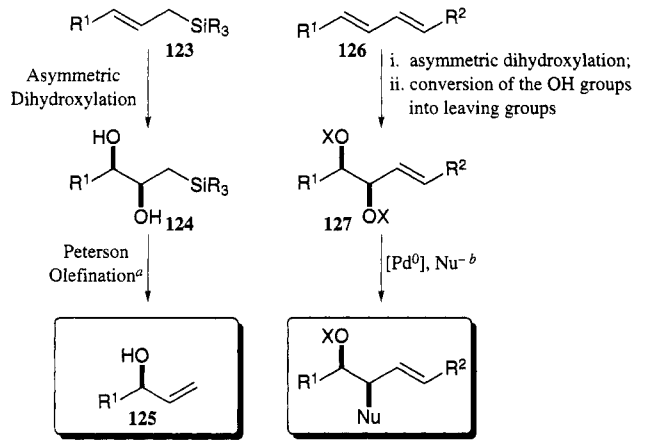


[a] See ref 215. [b] See ref 216.

3.1.5.1. Preparation of Enantiomerically Enriched Secondary Allylic and Propargylic Alcohols. *a. Allylic Alcohols.* Optically active, secondary allylic alcohols **125** are useful chiral building blocks, and they are readily obtained from allylsilanes in only two steps: asymmetric dihydroxylation, followed by Peterson elimination[40] (Scheme 63 and Table 46).

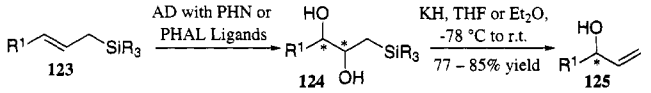
The starting silanes **123** are available by a variety of reactions[218] and they have been prepared in this

Scheme 63. Selective Manipulation of Diols Based on the Proximity to a Functional Group



[a] See ref 40. [b] See ref 217.

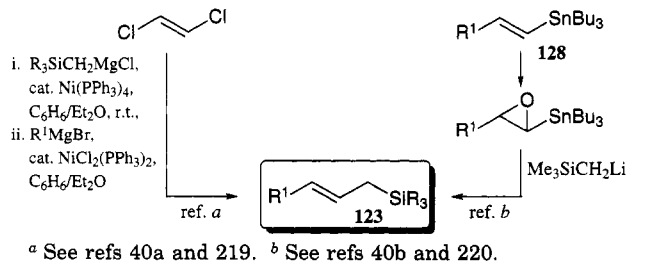
Table 46. Preparation of Allylic Alcohols from Allylsilanes[†]



Entry	Substrate	Product	Ligand	% ee
1[a]	$^nC_5H_{11}$, SiMe$_3$	$^nC_5H_{11}$, HO	DHQD-PHN	91[c]
2[a]	$^nC_5H_{11}$, SiMe$_3$	$^nC_5H_{11}$, HO	DHQ-PHN	87[c]
3[a]	SiMe$_3$	HO	DHQD-PHN	95[c]
4[a]	SiMe$_3$	HO	DHQD-PHN	94[c]
5[a]	SiMe$_3$	HO	DHQD-PHN	35[c]
6[b]	SiMe$_3$	HO	$(DHQ)_2PHAL$	68[d]

[†] The reactions in entries 1–5 were performed at room temperature. [a] See ref 40a. [b] See ref 40b. [c] 13 mol % of the ligand was used. [d] 2 equiv of AD-mix-α (i.e. 2.8 g per 1 mmol of the olefin) was used.

Scheme 64. Preparation of Allylsilanes

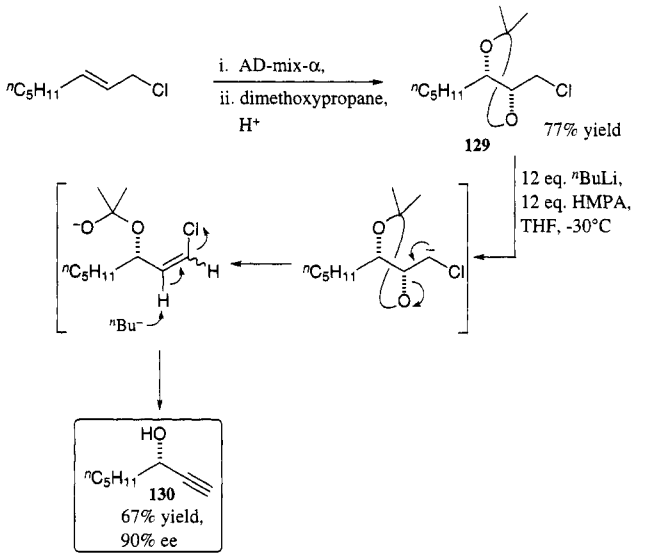


[a] See refs 40a and 219. [b] See refs 40b and 220.

context by two methods, starting either from (*E*)-1,2-dichloroethylene[40a,219] or from vinylstannanes **128**[40b,220] (Scheme 64).

Unfortunately, allylsilanes give only moderate enantioselectivities under the normal AD conditions and a recent optimization study[40a] has uncovered the following trends. Increasing the size of the silyl substituents causes the enantioselectivity to drop and

Scheme 65. Formation of Optically Active Propargylic Alcohols by Base-Induced Fragmentation of 1-Chloro-2,3-acetonides[221]



it is best to use a trimethylsilyl group. Thus, allyltrimethylsilane (**123**, R^1 = H, R = Me) gives the corresponding diol with AD-mix-β in only 13% ee, while allyltriisopropylsilane (**123**, R^1 = H, R = *i*-Pr) yields an almost *racemic* compound under identical conditions. This observation may be related to a general problem with the phthalazine ligands which do not respond well to branching in close proximity to the double bond (for example, see Table 1, entry 11), especially if the branched substituent should reside in the binding pocket of the ligand (i.e. the southwest quadrant of the mnemonic device, cf. Figures 3 and 5). In certain cases, the phenanthryl ether ligands **4** (DHQ-PHN and DHQD-PHN) give *higher* enantioselectivities than the phthalazine ligands **1** and the diol derived from allyltrimethylsilane (**123**, R^1 = H, R = Me) has been obtained with 76% ee. As expected, *trans*-disubstituted olefins **123** ($R^1 \neq$ H) (Table 46, entries 1–4 and 6) are better substrates for the AD than terminal or trisubstituted alkenes (entry 5). These *trans*-disubstituted allylic silanes all offer a fair-to-good alternative group for the binding pocket when the offending CH_2SiMe_3 group resides in the relatively open NE quadrant of the mnemonic device (Figure 5).

As mentioned above, the reason for the poor performance of the phthalazine ligands with allyl- and vinylsilanes is the presence of a bulky group in close proximity to the double bond. Generally, pyrimidine ligands perform better than the phthalazines in such cases[24] and, not surprisingly, a much better enantiomeric excess was obtained with vinyltrimethylsilane using $(DHQD)_2PYR$[37] (88% ee, cf. Table 1, entry 12) compared to 46% ee, obtained with $(DHQD)_2PHAL$[40] (Table 1, entry 12).

b. Secondary Propargylic Alcohols.[221] Base-induced fragmentation of 1-chloro-2,3-acetonides (**129**) affords secondary propargylic alcohols **130**[221] (Scheme 65). The reaction proceeds by a mechanism similar to that for the fragmentation of 1-chloro 2,3-epoxides,[222] by elimination of an intermediate α-chlorocarbanion and subsequent dehydrochlorination of the resulting vinyl chloride.

Scheme 66. Formal Synthesis of Vitamin E[221]

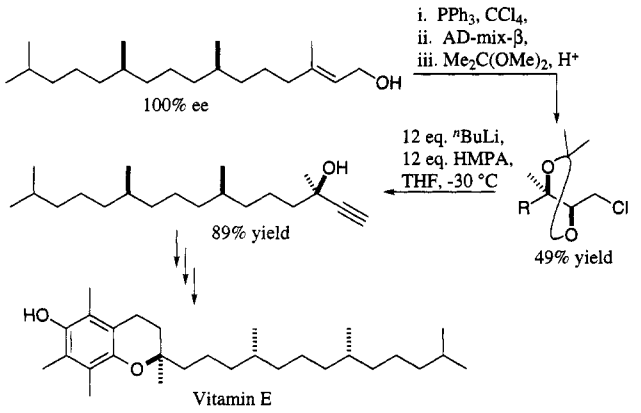
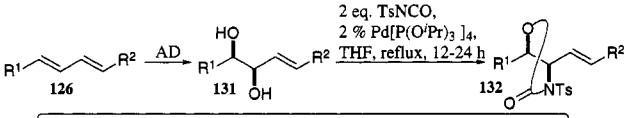


Table 47. Formation of Oxazolidin-2-ones from Dienes[217]



Entry	Olefin[a]	Product	% yield (from enediol **131**)	% ee
1			86	93
		trans:cis 6 : 1		
2			81	99
3			67	98
4			80	92

[a] For the preparation of the ene diols in entries 1, 2, and 4, see ref 116a; for the diol in entry 3, see ref 217.

An analogous reaction sequence has been used in a recent formal synthesis of vitamin E starting from phytol[221] (Scheme 66).

3.1.5.2. Selective Substitution of the Allylic OH Group of Ene Diols. As shown in section 2.4, the asymmetric dihydroxylation of conjugated dienes yields ene diols with high enantiomeric excess. The synthetic utility of these highly functionalized compounds is enhanced further by the selective substitution of the allylic OH group via Pd-stabilized allyl cations.[217]

Treatment of an ene diol **131** with 2 equiv of *p*-toluenesulfonyl isocyanate in the presence of catalytic amounts of Pd(0) gives oxazolidin-2-ones (**132**) via initial formation of the biscarbamate, ionization to the Pd-stabilized allyl cation and subsequent intramolecular trapping by the nitrogen of the other carbamate group. As shown in Table 47, this reaction has a wide scope and double-bond isomerization only occurs to a limited extent in certain cases.

The vinyloxazolidin-2-ones, prepared by this methodology, are valuable chiral building blocks, since they constitute synthetic precursors to amino alcohols.

Table 48. Epoxide and Cyclic Sulfate Building Blocks

Entry	Precursor	Building Block	Method of Preparation	Applications
	Epoxides			
1			Orthoester method[a]	general building block
2			Orthoester method[b]	→ β-blocker[b]
	Vinyl Epoxides			
3			Orthoester method[c]	→ allylic alcohols[d] → δ-lactones[e]
	Hydroxy Epoxides			
4			Base mediated cyclization[f]	general building block[g]
5			AD and base treatment[h]	general building block
	Glycidaldehyde Equivalents[i]			
6			*via* tosylate[j] or orthoester method[a]	general building block[i]
7			SO_2Cl_2, imidazole, CH_2Cl_2[k]	Glycid-aldehyde equivalent[k]
	Glycidic Esters			
8		**133**	Orthoester[a] or HBr/HOAc[l] methods	intermediates for drug synthesis[n]
9		**134**	*via* α-tosylate or nosylate[m]	

[a] Cf. Table 42, Scheme 50, and refs 50, 197, and 198. [b] Cf. Scheme 52 and ref 41a. [c] Cf. Schemes 51 and 53 and ref 206. [d] References 223–225. [e] Reference 226. [f] Reference 39. [g] For reviews, see ref 6a and 158. [h] Cf. eq 5 and ref 211. [i] Reference 160. [j] Cf. Scheme 29 and ref 44a. [k] Reference 227. [l] Cf. Scheme 49 and refs 153 and 193. [m] Cf. Schemes 33 and 34 and refs 153 and 154. [n] Cf. section 3.1.1. and refs 50, 154, 164, 198d, 228, and 229.

3.2. Preparation of Chiral Building Blocks

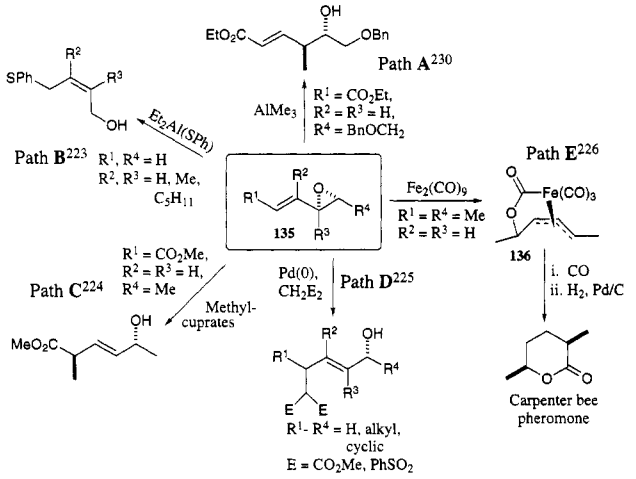
The AD reaction is ideally suited for the preparation of chiral building blocks for asymmetric synthesis, due to its wide scope and normally excellent enantioselectivity. A large number of chiral synthons have been prepared via the AD in recent years and most of the synthetic applications have already been discussed in detail in the previous chapters. This section briefly lists the most important chiral synthons and the discussion is focused on those compounds which have not been mentioned earlier.

3.2.1. Electrophilic Building Blocks

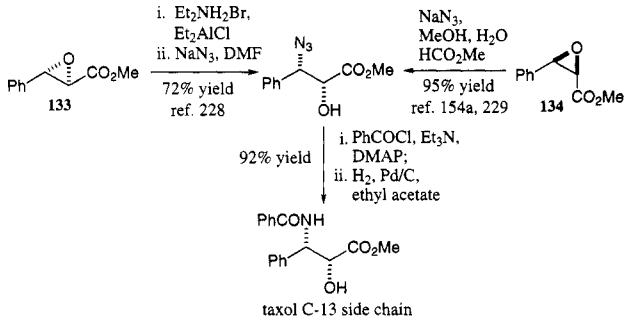
Chiral epoxides and their synthetic equivalents, the cyclic sulfates, as well as halohydrins and glyceraldehyde derivatives are versatile chiral building blocks. Their electrophilic character facilitates bond-forming transformations and these chiral synthons have been extensively used in syntheses of natural products and other biologically active compounds.

3.2.1.1. Chiral Epoxides and Cyclic Sulfates. Some epoxide and cyclic sulfate building blocks which have recently been prepared using the AD reaction are listed in Table 48. The formation and synthetic applications of cyclic sulfates and epoxides are dis-

Scheme 67. Some Synthetic Applications of Vinyl Epoxides



Scheme 68. Preparation of the Taxol C13 Side Chain via Glycidic Esters



cussed in depth in chapters 3.1.2 and 3.1.3., respectively.

Vinyl epoxides **135** are precursors for homoallylic alcohols, allylic alcohols, and δ-lactones. Thus, S_N2 opening with Me_3Al provides homoallylic alcohols[230] (Scheme 67, path A), whereas S_N2' opening, leading to allylic alcohols, can be effected with certain aluminum reagents[223] (path B), organocuprate reagents[224] (path C), and under Pd(0) catalysis[225] (path D). In contrast, treatment with $Fe_2(CO)_9$ and carbonylation of the resulting π-allyltricarbonyliron lactone **136**, provides access to δ-lactones[226] as exemplified by the synthesis of the carpenter bee pheromone (path E).

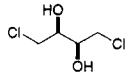
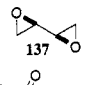
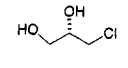
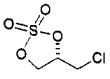
The glycidic esters **133** and **134** (Table 48, entries 8 and 9) are useful intermediates in the synthesis of β-amino-α-hydroxy acids, for example phenylisoserines[154a,228,229] (taxol side chain) as shown in Scheme 68.

Additionally, certain biologically active compounds, such as the antibiotic chloramphenicol,[164] the leukotriene antagonist SKF 104353,[50] and the cardiac drug (+)-diltiazem[198d] (a Ca-channel blocker), have been prepared via glycidic ester intermediates (cf. Schemes 34, 52, and 55, respectively).

Highly functionalized, chiral C_3 and C_4 synthons with more than two electrophilic centers are listed in Table 49.

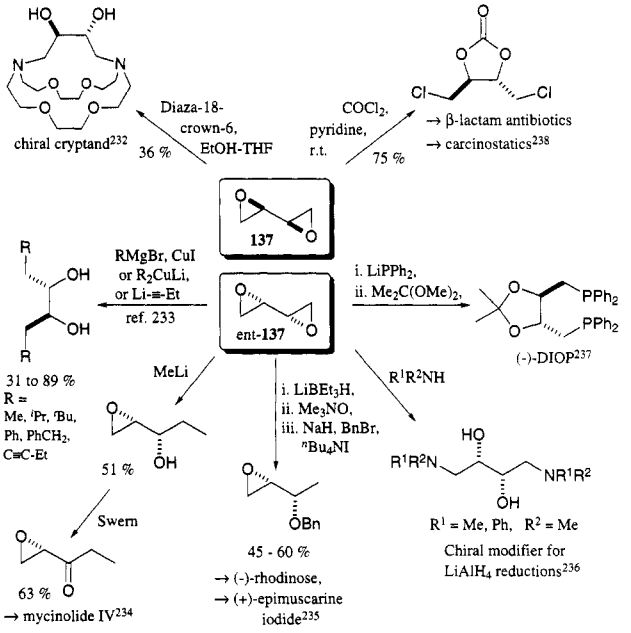
Bisepoxide **137** (Table 49, entry 1) is a versatile chiral building block and some applications are shown in Scheme 69.

Table 49. Ambident Electrophiles

Entry	Precursor	Building Block	Method of Preparation	Applications
1			Base mediated cyclization[a]	cf. scheme 69
2			SO_2Cl_2, imidazole, CH_2Cl_2[b]	C_3 building block[b] (epichlorohydrin equivalent)

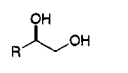
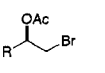
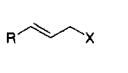
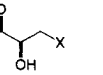
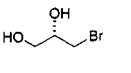
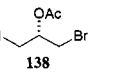
[a] Reference 39. [b] Reference 231.

Scheme 69. Synthetic Applications for Bisepoxide 137



3.2.1.2. Halohydrin Building Blocks. Vicinal halohydrins may be regarded as synthetic equivalents of epoxides. However, in contrast to epoxides, they are not ambident electrophiles, since the site of nucleophilic attack is already predetermined by the position of the halogen (provided that *in situ* cyclization to the epoxide is prevented by appropriate choice of a hydroxyl protecting group and/or the reagent). As described in sections 3.1.3.1 and 3.1.3.2, halohydrin esters may be prepared from diols in a highly regioselective fashion either by the HBr/HOAc method[153,193] or by the orthoester procedure[50,197,198] (Table 42). Some examples are shown in Table 50.

Table 50. Chiral Halohydrin Building Blocks

Entry	Precursor	Building Block	Method of Preparation	Applications
1			Orthoester method[a]	precursor for methyl carbinols[b]
2		 X = Cl, Br, I	Dihydroxylation with 'buffered' AD-mix[c]	general building block
3		 138	Orthoester method[d]	densely functionalized C_3 building block[d]

[a] Cf. Table 42 and refs 50, 197, and 198. [b] Cf. Table 43 and ref 123. [c] Cf. Tables 1 and 3, section 2.2.1.1, and ref 39. [d] Cf. Scheme 70 and ref 38a.

Scheme 70. Synthesis of Carnitine and GABOB using the Building Block 138[38a]

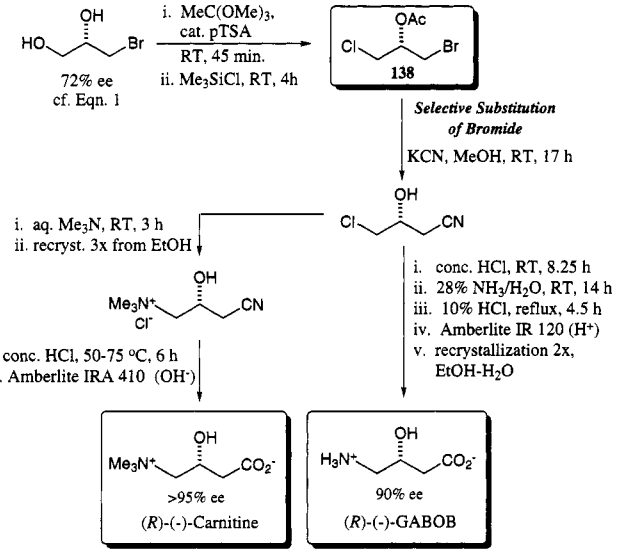
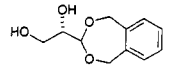
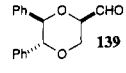
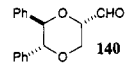


Table 51. Glyceraldehyde Building Blocks

Entry	Precursor	Building Block	Method of Preparation	Applications
1			catalytic hydrogenation[a]	chemo-enzymatic syntheses of carbohydrates[a]
2		 139	cf. scheme 71[b]	C_3 building block[b,c]
3		 140		

[a] Cf. eq 2, Scheme 72, and refs 44a and 59. [b] Reference 241. [c] Reference 239.

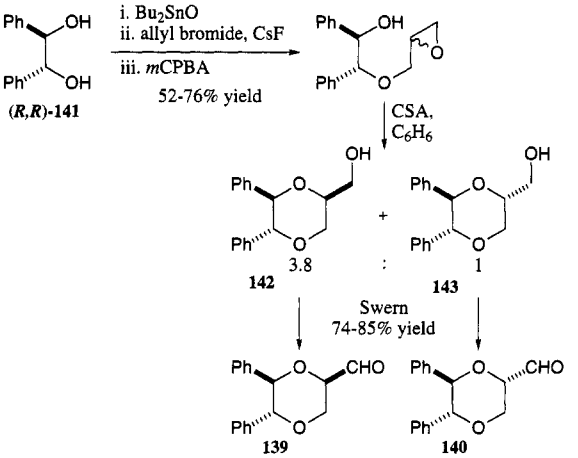
The chloro bromo acetate **138** (Table 50, entry 3) is a densely functionalized C_3 building block with a different functional group attached to each carbon atom. Intriguingly, the presence of two *different* halides at the termini of **138** causes the molecule to be chiral and enables selective manipulation. Thus, **138** is the central intermediate in the syntheses of (*R*)-(−)-carnitine and (*R*)-(−)-γ-amino-β-hydroxybutyric acid[38a] (GABOB) (Scheme 70).

3.2.1.3. Glyceraldehyde Building Blocks. Glyceraldehyde is a useful C_3-building block that has been employed in a number of natural product and drug syntheses.[239] While the (*R*)-enantiomer of glyceraldehyde may be prepared from D-mannitol,[239,240] the (*S*)-isomer is less readily available, due to the cost of L-mannitol. Some (*R*)- and (*S*)-glyceraldehyde equivalents that have been synthesized using the AD reaction are shown in Table 51.

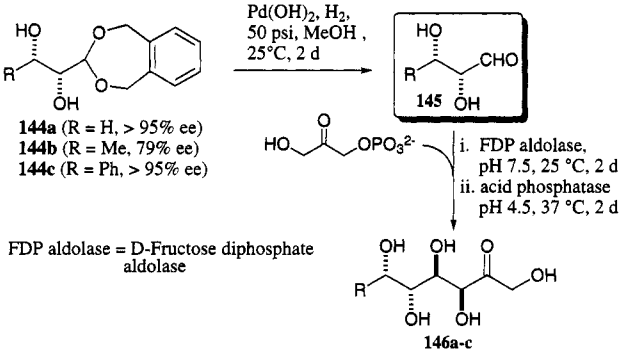
The syntheses[241] of glyceraldehyde synthons **139** and **140** (Table 51, entries 2 and 3) start with (*R,R*)-stilbenediol [(***R,R***)-**141**], which is available in greater than 99% ee from the AD of stilbene (Table 3, entry 7). Selective monoallylation via the stannylene acetal, followed by epoxidation and acid-catalyzed epoxide opening affords a separable 3.8:1 mixture of the diastereomeric alcohols **142** and **143**, which are oxidized under Swern conditions to provide the aldehydes **139** and **140**, respectively (Scheme 71).

Glyceraldehyde **145** (R = H), prepared by catalytic hydrogenolysis of **144a**, has been used in the chemoenzymatic synthesis of carbohydrates,[59] e.g. L-fructose (**146a**) (Scheme 72). A large number of other ketoses have been prepared by this route.

Scheme 71. Preparation of Glyceraldehyde Synthons 139 and 140[241]



Scheme 72. Chemoenzymatic Synthesis of D-Fructose and Its Analogs[59]

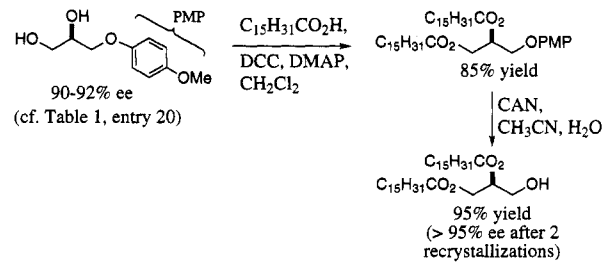


3.2.2. Chiral Diol and Polyol Building Blocks

Polyols are important precursors for carbohydrate derivatives, glycerolipids, and other biologically relevant compounds. Some polyol building blocks are summarized in Table 52.

The AD reaction of aryl allyl ethers proceeds with high enantioselectivity (cf. Table 1) and leads to chiral glycerol derivatives, intermediates in the preparation of β-blockers[41] (cf. Scheme 52) and glycerolipids[61b,242] (Scheme 73).

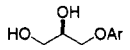
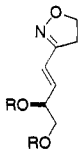
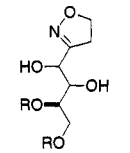
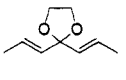
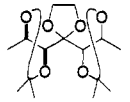
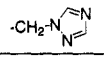
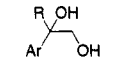
Scheme 73. Synthesis of Dipalmitoylglycerols[61b,242]



3.2.3. Chiral Monohydroxy Compounds Derived from Diols

Chiral allylic alcohols, propargylic alcohols, and methyl carbinols are versatile building blocks for natural product and drug synthesis. Table 53 sum-

Table 52. Polyol Building Blocks

Entry	Precursor	Building Block	Method of Preparation	Applications
1			AD reaction[a]	→ β-blocker[b] → glycerolipids[c]
2			AD reaction[d]	→ aminosugars
3			AD reaction[e]	→ carbohydrates
4	 R = CH_2OBn, CH_2OMe, CH_2Br, CH_2Cl 		AD reaction[f,g]	→ Azole Antifungals[g]

[a] Cf. Table 1 and refs 41, 61b, and 242. [b] Cf. Scheme 52. [c] Cf. Scheme 73. [d] Cf. Table 13 and ref 75. [e] Cf. Scheme 21, Table 21, and ref 118. [f] Cf. Table 2 and ref 47. [g] References 243 and 244.

marizes some of the compounds that have been prepared using the AD reaction.

Allylic alcohols may be prepared by Peterson elimination of diols derived from allyl silanes[40] (cf. section 3.1.5.1), kinetic resolution[33,111] (cf. section 2.3.2), S_N2' addition of organocuprates to cyclic sulfites derived from ene diols[187] (cf. Scheme 42), and elimination of cyclic sulfites[188] (cf. Scheme 44). Propargylic alcohols are available by base-induced fragmentation of chloro acetonides[221] (cf. Schemes 65 and 66) and methyl carbinols may be prepared by tin hydride reduction of bromohydrin esters[123] (cf. Table 43).

3.2.4. 5- and 6-Membered Heterocycles

The AD reaction has been employed for the preparation of small heterocyclic compounds, which are useful building blocks for asymmetric synthesis (Table 54).

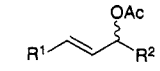
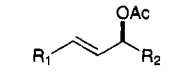
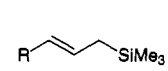
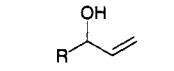
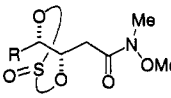
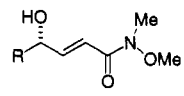
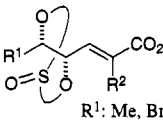
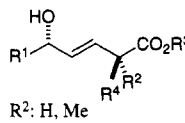
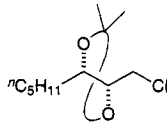
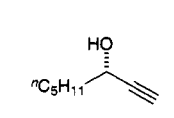
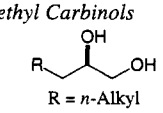
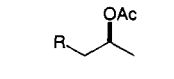
In summary, the great strength of the AD reaction is that it provides ready access to enantiomerically enriched building blocks for asymmetric synthesis, starting from simple and inexpensive olefinic precursors. In a number of cases, the AD reaction has superseded natural products, such as carbohydrates, as a source of optically active compounds, since the use of "tailor made" starting materials greatly reduces the number of synthetic transformations and protecting group manipulations.

3.3. Preparation of Chiral Auxiliaries for Other Asymmetric Transformations

3.3.1. Preparation of (1R,2R)-trans-2-Phenylcyclohexanol

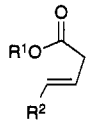
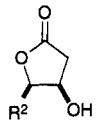
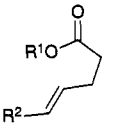
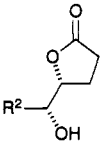
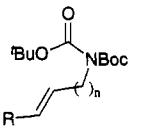
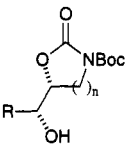
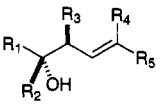
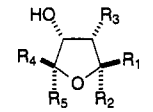
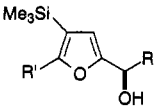
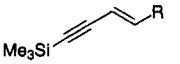
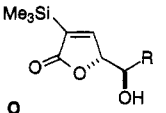
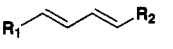
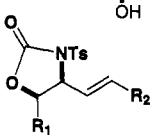
(1*R*,2*S*)-*trans*-2-Phenylcyclohexanol (**147**) was first introduced by Whitesell as a chiral auxiliary for an asymmetric glyoxalate ene reaction.[246] Since its introduction, it has found many additional applica-

Table 53. Chiral Monohydroxy Building Blocks

Entry	Precursor	Building Block	Method of Preparation	Applications
	Allylic Alcohols			
1	 R^1 = Me, Ph R^2 = Me, $^cC_6H_{11}$, $^nC_8H_{17}$, Ph		kinetic resol. using the AD[a]	general building block
2	 R = $^nC_5H_{11}$, $^iC_3H_7$, $^cC_6H_{11}$, Ph		AD and Peterson elimination[b]	general building block
3			Base induced elimination[c]	γ-hydroxy enal equivalent [→Coriolic Acid]
4	 R^1: Me, BnO R^3: Me, Et	 R^2: H, Me R^4: Me, ^{n}Bu	Cuprate Addition[d]	→ carpenter bee pheromone
	Propargylic Alcohols			
5			Base induced fragmentation[e]	→ vitamin E, prostaglandins
	Methyl Carbinols			
6	 R = *n*-Alkyl		Orthoester method and reduction[f]	→ Aspicillin, antibiotic A26771B, WCR sex pheromone

[a] Cf. section 2.3.2., Tables 18 and 19, and refs 33 and 111. [b] Cf. section 3.1.5.1, Table 46, and ref 40. [c] Cf. Scheme 44 and ref 188. [d] Cf. Scheme 42 and ref 187. [e] Cf. Schemes 65 and 66 and ref 221. [f] Cf. Table 43 and ref 123.

Table 54. Heterocyclic Chiral Building Blocks

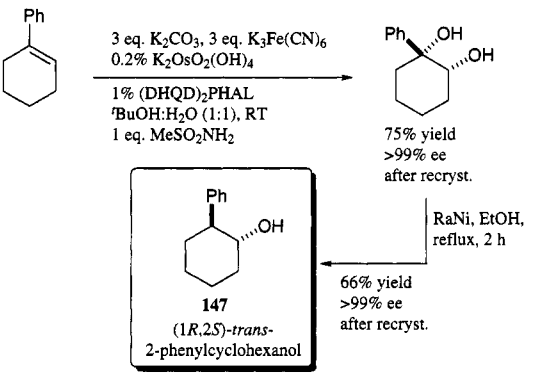
Entry	Precursor	Building Block	Method of Preparation	Applications
1			AD Reaction[a]	general building block
2			AD Reaction[a]	→ Muricatacin, Solamin, Reticulin
3			AD Reaction[b]	selectively protected dihydroxy amine synthon
4			AD, cyclic sulfate form., 5-*endo* cyclisation[c]	Highly functionalized tetrahydrofuran[d]
5			AD reaction, hydromagnesiation, R'CN or CO_2 trappping[e]	ge neral building block
6				
7			AD reaction, reaction with TsNCO and Pd(0)[f]	amino alcohol synthon

[a] Cf. section 3.1.4.1, and Schemes 59 and 60, and refs 114, 210, 212, and 213. [b] Cf. section 3.1.4.2, Table 45, and ref 211. [c] Cf. Scheme 37 and ref 179. [d] Reference 245. [e] Cf. section 2.4.4, Scheme 25, and ref 131. [f] Cf. section 3.1.5.2, Table 47, and ref 217.

tions in asymmetric synthesis. A review detailing the development and uses of this as well as other cyclohexyl-based auxiliaries has recently appeared.[247] Previous preparations of this compound in enantiomerically pure form have relied upon the copper-catalyzed opening of cyclohexene oxide by a phenyl Grignard reagent[248] followed by enzymatic resolution of the corresponding acetate esters[246,249] or preparatory scale separation of para-substituted benzoate esters by chiral HPLC.[250] In addition, a route has been developed that relies upon the asymmetric hydroboration of phenylcyclohexene by monoisopinocampheylborane.[251] It is now possible to prepare this auxiliary on a multigram scale in >99% ee in a two-step synthesis from phenylcyclohexene[252] (Scheme 74).

The asymmetric dihydroxylation of phenylcyclohexene using $(DHQD)_2PHAL$ as chiral ligand proceeded in 98% yield and 98% ee. After a single recrystallization from EtOAc–hexane (1:5), solid diol product could be isolated in 75% yield and >99% ee. Reductive removal of the benzylic hydroxyl group by Raney nickel proceeded very smoothly and provided pure (1*R*,2*S*)-*trans*-2-phenylcyclohexanol in 66% yield and >99% ee after recrystallization from pentane.[252] The identical sequence using $(DHQ)_2PHAL$ gives the 1*S*,2*R*-enantiomer *ent*-**147** in essentially identical yields and enantiopurity.

Scheme 74. Preparation of (1*R*,2*S*)-*trans*-2-Phenylcyclohexanol[252]



3.3.2. Optically Pure Hydrobenzoin (Stilbenediol) and Derivatives

Enantiomerically pure C_2-symmetric 1,2-diols and their derivatives have proved useful as chiral ligands or ligand precursors for several asymmetric processes. In addition to the tartrate esters, stilbenediol-based auxiliaries have also found wide use. Stilbene is the best substrate to date for the asymmetric dihydroxylation reaction (cf. Table 3, entry 7) and a process has been developed for the production of stilbenediol (>99% ee) on a kilogram scale, which is performed at room temperature in a 5-L flask and the insoluble, solid diol product is isolated by simple filtration of the reaction mixture.[253]

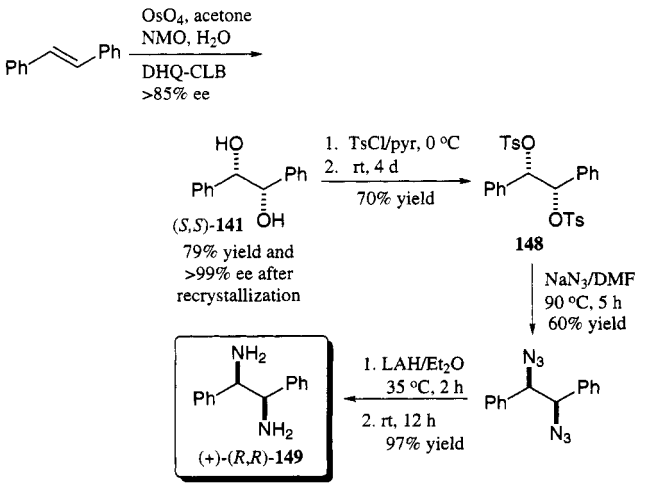
The use of stilbenediol and its derivatives as chiral auxiliaries has been reported for a variety of asymmetric reactions including asymmetric hydrogenation,[254] asymmetric Michael addition,[255,256,257] asymmetric cyclopropanation,[258] and asymmetric allyl and crotyl boration.[259] Stilbenediol has also been used for the production of chiral crown ethers for asymmetric phase-transfer catalysis,[260] as well as serving as a precursor for the production of stilbene diamine[261] which itself is a valuable ligand for asymmetric synthesis.[262] While most of the results described below represent only preliminary studies, they are nonetheless indicative of the potential utility for stilbenediol-based derivatives as ligands or auxiliaries in asymmetric processes.

3.3.2.1. Preparation of Stilbenediamine. Enantiomerically pure C_2-symmetric diamines are finding increasing application in asymmetric synthesis. Among this class of compounds, stilbenediamine (**149**) has proven particularly valuable. Corey recently used this compound to prepare a chiral mediator for asymmetric Diels–Alder, aldol, and allylmetalation reactions.[262] In addition, stilbenediamine, along with other C_2-symmetric diamines, has been used for the preparation of the chiral salen ligands which are highly effective for the asymmetric epoxidation of isolated olefins.[4]

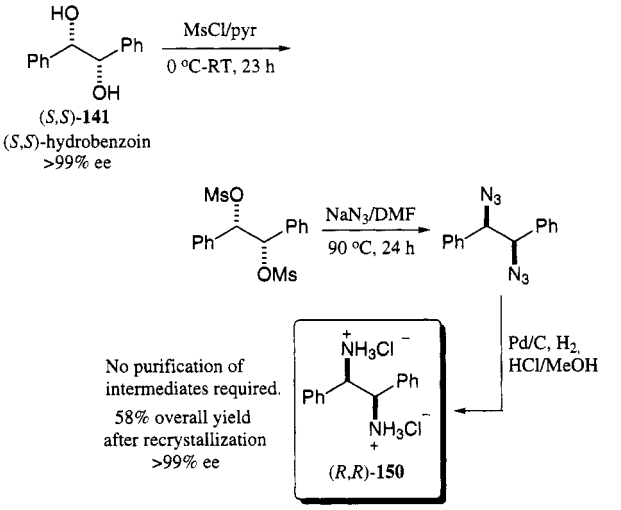
Previous routes to optically pure stilbenediamine have entailed resolution of the racemic diamine.[262a,263] Salvadori has developed a four-step procedure using *trans*-stilbene as starting material[261] (Scheme 75). Thus, *trans*-stilbene is readily converted to the enantiomerically pure diol (*S,S*)-**141** by the asymmetric dihydroxylation reaction. After conversion to the bis-*p*-toluenesulfonate **148**, double displacement with sodium azide followed by reduction provides enantiomerically pure (+)-(*R,R*)-stilbenediamine [(*R,R*)-**149**] in 32% overall yield.

It should be noted that the dihydroxylation reaction in this sequence proceeded in >85% ee using the DHQ-CLB ligand. The enantiomeric excess was increased to >99% by recrystallization. The recrystallization step can be obviated by using the phthalazine class of ligands in the dihydroxylation step which reproducibly provides the diol in ≥99% ee.

Scheme 75. The Preparation of Stilbenediamine via Asymmetric Dihydroxylation[261]



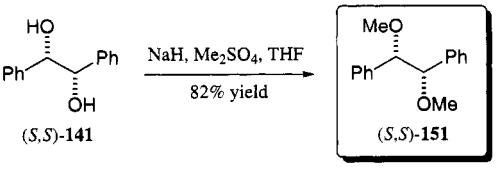
Scheme 76. Preparation of (*R,R*)-Stilbenediamine Bishydrochloride [(*R,R*)-150] from (*S,S*)-Hydrobenzoin[264]



Recently, Chang has developed a route to the bishydrochloride salt (*R,R*)-**150** of (*R,R*)-stilbenediamine[264] (Scheme 76). In analogy to Salvadori's work, this synthesis proceeds via the diazide prepared from the activated diol. The diamine bishydrochloride is obtained after catalytic hydrogenation in acidic methanol in 58% overall yield from stilbene. No purification of intermediates is required and the final product can be easily recrystallized from methanol.[264]

This procedure offers advantages over earlier resolution-based methods, since it uses only readily available starting materials and it is also suitable for the preparation of either enantiomer through proper choice of ligand for the AD step. In addition, the method may be adapted for the preparation of other enantiomerically pure diamines, provided the corresponding AD substrates contain no functional groups which are incompatible with osmium tetroxide.

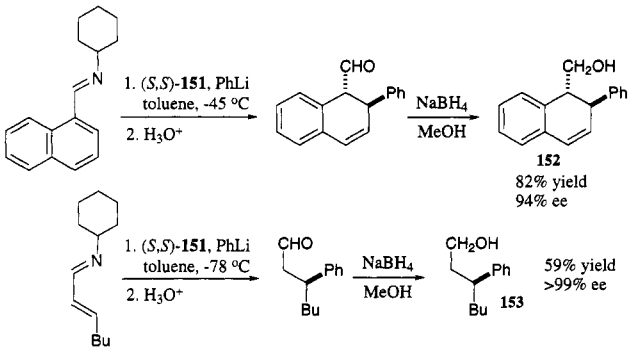
3.3.2.2. Stilbenediol Derivatives in Asymmetric Michael Reactions. Stilbenediol derivatives have also found applications in asymmetric Michael reactions. For example, Tomioka has used the dimethyl ether (*S,S*)-**151** of (*S,S*)-hydrobenzoin, prepared according to eq 6, to mediate the enantioselective conjugate addition of organolithium reagents to α,β-unsaturated aldimines as well as to BHA esters of naphthalenecarboxylic acid.[256]



eq 6

Examples of these Michael additions are shown below. Conjugate addition, followed by imine hydrolysis and reduction provided the desired optically enriched alcohol products **152** and **153** in good yields[256a] (Scheme 77). Interestingly, it was found that the reactions do not proceed smoothly in the absence of the chiral auxiliary. Thus, the auxiliary

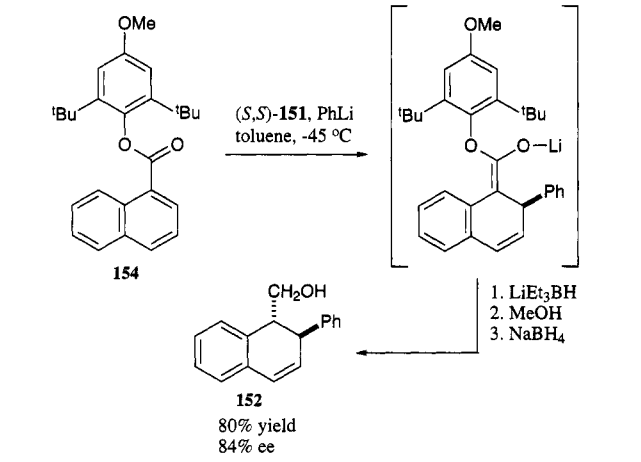
Scheme 77. Asymmetric Conjugate Addition Reactions Controlled by (*S,S*)-151[256a]



not only controls the stereochemical course, but it also promotes the addition.

A similar series of reactions was performed using the BHA esters of naphthalenecarboxylic acid[256b] (Scheme 78). Thus, addition of phenyllithium to the

Scheme 78. Asymmetric Conjugate Addition Reaction Controlled by (*S,S*)-151[256b]



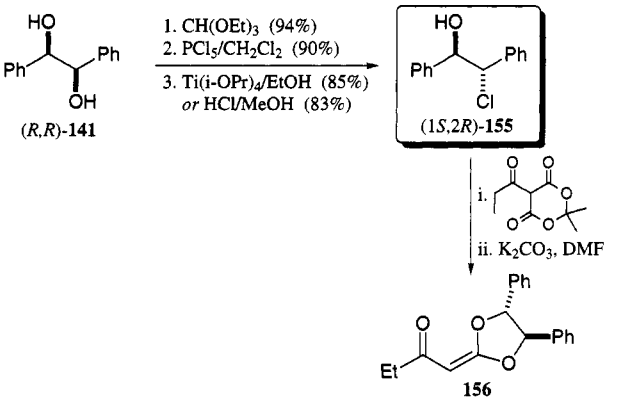
BHA ester **154** in the presence of (*S,S*)-**151** in toluene at −45 °C, followed by reduction of the intermediate ketene derivative provided alcohol **152** in 80% yield and 84% enantiomeric excess. Additional work in this area established that the conjugate addition reactions of both the aldimine and ester substrates could be carried out efficiently with substoichiometric amounts of the chiral auxiliary.[256]

In a related endeavor Konopelski has prepared both enantiomers of 2-chloro-1,2-diphenylethanol (**155**) and used them to synthesize chiral acyl ketene acetals **156**[192b,257] (Scheme 79).

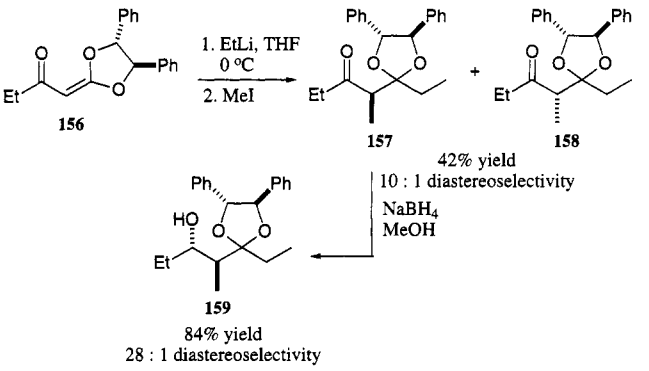
The acyl ketene acetal **156** was used for diastereoselective conjugate addition/alkylation sequences[257] (Scheme 80). Thus, treatment of **156** with ethyllithium at 0 °C in THF followed by *in situ* methylation with MeI provided **157** as the major product of a 10:1 diastereomer mixture. Interestingly, the major diastereomer **157** could be stereoselectively reduced to the *anti* alcohol product **159**, a stereochemical result which is difficult to achieve using conventional aldol technology.

3.3.2.3. Auxiliaries for Asymmetric Allylboration. Hoffman has used (*R,R*)- and (*S,S*)-1,2-dicyclohexylethanediol (**160**) as a chiral auxiliary for the diastereoselective asymmetric chain extension of

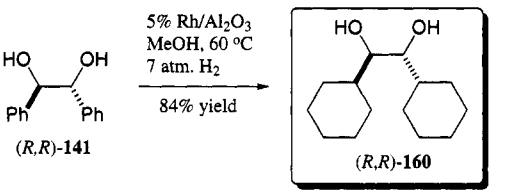
Scheme 79. Preparation of Acyl Ketene Acetal 156 via Chlorohydrin 155[192b,257]



Scheme 80. Reaction of the Enantiopure Ketal Derived from (1*S*,2*R*)-155[257]

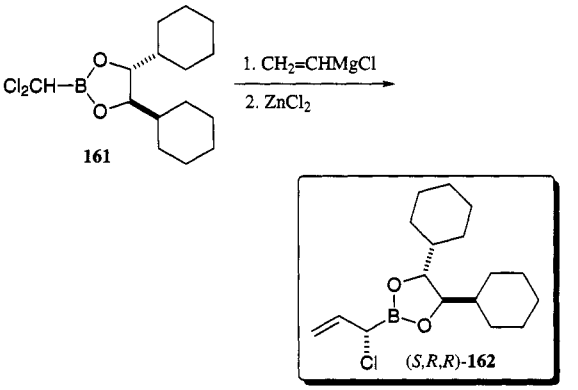


alkylboronic esters.[259] The diol was easily prepared by hydrogenation of hydrobenzoin (**141**) over 5% rhodium on alumina catalyst[259b] (eq 7).



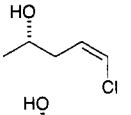
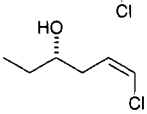
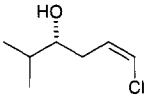
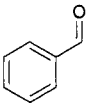
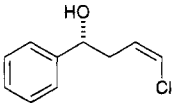
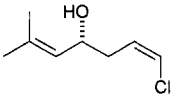
eq 7

Allylboronate **162** is formed by addition of vinylmagnesium chloride to the alkylboronic ester **161** and subsequent $ZnCl_2$-catalyzed rearrangement of the intermediate ate complex[259] (eq 8). Thus, chirality transfer from the auxiliary allows diastereoselective access to α-substituted allylboronate reagents by asymmetric chain extension of alkylboronic esters.[259,265]



eq 8

Table 55. Enantioselective Allylboration of Aldehydes with Reagent (*R,R*)-162[259c]

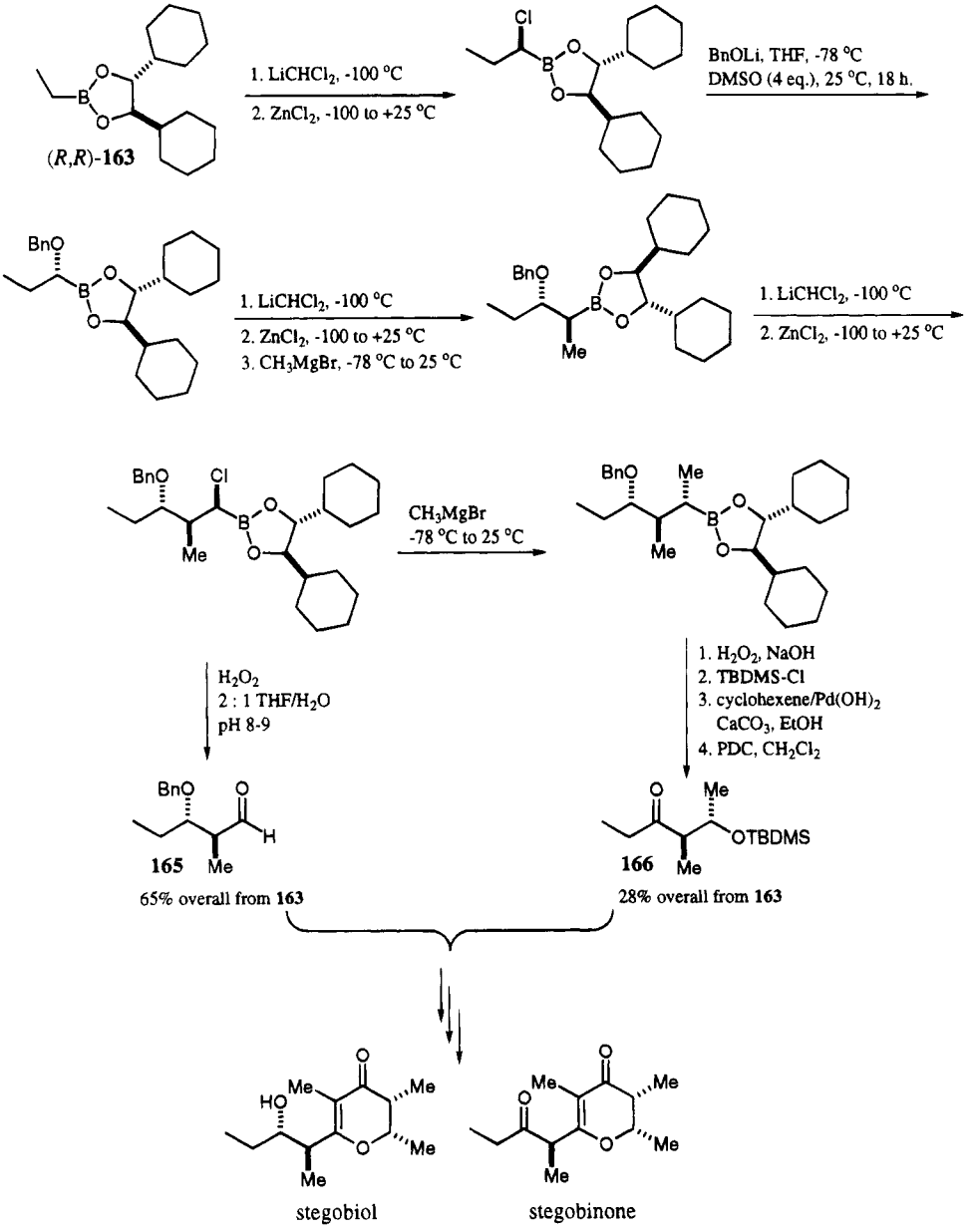
Entry	Aldehyde	Product	Yield (%)	% ee
1			78	>99
2			81	>99
3			89	>99
4			79	>99
5			76	99

The allylboronate reagent **162** was used for the enantioselective allylboration of aldehydes.[266] The results are summarized in Table 55.[259c]

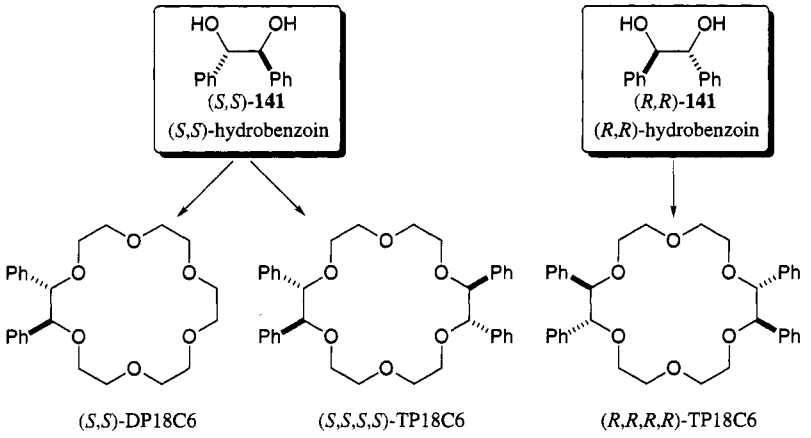
Matteson has used dicyclohexylethanediol to direct the asymmetric chain extension of alkyl boronic esters (Scheme 81). The ultimate synthetic targets were aldehyde **165** and ketone **166**, two key intermediates in the asymmetric synthesis of stegobiol and stegobinone, pheromones of the drugstore beetle.[267]

Previous work had demonstrated that asymmetric chain extension reactions utilizing C_2-symmetric directing groups proceed with diastereoselectivities > 1000:1.[268,269] An added advantage of this approach is that none of the intermediate compounds required any purification. The central aldehyde and ketone intermediates, **165** and **166**, respectively, were purified by distillation and then used in a fragment assembly aldol reaction and elaborated into the natural products stegobiol and stegobinone.[267] The only chromatographic separation required in the

Scheme 81. Asymmetric Synthesis of Stegobiol and Stegobinone[267]



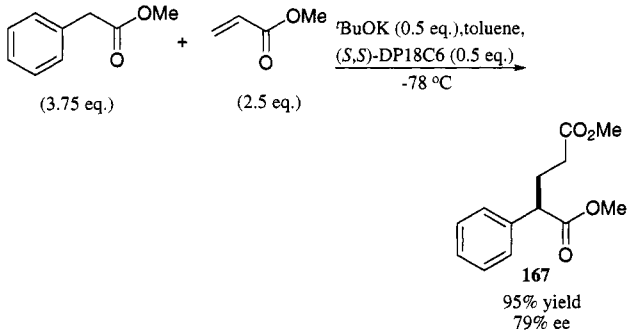
Scheme 82. Hydrobenzoin-Derived Crown Ethers Used in Asymmetric Catalysis[260]



entire sequence was in the final purification of stegobiol.

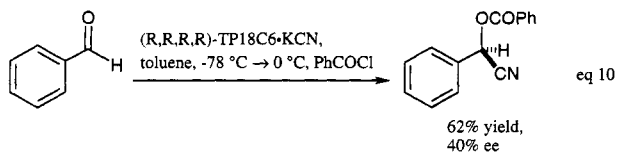
3.3.2.4. Chiral Crown Ether Catalysts. Chiral crown ethers[270] have been used in molecular recognition processes for the enantiomeric differentiation of racemic substrates as well as serving as chiral reagents or catalysts for asymmetric transformations. Several studies have utilized crown ether derivatives wherein chirality is introduced into the backbone through the incorporation of enantiomerically pure hydrobenzoin segments[260] (Scheme 82).

As an example of their use in asymmetric catalysis, Stoddart reported that (*S,S*)-DP18C6 mediated the asymmetric Michael addition of methyl phenylacetate to methyl acrylate, producing the diester product **167** in 95% yield and 79% enantiomeric exces[255] (eq 9).



Equation 9. (*S,S*)-DP18C6-mediated Michael addditon of methyl phenylacetate to methyl acrylate.[255]

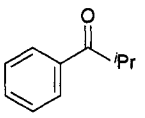
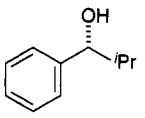
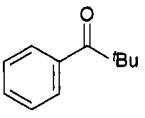
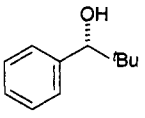
Stoddart has also reported that catalytic amounts of complexes of (*R,R,R,R*)-TP18C6 with potassium cyanide promote the phase-transfer acylcyanation of benzaldehyde, when benzoyl chloride is used as a trapping reagent[260b] (eq 10). The optically active benzoylated cyanohydrin complex was obtained in 40% enantiomeric excess.



eq 10

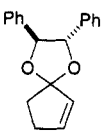
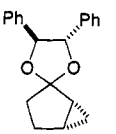
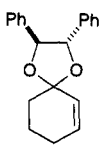
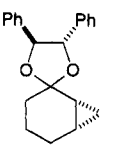
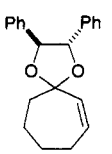
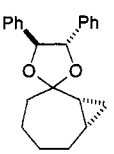
In addition, 1:1 adducts of (*S,S,S,S*)-TP18C6 with ammonia–borane mediate the enantioselective reduction of prochiral aromatic ketones[260a,b] (Table 56).

Table 56. Asymmetric Reduction of Aryl Ketones Mediated by (*S,S,S,S*)-TP18C6[260a,b]

Substrate	Product	Yield (%)	% ee
		71	67
		73	64

3.3.2.5. Chiral Ligands for Asymmetric Cyclopropanation. Enantiopure ketals formed with stilbene diol mediate the diastereoselective cyclopropanation of a proximate olefinic bond[258b] (Table 57). Previous work in this area had utilized ketals prepared from 1,4-di-*O*-benzyl-L-threitol and the diastereoselectivities typically ranged from 7:1 to 9:1.[271] However, the diastereomers produced were neither chromatographically separable nor crystalline, which precluded the isolation of enantiomerically pure cyclopropyl ketones.

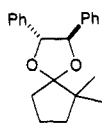
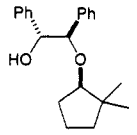
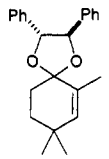
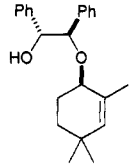
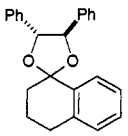
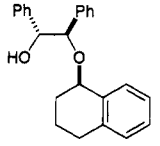
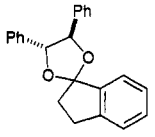
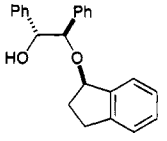
Table 57. Diastereoselective Cyclopropanation of Enantiomerically Pure Ene Ketals[258b]

Ene ketal	Major Product	Yield	Crude Diastereomer Ratio	mp, °C after recryst.
		66%	13 : 1	106-108
		90%	19 : 1	141-142
		77%	15 : 1	62-65

In contrast, good to excellent levels of diastereoselectivity were observed in the Simmons–Smith cyclopropanation reactions with ene ketals, formed by dehydrative ketalization of the corresponding enones with (*S*,*S*)-(−)-hydrobenzoin.[258b] In each case reported in Table 57, the mixtures of diastereomeric ketals were recrystallized from anhydrous ether to give the major diastereomer as a pure compound. Removal of the ketal (2.7 M aqueous HCl in MeOH) provided a route to enantiomerically pure cyclopropyl ketones.[258b]

3.3.2.6. Miscellaneous Applications. (*R*,*R*)-(+)-Hydrobenzoin derived ketals of cyclic ketones undergo highly diastereoselective reductions to enantiomerically pure secondary alcohols (Table 58).

Table 58. Diastereoselective Reduction of Enantiopure Ketals[272]

Ketal	Major Diastereomer	Diastereomeric Excess	Yield
		>98%	83%
		>98%	86%
		>97%	86%
		>98%	82%

Ketals of several cyclic ketones were prepared and then reduced under standard conditions (i.e. 6 equiv of DIBAL-H, CH_2Cl_2, 0 °C). Excellent levels of diastereoselectivity and good yields were observed in all cases.[272]

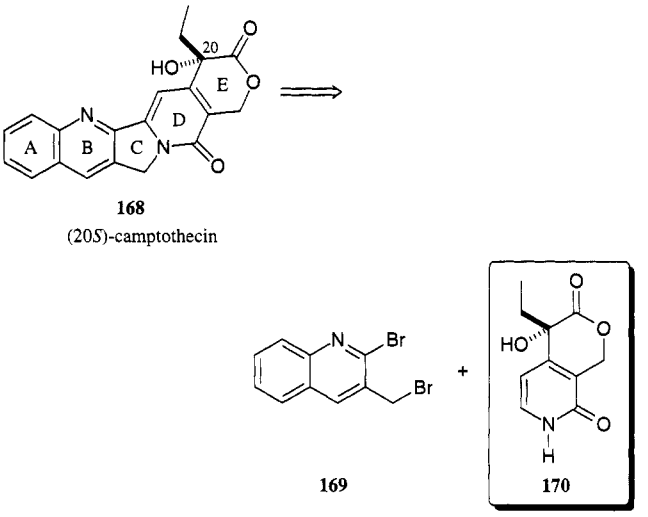
3.3.2.7. Summary. The preceding sections highlight the growing utility of enantiomerically pure C_2-symmetric diols and their derivatives as chiral ligands and auxiliaries in asymmetric reactions. Enantiopure hydrobenzoin and its derivatives have so far dominated these studies. This may be the result of several factors. First, it is commercially available. Second, it may be readily prepared in high enantiomeric excess[273] by asymmetric dihydroxylation of *trans*-stilbene, which to date is the best substrate for the AD reaction. Third, it can be released by hydrogenolysis, a crucial advantage for substrates containing acid-sensitive functionality.

In principle, however, any C_2-symmetric diol may be prepared by asymmetric dihydroxylation of the appropriate *trans*-olefin. In many instances the diols are crystalline, thereby offering a chance for optical enrichment by recrystallization. In addition, any number of diol derivatives (including C_2-symmetric diamines) may be prepared via the appropriate manipulations described in previous sections, thus suggesting many ligand possibilities for use in future asymmetric reactions.

4. Recent Applications: A Case Study

(20*S*)-Camptothecin (**168**) is a pentacyclic alkaloid that was first isolated in 1966[274] and is currently one of the most important anticancer lead compounds discovered by screening natural products. In spite of the large number of synthetic analogs that have been prepared showing improved efficacy as potential cancer treatments,[275] efficient synthetic routes to the biologically active (20*S*)-camptothecin are fairly limited.[276] Recently, Comins reported a highly convergent 10-step asymmetric synthesis of this target which utilizes the DE fragment **170** as the key chiral intermediate[277] (Scheme 83). Preparation of this intermediate, however, required stoichiometric amounts of (−)-8-phenylmenthol, an expensive chiral auxiliary. Given this potential obstacle, two research groups have recently investigated the possibility of introducing chirality in the DE fragment using the asymmetric dihydroxylation. Their work is summarized here.

Scheme 83. Retrosynthetic Analysis of (20*S*)-Camptothecin



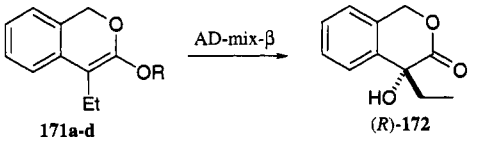
168
(20*S*)-camptothecin

169 **170**

With the goal of preparing optically active α-hydroxy lactones for use in a camptothecin synthesis, Curran gained key insights through model studies on closely related systems.[278] This effort identified three classes of alkenes: endocyclic ketene acetals, endocyclic enol ethers, and exocyclic α,β-unsaturated lactones, all of which were new classes of olefins for the AD reaction, while at the same time offering potentially attractive routes for an asymmetric synthesis of the DE fragment.

Data obtained from the asymmetric dihydroxylation of ketene acetal derivatives are presented in Table 59. Oxidation of **171a** and **171b** by the standard procedure with commercially available AD-mix-β was slow, but acceptable rates were obtained

Table 59. The Asymmetric Dihydroxylation of Endocyclic Ketene Acetals[278]

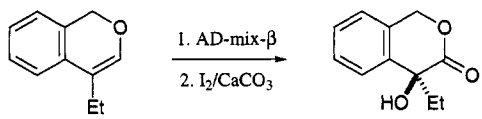


171a-d (*R*)-172

Substrate	R	(*R*)-172, ee	Yield
171a	TBDMS	40%	70%
171b	TIPS	30%	67%
171c	COPh	65%	82%
171d	$CO(CH_3)_3$	78%	100%

by increasing the concentration of Os and ligand to 0.5 and 2.5 mol %, respectively. Although the yields (67−70%) and ee's (30−40%) for these substrates were disappointing, improvements in both yield and ee were realized on moving to enol ester derivatives. Dihydroxylation of **171c** gave the desired α-hydroxy ketone in 82% yield and 65% ee, and enol pivalate **171d** gave the desired product in quantitative yield and 78% ee. However, for preparation of a DE ring fragment with the correct absolute configuration, dihydroxylations with this class of substrates would have to be carried out using AD-mix-α, which generally gives lower ee's than AD-mix-β.

For this reason, the AD reactions of endocyclic enol ethers were investigated. A marked improvement in enantioselectivity was anticipated since this would require use of the more selective dihydroquinidine ligands and enantioselectivities with trisubstituted olefins are generally better than those obtained with their tetrasubstituted counterparts. Dihydroxylation experiments carried out on **173** using the fortified AD-mix-β provided the crystalline hydroxylactol which was immediately oxidized ($I_2/CaCO_3$). The desired 7(*S*)-hydroxy lactone, possessing the correct absolute configuration for the synthesis of (20*S*)-camptothecin was obtained in 90% yield and 74% ee.[279]



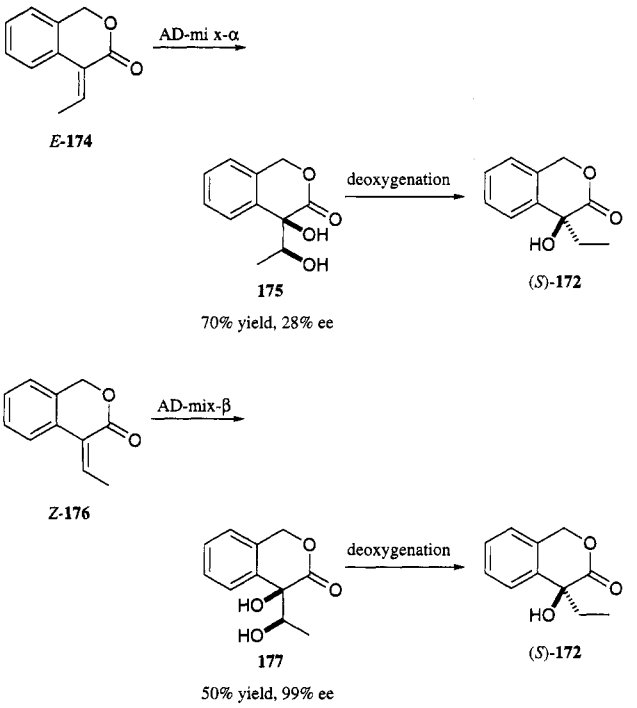
173 (*S*)-172 74% ee, 90% yield eq 11

(AD-mix-α, (*R*)-172, 63% ee, 89% yield)

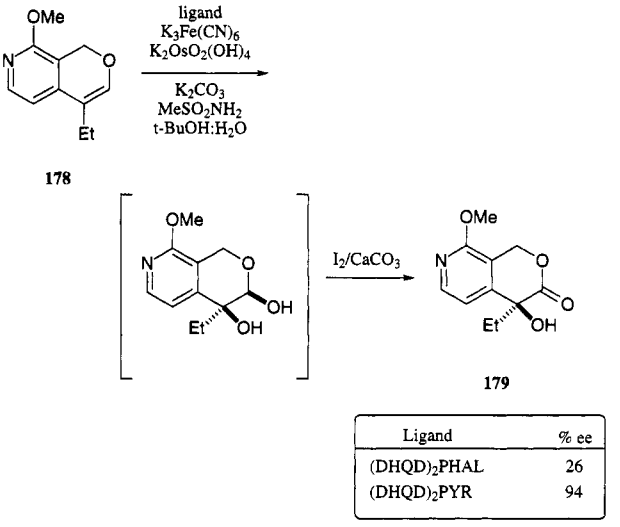
The other substrates investigated by Curran were the exocyclic alkenes **174** and **176** (Scheme 84). This approach is attractive since conjugated alkenes often give good results in the AD, however, extra synthetic steps are now required to remove the unwanted hydroxyl group. While the results with *E*-**174** were disappointing, dihydroxylation of *Z*-**176** with AD-mix-α provided the diol with the desired 7(*S*) configuration in 50% yield and 99% ee. It was subsequently found, however, that deoxygenation of the diol was not straightforward.

Independently, a group at Glaxo was also investigating an AD route to a chiral DE ring fragment.[280] Their investigations focused on the asymmetric dihydroxylation of enol ether **178**. When **178** was dihydroxylated under standard conditions with

Scheme 84. Asymmetric Dihydroxylation of Exocyclic α,β-Unsaturated Lactones[278]



Scheme 85. Asymmetric Dihydroxylation Route to the (20*S*)-Camptothecin DE Ring Fragment



Ligand	% ee
$(DHQD)_2PHAL$	26
$(DHQD)_2PYR$	94

$(DHQD)_2PHAL$ (i.e. AD-mix-β) followed by oxidation, the hydroxylactone (*S*)-**179** was obtained in 26% ee[281] (Scheme 85). When the same reaction was carried out using $(DHQD)_2$-PYR the same (*S*)-hydroxy lactone was produced in 94% ee! Even more impressive, conversion of (*S*)-**179** to the corresponding pyridone (*S*)-**170** was carried out by refluxing in 1 N hydrochloride acid after which crystalline enantiomerically pure (>95% ee) (*S*)-**170** was collected by filtration of the reaction mixture.

This AD route to (*S*)-**179** developed by Fang at Glaxo is the one used to prepare a camptothecin analog which is now in phase II clinical trials. As such, it appears to be the best example of the AD in a practical application. This camptothecin story also underscores another important trend in the AD's development, which is that the PYR ligands are an important complement to the PHAL ligands. While

the PHAL ligands are certainly the best for *typical trans*-disubstituted, trisubstituted, and many tetrasubstituted, as well as 1,1-disubstituted olefins, the PYR ligands exhibit dramatic improvements for special cases in each of these classes. In fact, at the time of this writing, the most interesting AD results coming in from groups around the world are those which define the differences between the PHAL and PYR ligands.

Extensive structural and mechanistic studies have led to a good understanding of the nature of the binding pocket in the PHAL ligands[26,27] (cf. section 1, Figure 3). A similar campaign is now underway to map out the more spacious binding pocket of the PYR ligands.

5. Conclusion

The stoichiometric osmylation of olefins as perfected by Criegee in the 1930s is generally regarded as the most reliable synthetic transformation available to organic chemists. The reasons are simple: OsO_4 reacts with *all* olefins, and it reacts *only* with olefins. Admittedly, the "all" and "only" in this latter statement are used with some poetic license; however, no other known organic reaction comes close to achieving such enormous scope coupled with such great selectivity.

Of course even a very reliable reaction will see little use unless it provides a needed synthetic transformation. The stereospecific *cis*-dihydroxylation of olefins achieved by OsO_4 is one of the most valued transformations for introducing functionality into organic molecules. The olefinic functional group is ubiquitous in organic synthesis because it is easy to introduce, and because it is stable to the acid/base catalysis generally employed to construct carbon skeletons. Then, at just the right moment in a synthetic sequence, the olefin's presence is dramatically revealed by oxidative 1,2-addition of heteroatoms. The ability to emplace heteroatoms in this otherwise difficult to achieve[282] 1,2-relationship is another crucial reason why so many organic syntheses employ one or more olefin oxidation steps.

With most olefins, the AD also provides the nearly quantitative yield of diol one has come to expect in catalytic osmylations through experience with the Upjohn Process.[14] [The latter process is renowned for effecting "spot-to-spot" transformations yielding pure diol without chromatography.] These high yields taken together with the enormous scope documented for the AD in this review make it easy to predict that henceforth olefins will be seeing more of OsO_4 than ever before.

Regarding enantioselectivity and especially, scope, the AD system is unique among selective man-made catalysts. Two factors in particular are believed to contribute to the AD's success: (1) it is the first highly effective nonenzymic catalyst depending on noncovalent binding for rate acceleration and selectivity,[26,27] and (2) it is the most dramatic example to date of "ligand accelerated catalysis" (a term we coined while studying the phenomenon in this system[18]). The importance of the LAC phenomenon in asymmetric catalysis is the subject of a recent review.[8d] The newer observation of "noncovalent" binding effects seems to offer exciting prospects for designing even better AD ligands as well as selective catalysts for other transformations.

Table 60. Comparison of the AD with Enzymatic Catalysts[a]

catalyst	turnover (min^{-1})
chymotrypsin	6000
asymmetric dihydroxylation	*3000*
DNA polymerase	900
tryptophan synthetase	120
lysozyme	30

[a] AD value from the reaction of 2-vinylnaphthalene with $(DHQD)_2PHAL$ in the original NMO system (acetone/water (10:1), room temperature). Enzyme values from ref 284.

The putative binding pocket/cleft for which there is strong evidence[26] with the PHAL ligands (Figure 3) is, of course, reminiscent of the ubiquitous, noncovalent binding phenomena in enzymatic catalysis. Since organic chemistry still trails its vitalistic origins, many will feel comfortable calling such binding "enzyme-like". However, while these AD catalysts share some properties with enzymatic catalysts, they have the distinctly nonenzymatic attribute of combining high selectivity with enormous substrate scope, as well as the ability to produce either enantiomer at will. Such features make these catalysts powerful tools, both for planning and for executing asymmetric syntheses of chiral organic molecules.

The ligand acceleration phenomenon can support extremely efficient catalysis. For the AD of 2-vinylnaphthalene in the homogeneous acetone/water system using NMO and $(DHQD)_2PHAL$, a turnover number of 3000/min at 25 °C has been determined.[283] This value is comparable to the turnover number of many enzymes (Table 60). The turnover number in the AD is often limited by the rate of hydrolysis of the intermediate osmate ester. The rate of formation of the osmate ester from 2-vinylnaphthalene, OsO_4, and $(DHQD)_2PHAL$ in *tert*-butyl alcohol has been shown to be extremely rapid ($k_c = 35600\ M^{-1}\ min^{-1}$),[26] and a turnover number much higher than the measured 3000/min would be possible if the hydrolysis step were not rate limiting. From a process research perspective, one of the most important remaining challenges for improving the AD is to find yet better ways to increase the rate of osmate ester hydrolysis and thereby increase catalytic efficiency.

Finally, the discovery of a "binding pocket" in the PHAL and PYR ligands anticipates limitations in substrate scope. Such limitations have indeed been found with the parent ligands.[36] New ligands with tighter binding pockets are now being synthesized to see if we can add back to our catalysts some of the substrate-restriction/recognition features seen with enzymes. These studies are more aimed at testing hypotheses about the mechanism and the binding pocket than at producing new ligands with tailored "lock-and-key" properties. After all, from a synthetic chemist's viewpoint, the most attractive feature of man-made selective catalysts is their great scope.

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Appendix

The following is a list of all the publications from the Sharpless group relating to osmium-catalyzed oxidations of olefins, including all the asymmetric dihydroxylation publications beginning with the Hentges paper in 1980. It is hoped that access to the titles will facilitate location of specific topics of interest.

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Asymmetric Dihydroxylation—Discovery, Development, and Substrate Scope

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(63) The procedure for the recovery and recycling of the ligand has been developed by Dr. Yun Gao of Sepracor for the large-scale AD of *m*-chlorostyrene (personal communication).
(64) Recipe for the preparation of 1 kg of AD-mix-α or AD-mix-β: Potassium osmate $[K_2OsO_2(OH)_4]$ (1.04 g) and $(DHQ)_2PHAL$ (for AD-mix-α) or $(DHQD)_2PHAL$ (for AD-mix-β) (5.52 g) were ground together to give a fine powder, then added to powdered $K_3Fe(CN)_6$ (699.6 g) and powdered K_2CO_3 (293.9 g), and finally mixed thoroughly in a blender for ca. 30 min. The resulting orange powder should be kept dry and is ready to use.
(65) The 1.4 g of AD-mix, needed for the AD of 1 mmol of olefin, contains the following amounts of reagents: 1.46 mg (0.004 mmol) of $K_2OsO_2(OH)_4$, 7.73 mg (0.01 mmol) of $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$, 980 mg (3 mmol) of $K_3Fe(CN)_6$, and 411 mg (3 mmol) of K_2CO_3.
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(109) The relative rate can be calculated by use of the following equation:

$$k_{rel} = \ln(1 - C)(1 - ee)/\ln(1 - C)(1 + ee)$$

This is an adaptation of an equation first presented by Kagan[110] where C is the percent conversion/100 and ee is the percent enantiomeric excess/100. This equation may also be used to calculate the percent conversion necessary to achieve a desired enantiomeric excess by substituting into the equation the desired ee and the ratio of rate constants (i.e., k_{rel} or k_f/k_s). Knowledge of any two of the reaction variables allows calculation of the third.

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