Chapter 6: Olefin Dihydroxylation

6.1 Introduction

The dihydroxylation reaction of alkenes and OsO₄ is one of the most powerful transformations in asymmetric synthesis. A large number of electronically and sterically diverse alkenes are converted to the corresponding diols under mild, neutral conditions. The reaction has long been known to be highly stereospecific allowing for the formation of either class of 1,2-syn or 1,2-anti diols as exclusive function of the starting alkene diastereomer. The dihydroxylation reaction with OsO₄ also displays exceptional functional group chemoselectivity and generally considered to be compatible with most other functional groups. While OsO₄ readily reacts with olefins at ambient temperatures in a wide range of solvents, it leaves aromatic rings, amines, carbonyls, acetals, amides, and diols undisturbed. Additionally, in many cases it is possible to effect the selective dihydroxylation of an olefin in the presence of others on the basis of subtle steric and electronic differences. It is not surprising that the reaction enjoys wide applications in a myriad of synthetic strategies.

The use of stereoselective dihydroxylation reaction of OsO₄ had been appreciated in the early synthetic strategies toward complex molecules. Thus, while exceptions to the facial selectivity have appeared, the introduction of diols on the least hindered face of multiply-fused ring systems with accessible convex surfaces and inaccessible concave surfaces played an important role in the synthesis of many natural products. Detailed understanding and exploitation of acyclic stereocontrol allowed the diastereoselective dihydroxylation reaction to be extended to non-cyclic structures. Some of the earliest studies on acyclic stereocontrolling elements were documented by Kishi who elegantly demonstrated that allylic alkoxy groups could exert considerable stereocontrol in conformationally flexible systems.

Recent exciting developments in enantioselective, catalytic olefin dihydroxylation allow simple, inexpensive alkenes to be transformed to high value-added diols that serve as useful, versatile building blocks for asymmetric synthesis. Unlike most other catalytic, asymmetric reactions for organic synthesis, these processes can be conducted reliably with low catalytic loading (<1 mol %) without special precautions against the exclusion of moisture or oxygen.

In a complex molecular synthesis, information regarding the relative rates of alkene dihydroxylation as a function of substitution can be important in the design of a synthetic strategy. As the table in the aside shows, the rates of olefin dihydroxylation by OsO₄ increase monotonically with increasing alkene substitution; additionally, and alkenes substituted with electron donors will can react in preference to otherwise unsubstituted alkene or an alkene that is substituted with an inductively electron withdrawing moiety. The effects of steric and electronics on olefin dihydroxylation in the context of natural product synthesis are illustrated by two examples shown below. The selective dihydroxylation and cleavage reaction of 1 was reported by Meinwald in a synthesis of muzigadia (3). The substrate for dihydroxylation includes three different substituted alkenes, a 1,1-disubstituted alkene along with two trisubstituted olefins. Only the electron rich vinyl ether is observed to undergo reaction to give the decalone product.

<table>
<thead>
<tr>
<th>Olefin</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-undecene</td>
<td>1.0</td>
</tr>
<tr>
<td>2-methyl-1-tridecene</td>
<td>1.3</td>
</tr>
<tr>
<td>Z-5-decene</td>
<td>2.0</td>
</tr>
<tr>
<td>E-5-decene</td>
<td>4.2</td>
</tr>
<tr>
<td>citronellyl benzoate</td>
<td>4.7</td>
</tr>
<tr>
<td>2, 3-dimethyl-2-octene</td>
<td>23</td>
</tr>
</tbody>
</table>

Relative Rates of Dihydroxylation with OsO₄.
A second example of a selective osmylation comes from the synthesis of avermectin by Danishefsky and co-workers. The terminal olefin in 4 was observed to undergo dihydroxylation to the exclusion of reaction at the trisubstituted alkene. In this case, the inductive electron withdrawing character of the allylic silyloxy ether renders is sufficient to render it substantially less reactive than the homoallylic monosubstituted olefin. Thus, the relatively subtle inductive electronic effect of an electron-withdrawing allylic ether can override the known reactivity patterns of alkenes in which increasing substitution leads to enhanced reaction rates. Despite these generalizations, caution is warranted when predicting selectivities in complex systems with potentially competing olefins because various combinations of steric, electronic, stereo-electronic, and even directing effects can play a role in controlling selectivity. Moreover, in the presence of ligands for Os, a reversal of selectivity has been observed.

The utility of the vicinal diol products of olefin dihydroxylation reactions is quite broad and has been the subject of reviews. In an effort to further expand and develop applications of vicinal diols, Sharpless has examined a variety of methods for their conversion to epoxides as well as the activation of such diols such that their chemistry parallels many of the known reactions of the more commonly employed epoxides. In this regard, the conversion of diol 11 into a cyclic sulfate 13 through a two step sequence of reactions renders the system susceptible to nucleophilic attack.

### X.2.1 Diastereoselective Dihydroxylation

Substrate controlled diastereoselective dihydroxylation is an important tool in complex molecule assembly. The presence of an allylic, homoallylic or even bis-homoallylic stereocenter can substantially influence the facial selectivity in the approach of dihydroxylation reagent onto the olefin face. A large collection of empirical data coupled with detailed analyses have resulted in a number of predictive models for
diastereoselectivity in alkene dihydroxylation, despite the considerable controversy concerning the details of the mechanism, especially in regard to a [3+2] or [2+2] mechanism (see aside).\textsuperscript{6,7,8,9} Three general models have gained prominence as they have been invoked commonly to account for diastereoselectivity in olefin dihydroxylation.

All three models have been proposed as a means of accounting for the large body of empirical data that is now available concerning diastereoselective alkene dihydroxylation. The predictive value is derived by inference, and it is well worth considering that they offer a general, simplified rationalization for a reaction that is notorious for its mechanistic complexity. As a simplification, the models do not consider the effect of a putative a alkene•Os complex or the relative rates of diastereomeric pi-complexes in the step that leads to dihydroxylation. Moreover, it is also possible that such complexes are in equilibrium with a metallooxetane intermediate that results from formal [2+2] cycloaddition. The reversibility of such a cycloaddition and the potential for such product to rearrange to the osmate ester further complicate any analysis. It is not surprising, therefore, that exceptions to the predictive models are numerous.

X.2.3 Acyclic Stereocontrol

In the design of a synthesis plan incorporating a diastereoselective dihydroxylation reaction where a high degree of predictibility is desired it is helpful to rely on closely related literature precedence. In this regard, a myriad of examples are now available for consultation on the diastereoselective alkene dihydroxylation reaction. Following a series of pioneering investigations of diastereoselective alkene dihydroxylation, Kishi devised a series of empirical rules for predicting the stereochemical outcome of reactions of olefins with OsO$_4$. The Kishi empirical rule predicts that the diol diastereomer will be preferentially formed that results from OsO$_4$ attack at the olefin face opposite to the allylic alkoxy or hydroxy group in a conformer that minimizes unfavorable non-bonded 1,2- and 1,3-allylic interactions. From the cases examined the major end-product is that with 1,2- \textit{anti} arrangement between the newly formed stereocenter and the pre-existing alkoxy or hydroxy center. Kishi compiled a helpful set of illustrative examples that are summarized below, as these demonstrate the scope, consistency and predictability of the dihydroxylation reaction.\textsuperscript{10}
A few of the structural details that remarkably influence the degree of stereoselection are worth underscoring. First, allylic hydroxy or alkoxy substituents exert a stronger influence than non-heteroatom substituents. This, of course, suggests that an electronic effect may be operative in influencing stereoselectivity. Thus, both allylic alcohols and ethers elicit high levels of stereofacial differentiation; however, in certain instances the corresponding acetate esters lead to near complete loss of stereoselectivity (compare 25 and 28). A second feature of the dihydroxylation reaction worth considering is the fact that in contrast to alkene epoxidation, the osmylation reagent does not typically form hydrogen bonds and therefore does not respond to hydroxyl directing effects (vide infra). The fact that both alcohols and ethers give comparable diastereoselectivity is consistent with the lack of hydrogen-bonding effects. Third, as is always observed in reaction of acyclic substrates where stereocontrol is dictated by minimization of allylic non-bonded interactions, cis-olefins are typically more selective than the trans counterpart. In some instances, it has been noted that the use of stoichiometric amounts of OsO₄ often results in higher selectivity (15%) than the corresponding reactions employing catalytic OsO₄ (0.05 eq OsO₄, 2 eq N-methylmorpholine-N-oxide).

The dihydroxylation of α,β-unsaturated esters and ketones is an often used transformation in complex molecule synthesis. In this regard, a series of elegant methodological studies by Stork has revealed that the dihydroxylation of γ-hydroxy enoates can be highly stereoselective.¹¹ Thus, dihydroxylation of 31 afforded triol 32 as the sole product. To account for the observed stereochemical outcome, a transition state model (17) was proposed involving a conformer wherein the hydroxyl group is nearly coplanar with the olefin with subsequent attack of the Os-reagent occurring at the enoate face that is most sterically accessible. The selection of this conformer for this olefin class is based on the supposition that the
energetically favored arrangement for the system is one in which the electron withdrawing substituent is positioned orthogonally to the π-system in a manner that precludes hyperconjugation with the electron deficient enoate. In such a conformer the more electron rich allylic σ_{C-C} can effectively interact with the low-lying enoate π* orbitals.¹²

![chemical structure](image)

The stereochemical outcome of the dihydroxylation reaction of the complementary Z-enoate is revealing. Dihydroxylation of 34 yields triols 35 and 36 in 7 : 1 diastereomeric ratio with complete reversal of diastereoselectivity compared to 31. The fact that the relative configuration of the β-hydroxyl moiety is opposite to that observed with 31 suggests that allylic A₁,₃ interactions override any intrinsic stereoelectronic effects.

![chemical structure](image)

The dihydroxylation of electron deficient alkenes has been extended to dienoates (37).¹³ Thus when the 37 is treated with OsO₄ under catalytic conditions lactol 38 is formed to the exclusion of epimeric lactone 39. The preference for dihydroxylation to take place at the double bond most distant from the electron-withdrawing C=O group appears to be quite general and has been observed in enantioselective, catalytic dihydroxylation reactions. This reaction has found application in the synthesis of verrucosidin (X).

![chemical structure](image)

Evans has examined the dihydroxylation of 1,1-disubstituted olefins of 40, 43, 46 in a study aimed at the synthesis of cytovaricin (49).¹⁴ Consistent with the Kishi empirical model, the 1,2-anti diastereomer is isolated as the major product from the reaction. Interestingly, an increase in the steric of the protecting group on the allylic silyloxy ether led to an unexpected erosion in the diastereofacial selectivity.

![chemical structure](image)
The observed stereochemical outcome in the dihydroxylation of 40, 43, 46 has been rationalized by considering steric interactions in a conformer model that positions the hydroxyl group in the inside position of 50. Minimization of A_{1,2}-allylic interactions as indicated in 50 reveals the more stable ground-state conformer. Dihydroxylation is proposed to take place from the least hindered olefin face opposite the larger group (R_L in 50). The trend towards diminished selectivities as the protecting group on the hydroxyl increases in size consequently results from its increased ability to shield the otherwise more accessible olefin face opposite R_L.

![Diagram](attachment:image.png)

The validity of this model was further tested in a series of experiments which examined the effect on the product diastereoselectivity as a function of the size of the allylic substituent R_L. The postulated model is further validated by the stereochemical trend observed with 54 and 55, wherein the diastereoselectivity improved from 5:1 to 17:1 (R_L = Et versus R_L = iPr).

![Diagram](attachment:image.png)

**X.2.4 Exocyclic Olefins**

Vedejs has carried out a series of elegant mechanistic studies with conformationally locked exocyclic cycloalkenes with the aim of factoring out and identifying any stereoelectronic preferences in the dihydroxylation reaction. It was observed that the dihydroxylation reaction of axial and equatorial substituted cyclohexylidine systems exhibit divergent stereochemical outcomes. For example, the cyclohexane with a locked equatorial methoxy group 66 shows good selectivity for equatorial dihydroxylation product 68 while, in contrast, the diastereomer with an axial methoxy substitution 78 displays clear preference for axial attack.
The stereochemical patterns observed above are not easily explained by the basis of steric effects. Analysis of the kinetics of the reactions reveal that substitution with an axial alkoxy group as in 78 retards the rate of dihydroxylation by two order of magnitude when compared to the substrate possessing equatorial alkoxy substitution 67. The observation of trans di-axial dihydroxylation products 72, 75, 78, and 81 apparently results from the fact that axial dihydroxylation is affected to a lesser extent than equatorial attack by the electronic effect. Substrates 84 and 87 were designed and examined to probe whether the suppressed rate of equatorial attack may be due solely to steric influences. When 84 was allowed to react with OsO4 similar stereochemical results were observed as with as with 66. However, stereoselectivity in the dihydroxylation of the diastereomeric spirocycle 87 considerably erodes to 1:1. Thus the observed selectivities cannot be easily accounted by models based on steric or electronic effects alone as it is clear that a combination of these factors are operating. These results underscore the perilous nature of crafting generalize stereochemical models for the olefin dihydroxylation reaction wherein a subtle interplay of steric and stereo electronic effects must be dealt with in addition to the less well-understood and studied effects at the metal center.

X.2.5 Endocyclic Olefins

In general, the dihydroxylation of cyclic, allylic hydroxy alkene derivatives follows the general stereochemical guidelines outlined for acyclic olefins, giving products formed from addition of OsO4 anti to the existing allylic substituent. For example, each of the olefins 90, 91 or 92 experienced osmylation from the convex face to afford products consistent with the empirical predictive model of Kishi.
Predicting the stereochemistry of dihydroxylation of endocyclic olefins of bicyclic substrates can in general, with some notable exceptions, be relatively straightforward. The reaction of vinyl ether 6 is an example of a stereoselective dihydroxylation wherein the olefin diastereofaces are differentiated by the bridgehead methyl group. In general, dihydroxylation stereochemistry is consistent with a steric approach model with reaction occurring from the convex face of the bicycle, as illustrated by olefins 96, 97 and 98.

The reactions of 102 and 105 were examined by Smith in a study aimed at the total synthesis of xanthocidin (x). They illustrate the effect of competing steric demands in a highly hindered system and the complementary stereochemical results that can be obtained by variation of the size of adjacent allylic ethers. The dihydroxylation of 102 provided not the exo-isomer 104 as would be expected by comparison to the trend observed with the above examples 96-98. In this instance approach of the reagent from the concave olefin face is more facile than the alternate approach from the side syn to the allylic isopropyl. Post facto, it seems resonable that the effective size of the isopropyl group is accentuated as a consequence of the vinyl methyl substituent. Thus, minimization of $A_{1,2}$ Me $\leftrightarrow ^3$Pr and 1,5-syn pentane interactions leads to positioning of the isopropyl nearly orthogonal to the C=C plane with one of the isopropyl methyl groups shielding the convex olefin face. Increasing the steric environment of the concave face by the introduction of a trimethylsilyl ether leads to reversal of stereochemistry to provide exclusively 106.
X.2.6 Other effects: Putatively Directed Dihydroxylations

A generally accepted feature of the dihydroxylation reaction has been its insensitivity to hydroxyl directing effects by either coordination or hydrogen-bonding. There has been lack of definitive data to support mechanisms involving the synergistic participation of alkoxy or hydroxyl groups; in most cases, a simpler steric model adequately accounts for the stereochemical results. The osmylation of geraniol provides a test of the potential participation by an allylic group in influencing the course of regioselectivity in a dihydroxylation reaction. Based on the principles discussed earlier, it is not at all surprising that functionalization takes places predominately at the more electron-rich trisubstituted olefin to afford the 1,6-diols 109, 112, 115 and 118. The observed improvement in chemoselectivity upon protection of the allylic hydroxyl group as an ether or ester is suggestive of a hydroxyl mediated hydrogen-bonding effect exerting some influence. The dihydroxylation of allylic tosyl amide represents an interesting case wherein the reaction of 117 with OsO₄ leads to considerable erosion in the chemoselectivity of the dihydroxylation reaction. These observations have led to the suggestion that weak hydrogen bonding effects exist, that are incapable of overriding the inherent electronic preference for dihydroxylation of the more electron rich substituted olefin.

Although the above results seem to suggest that any directing effect would be of dubious utility for synthetic applications, there have been some intriguing observations recently. Donohoe has reported a stoichiometric dihydroxylation reagent that responds to hydrogen-bonding directing effects from a suitably disposed proximal hydroxyl group. The complexation of OsO₄ with tetramethylethylenediamine (TMEDA) leads to a reagent giving a 25:1 preference for the formation of 122 in the dihydroxylation of 120. Thus, the regiochemical outcome of dihydroxylation by the OsO₄•TMEDA complex is complementary to the more traditional dihydroxylations, providing products with stereochemistry consistent with a hydroxyl directed mechanism.
As summarized in Table 1, the apparent directing influence of an allylic hydroxyl group appears to be a general phenomenon for OsO₄•TMEDA mediated dihydroxylations. Dihydroxylation of allylic cyclohexenols with OsO₄ under stoichiometric or catalytic conditions (NMO) provides the expected anti-dihydroxylation products (Entries 1, 2, 4, and 5), a result consistent with other cyclic substrates (c.f., 93-95). In sharp contrast, the use of OsO₄•TMEDA reagent affords the syn-triols (Entry 3) in >24:1 diastereomeric ratio.

The ability of TMEDA to influence the regioselectivity of osmylations is consistent with an observation that had been noted in earlier studies wherein presence of tertiary amines led to an increase in the relative amount of diol adduct proximal to Bronsted-acidic functional groups. In this regard, catalytic osmylations employing trimethylamine-N-oxide as reoxidant furnish triethylamine as a co-product and display a tendency to form syn products in non-hydrogen bonding solvents (Entries 2 and 5). Moreover, it is important to note that catalytic osmylations that rely on reoxidants free of amine by-products often display the same levels of regioselectivity as stoichiometric OsO₄.

Table 1. Comparison of OsO₄•TMEDA with other oxidizing conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Conditions</th>
<th>Syn-syn</th>
<th>Syn-anti</th>
<th>Ratio syn : anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>A</td>
<td></td>
<td></td>
<td>1 : 6</td>
</tr>
<tr>
<td>2</td>
<td>tBu</td>
<td>B</td>
<td></td>
<td></td>
<td>1 : 2</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td>24 : 1</td>
</tr>
<tr>
<td>4</td>
<td>OH</td>
<td>A</td>
<td></td>
<td></td>
<td>1 : 15</td>
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<tr>
<td>5</td>
<td>tBu</td>
<td>B</td>
<td></td>
<td></td>
<td>1 : 3</td>
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<tr>
<td>6</td>
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<td>HN₂CCl₃</td>
<td>A</td>
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<td>1 : 1.5</td>
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<td>8</td>
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<td>B</td>
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<td></td>
<td>nr</td>
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<tr>
<td>9</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td>&gt;20 : 1</td>
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<tr>
<td>10</td>
<td>HN₂CCl₃</td>
<td>A</td>
<td></td>
<td></td>
<td>1 : 3</td>
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<td>11</td>
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<td></td>
<td>5 : 1</td>
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</table>
In addition to allylic alcohols, substrates possessing allylic amides have been examined (entries 7-13). The trichloroimidates displayed a preference for dihydroxylation syn to the existing amide moiety, consistent with the posited hypothesis that the use of stoichiometric OsO₄•TMEDA complex responds to hydrogen bonding effects.\(^{22}\)

A number of select examples of dihydroxylation reactions displaying anomalous regioselectivities have been documented. Of these, the dihydroxylation of alkene-sulfoxide \(123\) is particularly striking. Reaction of \(123\) with OsO₄ affords \(125\) in \(>20\) to 1 diastereoselectivity with a preference for the anti diastereomer predicted by the Kishi model. It is important to note that in addition to reaction at the olefin, oxidation of the sulfoxide to the sulfone has also occurred. Interestingly, however, the epimeric sulfoxide \(124\) leads to the formation of the other diastereomeric sulfone diol. The results imply that olefin dihydroxylation is faster than the sulfoxide to sulfone oxidation and, importantly, that the sulfoxide has a directing influence that overrides any steric or stereoelectronic effect imparted by the allylic amide.\(^{23}\) This example constitutes a rare illustration of a stereoselective dihydroxylation directed by a remote \(\delta\)-functional group.

X.3 Reagent-Controlled Dihydroxylation: Stoichiometric and Catalytic Reactions

In the early investigations of OsO₄ by Criegee, it was noted that the presence of amine additives leads to substantial acceleration of the reaction of OsO₄ with olefins. Consequently, a number of groups have developed a variety of chiral diamine ligands for the stoichiometric, asymmetric dihydroxylation of olefins. Various levels of success have been observed as illustrated by the dihydroxylation of trans-stilbene with the ligands of Snyder (\(124\), 69% ee),\(^{24}\) Murahashi (\(128\), 73% ee),\(^{25}\) Yamada and Narasaka (\(129\), 90% ee),\(^{26}\) Corey (\(130\), 92% ee),\(^{27}\) Tomioka (\(131\), 95% ee, 97% ee),\(^{28,29}\) Fuji (\(132\), 98% ee),\(^{30}\) Hanessian (\(133\, 99\%\) ee),\(^{31}\) and Hirama (\(134\, >99\%\) ee).\(^{32}\) Of these reagents, that of Corey (\(130\)) has enjoyed wide application in diastereoselective synthesis due to its straightforward preparation and effective stereocontrol. This has been elegantly demonstrated in synthetic studies by Fuchs directed at the total synthesis of the cephalostatin family of pyrrole alkaloids.\(^{33}\) Introduction of the C-25 hydroxyl was achieved by the dihydroxylation reaction of the terminal olefin \(135\). The usual catalytic conditions with AD-mix-\(\alpha\) provided the desired isomer as the minor
component of 2:1 diastereomeric mixture.\textsuperscript{34} However, the use of 130\textcdot OsO\textsubscript{4} afforded the desired stereoisomer as a 4:1 mixture of diastereomers.

The use of bidentate diamine ligands with OsO\textsubscript{4} precludes the execution of the reaction with catalytic quantities of the reagent, as the diamine glycolate adducts resist re-oxidation and hydrolysis. In the absence of strongly coordinating chelating ligands, however, reoxidation of the osmium glycolates formed upon olefin dihydroxylation is rapid. Sharpless noted several unique characteristics of tertiary amines as ligands for Os: they bind reversibly to the metal center, and importantly elicit the same ligand accelerating effect as other amines. The use of chiral tertiary amines in a ligand-accelerated, catalytic process that furnishes optically active diols has been pioneered by Sharpless, leading to a remarkably successful reaction that constitutes one of the gold-standards of asymmetric catalysis.
The catalytic asymmetric dihydroxylation of olefins by OsO₄ and optically active tertiary amine ligands has become one of the most important asymmetric transformations for organic synthesis. In the first reports of a catalytic enantioselective dihydroxylation reaction, Sharpless documented a process for the enantioselective olefin dihydroxylation utilizing OsO₄, chinchona ligands, and stoichiometric N-methylmorpholine N-oxide (NMO). Under these conditions, optically active diols could be isolated in 80-90 % ee. The optical purity of the product glycolate products isolated from catalytic osmylations employing chinchona alkaloids was found to be slightly inferior the stoichiometric version. Subsequent mechanistic investigations that ensued revealed the origins of the stereochemical erosion in the catalytic process. In a mechanistic tour-de-force the operation of a second dihydroxylation process was identified. In this competing process the product Os-glycolate complex undergoes competitive reoxidation and participates in subsequent dihydroxylation reactions in competition with the Os•alkaloid complex. The development of a process that leads to the rapid breakdown of this intermediate was identified as critical to optimization of the enantioselectivities. In this regard, the use of aqueous potassium ferricyanide in the reaction instead of NMO circumvents the undesired pathway by accelerating the rate at which the glycolate complex undergoes hydrolytic cleavage. Further studies of the ligand structure and its effect on the product stereoselectivities afforded remarkable improvements in enantioinduction. At its current level of development, the asymmetric dihydroxylation reaction of Sharpless is one the most general and reliable enantioselective, catalytic reactions in synthetic chemistry. The rates, efficiency, and scope of the process rivals that of enzymatic catalysts. A number of excellent reviews have appeared which are indispensable in providing comprehensive summaries of the scope, utility, and applications of the catalytic asymmetric dihydroxylation.

An exceptional aspect of the asymmetric dihydroxylation is that it performs extraordinarily well with nearly all olefin classes. As a consequence of its generality, a standard recipe for the preparation of a stock mixture of OsO₄, ligand, and ferricyanide oxidant has been identified and is commercially available or easily prepared in the laboratory. The standard stock solution contains all the necessary components, including stoichiometric oxidant (typically three equivalents of K₃Fe(CN)₆), base (K₂CO₃), catalytic ligand (1 mol %) and catalytic osmium (0.4 mol %, as non-volatile K₂OsO₂(OH)₄). For most olefins, both enantiomeric diols are available by employing one of two chiral ligands: the bis-dihydroquinidine ether of phthalazine, (DHQD)₂PHAL and the bis-dihydroquinine ether (DHQ)₂PHAL. Although these ligands do not bear an enantiomeric relationship, they have been referred as pseudoenantiomeric as they provide complementary enantioselectivities.
The asymmetric dihydroxylation reaction is best performed under heterogeneous conditions or in a solvent consisting of a 1:1 mixture of water and tert-butyl alcohol. For example, all possible olefins from monosubstituted through tetrasubstituted provide chiral diols with typically >97% enantiomeric excess, with the exception of cis-disubstituted olefins which furnish adducts in 80% ee. In addition to unfunctionalized olefins, both electron rich and electron poor alkenes react with high levels of asymmetric induction, as summarized in Table 2. Ketone-derived alkyl or silyl enol ethers (Entry 1) are excellent substrates, providing alpha-hydroxy ketones upon work-up. This method offers a particularly effective means for the preparation of this ketone class with alternative strategies relying on stoichiometric chiral reagents or auxiliaries. Electron deficient olefins, such as alpha,beta-unsaturated esters and amides require increased loading of osmium to 1 mol % from the usual 0.4 mol % for reproducibly high selectivities and convenient rates. The reaction of divinyl ketone (Entry 6) illustrates the highly selective nature of the catalyst. The reaction delivers the mono-dihydroxylated ketone in excellent % ee and useful yield. The dihydroxylation of conjugated olefins provides a high-yielding route to diolalkenes because the olefin diol that results from the first dihydroxylation is sufficiently electronically differentiated from the starting material that formation of the tetraol from bis-dihydroxylation is minimized. As discussed earlier, it is typically the case that dihydroxylation conditions employing stoichiometric OsO₄ or catalytic variations with amine N-oxides as reoxidant leads to competitive rapid oxidation of sulfides or sulfoxides to the corresponding sulfones. However, a remarkable characteristic of the Sharpless dihydroxylation process is its chemoselectivity; thus in contrast to OsO₄/NMO with the catalytic process an olefin undergoes preferential oxidation leaving the sulfide intact. An additional interesting feature of the catalyzed reactions is the fact that the relative reactivity of substituted alkenes is different from the trends observed with OsO₄ alone. Thus, with the cinchona alkaloid based ligand (DHQD)₂PHAL trisubstituted olefins is by far most reactive. The reactivity data should find enormous use in the planning and execution of complex molecule syntheses.

Table 2. The scope of the OsO₄ catalyzed asymmetric dihydroxylation of olefins.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Olefin</th>
<th>Conditions</th>
<th>Product</th>
<th>ee</th>
</tr>
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<tr>
<td>1</td>
<td><img src="image1.png" alt="Molecule" /></td>
<td>A</td>
<td><img src="image2.png" alt="Molecule" /></td>
<td>93%</td>
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Despite the remarkable efficiency and selectivity of the dihydroxylation reaction, two alkene classes have been until recently recalcitrant to give diols in high enantioselectivities: cis alkenes and monosubstituted alkenes. New ligand classes are being continually developed that allow these substrates to participate in the reaction with increasing enantioselectivity. An intriguing approach has been developed for monosubstituted alkenes by Corey. In the model Corey has formulated, a [3+2] cycloaddition reaction occurs between olefin and the OsO₄•L complex within a hydrophobic pocket of the metal-ligand complex with a marked preference for aromatic groups. This lead to the investigation of terminal alkenes possessing an allylic 4-methoxybenzoate ester or phenolic ether as substrates for the catalytic dihydroxylation reaction. These substrates undergo dihydroxylation successfully to furnish adducts in high levels of enantioselectivity. Moreover, in addition to the successful dihydroxylation of protected parent allyl alcohols, the Corey modification expands the scope of the asymmetric dihydroxylation to include a wide range of 1,1-disubstituted, trans-1,2-disubstituted, and cyclic allylic alcohols in >97% ee.

X.5 Applications to Natural Product Synthesis
The mildness, selectivity and efficiency of the dihydroxylation reaction invites its use in the preparation of a myriad of structures. Its application can be found in numerous natural product synthesis as well as in the preparation of novel ligands and auxiliaries for other useful processes. For example, Hoffman’s crotylation reagent \(139\) is a powerful, enantioselective allylation reagent possessing many of the ideal properties of a reagent controlled process. A convenient, kilogram scale preparation of hydrobenzoin from the dihydroxylation of stilbene\(^{43}\) followed by aromatic ring reduction\(^{44}\) provides for an expeditious synthesis of this auxiliary.

![Chemical structures](image)

Figure 1. zaragozic acid C (AD-mixes – Carreira),\(^{45}\) zaragozic acid A (AD-mix-β – Nicolaou),\(^{46}\) Cytoblastin (OsO\(_4\)•TMEDA – Kishi),\(^{47}\) \((-)\)-hikizimycin (cat. OsO\(_4\), chiral amine, NMO – Schreiber).\(^{48}\)

Conclusion. The diastereoselective and enantioselective olefin dihydroxylation reaction is a powerful transformation for organic synthesis. It provides rapid entry into highly functionalized, chiral substrates that function ideally as building blocks for asymmetric synthesis. As a consequence of its wide substrate scope, the experimental efficiency, practicality, and reliability of the reaction it stands as one of the gold-standards of asymmetric catalysis. By any measure it possesses characteristics that are only matched by few other reactions.

References

5. For a review of cyclic sulfates, see: Lohray, B. B. Synthesis 1992, 1035-1052.


34 Based on comparison to slightly different substrates, the use of AD-mix-\( \alpha \) presents a diastereomeric matched case, i.e., the use of AD-mix-\( \beta \) would presumably provide considerably more of the undesired diastereomer.
41 Catalytic asymmetric dihydroxylation results with: allyl benzyl ether (61% ee and 91%),42 allyl triisopropylsilyl ether (3% ee and 98%)42 and 5-methoxyphenyl ether (90% ee, Wang, Z. -M.; Zhang, X. –L.; Sharpless, K. B. Tetrahedron Lett. 1993, 34, 2267-2270).