

CHAPTER 1

THE ALLYLIC TRIHALOACETIMIDATE REARRANGEMENT

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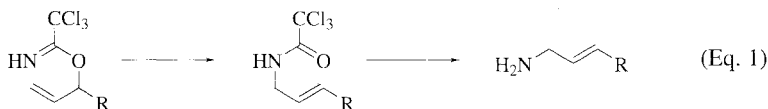
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INTRODUCTION

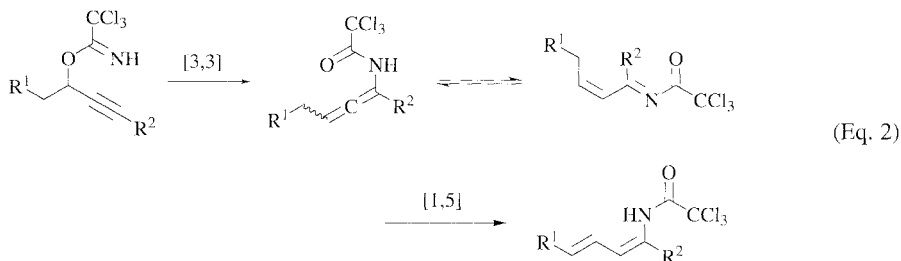
Sigmatropic rearrangements of allylic systems have found wide application in organic synthesis, with carbon-carbon bond forming rearrangements such as the Cope and Claisen rearrangements being particularly well known. The sigmatropic rearrangement of allylic imidates (also known as the "aza-Claisen" or "Claisen-imidate" rearrangement) offers a valuable entry into the preparation of protected allylic amines. Conversion of an imidate to the amide is essentially irreversible, with the transformation of the imidate to the amide being exothermic by about 15 kcal/mol.^{1,2} Since the discovery of the thermal allylic imidate rearrangement in 1937,³ a number of systems have been investigated for the practical preparation of allylic amines by this route, including urethanes, isourethanes, formimidates, benzimidates, isoureas and carbonimidothioates. However, it was the discovery and development of the rearrangement of allylic trichloroacetimidates that overwhelmingly demonstrated the widespread utility of this synthetic method (Eq. 1).⁴⁻⁶



The [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates (now generally referred to as the Overman rearrangement) or trifluoroacetimidates can be conveniently carried out either thermally or with Hg(II) or Pd(II) catalysis. The scope of the rearrangement is such that primary, secondary, and tertiary allylic amides are readily accessible, thus providing entry into a wide variety of nitrogen-containing products including amino sugars, nucleotides, amino acids, peptides, and various nitrogen heterocycles. In addition, the Overman rearrangement has found extensive application in the total synthesis of natural products. The recent development of chiral Pd(II) catalysts to promote asymmetric allylic trichloroacetimidate rearrangements with good enantioselectivity bodes well for the continued broad application of this amine synthesis.⁷⁻⁹

This chapter is limited to the discussion of allylic trichloro- and trifluoroacetimidate rearrangements. Several relevant reviews have appeared regarding the allylic imidate rearrangement,¹⁰ the use of allylic imidates in organic synthesis,¹¹ Hg(II)- and Pd(II)-catalyzed [3,3]-sigmatropic rearrangements,¹² enantioselective rearrangement of allylic imidates,^{13,14} and the preparation of allylic amines.¹⁵ Trichloroacetimidates of propargylic alcohols also undergo thermal [3,3]-sigmatropic rearrangement, giving *N*-acylamino-1,3-dienes as a result of tautomerization of the

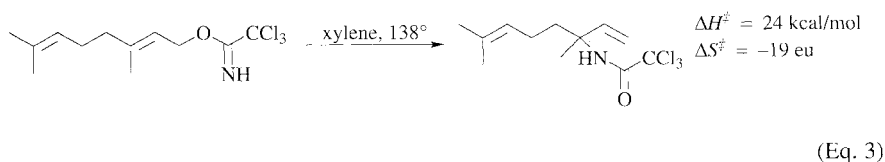
initially formed allenyl trichloroacetamide (Eq. 2).¹⁶ This more limited transformation is not reviewed in this chapter.



MECHANISM

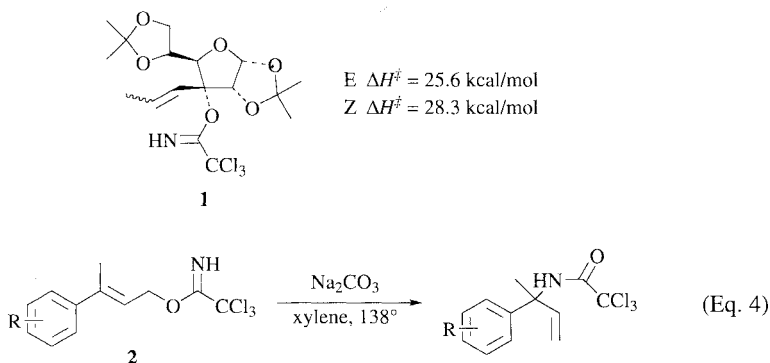
Thermal Rearrangements

The concerted nature of the allylic trichloroacetimidate rearrangement has been established by examination of thermodynamic parameters, solvent effects, regioselection, and stereoselection. Activation parameters for the thermal rearrangement of the trichloroacetimidate of geraniol (Eq. 3) are consistent with a [3,3]-sigmatropic rearrangement, with the large negative change in entropy being similar to that observed for Cope and Claisen rearrangements.⁶ An intermediate is not detected, even in cases where a highly delocalized allylic carbocation would result from the ionization of the trichloroacetimidate, as in the rearrangement of the trichloroacetimidate of cinnamyl alcohol.⁶ The observed regiochemical outcome of the allylic trihaloacetimidate rearrangement also lends support to the representation of this transformation as an essentially concerted process. For allylic trichloroacetimidates, the thermal rearrangement occurs with complete allylic oxygen-to-nitrogen transfer; the product arising from ionization and recombination, formal [1,3]-rearrangement, is rarely observed.¹⁷ As discussed in more detail shortly, solvent and substituent effects support the development of some charge separation in the transition state.

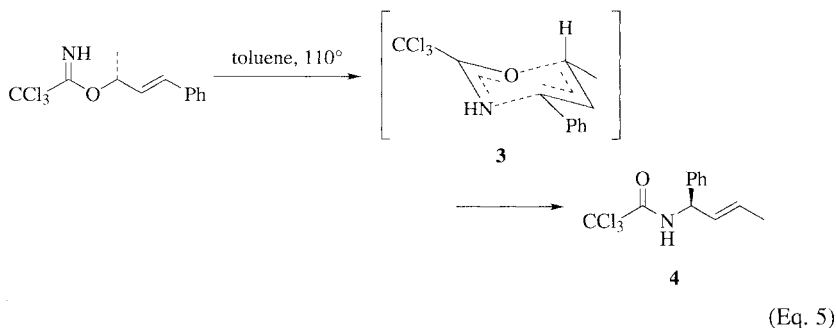


The thermal allylic trihaloacetimidate rearrangement follows first-order kinetics,^{6,18} with an assortment of steric and electronic substituent effects influencing the rate of the reaction. Alkenes having E double bonds tend to react more quickly than Z alkenes, a difference embodied in the ΔH^\ddagger -term for reaction of the E and Z isomers of imide 1.¹⁸ The rearrangement is facile for a wide variety of allylic alcohols, with doubly allylic alcohols reacting at room temperature, tertiary alcohols generally reacting at 80° ($t_{1/2} \sim 1$ hour), and primary alcohols reacting the least quickly ($t_{1/2} \sim 1$ hour at 140°).⁶ These reactivity trends are attributed to stabilization of posi-

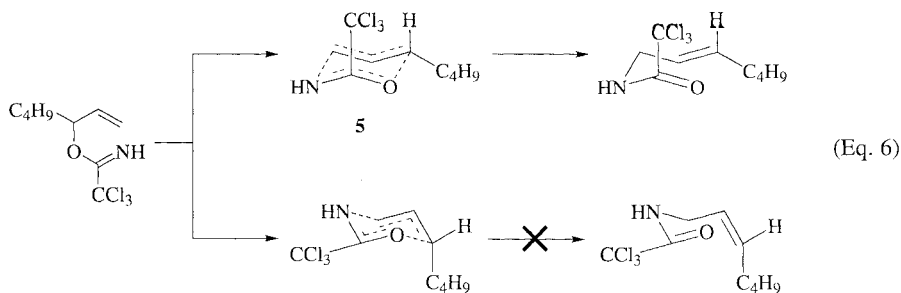
tive charge developed on the oxygen-bearing carbon in the transition state.⁶ A five-fold rate enhancement is observed in changing the solvent from xylenes to nitrobenzene in the rearrangement of the trichloroacetimidate of geraniol at 132°. This finding is consistent with the postulated charge development in the transition state, that is, partial negative charge on the electronegative $\text{HN}=\text{C}(\text{CCl}_3)\text{O}$ fragment and partial positive charge on the all-carbon allyl fragment.⁶ One observation is not readily rationalized by this model: the apparent increase in rate seen when para electron-withdrawing substituents are present in the rearrangement of cinnamyl substrates **2** shown in Eq. 4.¹⁹



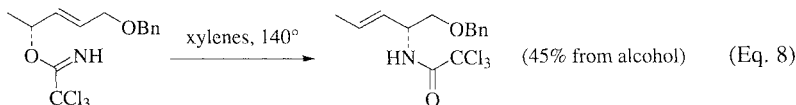
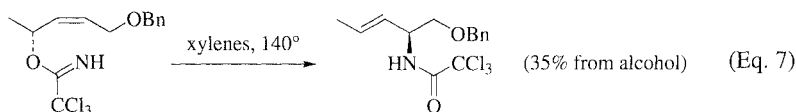
The excellent stereoselectivity of the allylic trihaloacetimidate rearrangement is typical of suprafacial [3,3]-sigmatropic processes, as complete transfer of chirality is a hallmark of this reaction. Thus, the trichloroacetimidate of (*R,E*)-4-phenyl-3-buten-2-ol rearranges to give the (*R,E*)-trichloroacetamide **4** with no loss of enantiomeric purity, an outcome which can be rationalized as arising from the preferred chair-like transition structure **3** (Eq. 5).²⁰



High selectivity for forming the *E* stereoisomer of the product is seen in rearrangements of virtually all trihaloacetimidates of secondary allylic alcohols, including trisubstituted allylic alcohols such as 4-methyl-3-penten-2-ol,^{6,21-23,81} and *E* and *Z* disubstituted allylic alcohols.²⁴⁻²⁶ For example, rearrangement of the trichloroacetimidate of 1-hepten-3-ol proceeds to give a 92% yield of the *E* isomer by transition state structure **5** having the *n*-butyl group in the preferred equatorial position (Eq. 6).⁶



As a result of the suprafacial nature of the rearrangement and the chair-like topography, either enantiomer of an E allylic amine can be prepared from the appropriate enantiomer of the starting allylic alcohol or from a configurationally related pair of alkene stereoisomers. An example of the latter strategy is shown in Eqs. 7 and 8.²⁴



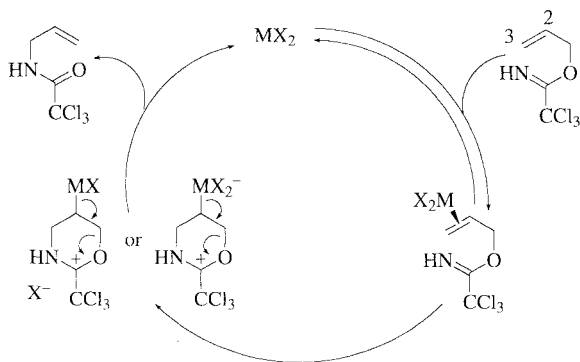
The allylic trichloroacetimidate rearrangement has not been the subject of *ab initio* or DFT theoretical studies. Early MNDO-PM3 semi-empirical molecular orbital calculations of the rearrangement of the trichloroacetimidate of allyl alcohol suggest an ion pair reaction pathway.¹⁸ In this study, an ion pair transition state is calculated to have an enthalpy of formation of 11 kcal/mol, more than 9 kcal/mol lower than the calculated enthalpy of formation for the transition state of the [3,3]-sigmatropic pathway. Nevertheless, experimental evidence is fully consistent with a concerted sigmatropic rearrangement pathway.

Metal-Catalyzed Rearrangements

The rearrangement of allylic trihaloacetimidates can also be induced by using metal catalysts, thus lowering the temperature required for rearrangement and sometimes leading to higher yields, cleaner reactions and/or better stereocontrol. Many allylic trichloroacetimidates, ranging from simple allylic trichloroacetimidates to highly functionalized substrates, rearrange rapidly in the presence of Pd(II) or Hg(II) catalysts. Although the first reports employed $\text{Hg}(\text{O}_2\text{CCF}_3)_2$,⁴ soluble complexes

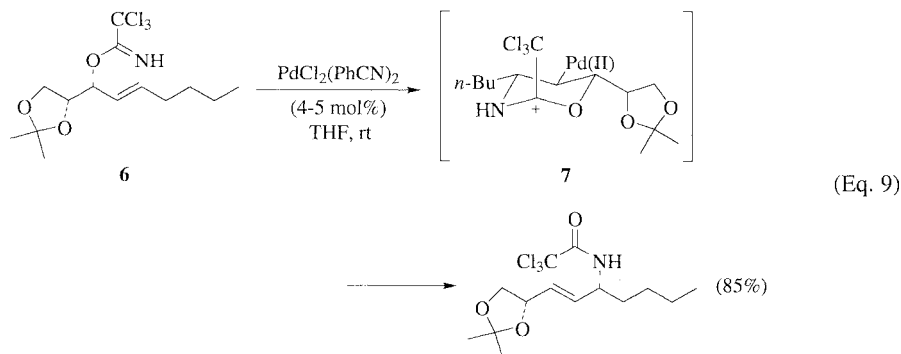
of PdCl_2 emerged as the most useful metal catalysts.²⁷⁻³¹ Rate accelerations are large (10^{12} is estimated for 1 M $\text{Hg}(\text{O}_2\text{CCF}_3)_2$),⁴ allowing many $\text{Pd}(\text{II})$ - and $\text{Hg}(\text{II})$ -catalyzed trichloroacetimidate rearrangements to be carried out at room temperature.

A cyclization-induced rearrangement mechanism in which the metal coordinates to the allylic double bond to bring about antarafacial intramolecular nucleophilic attack by the imidate nitrogen is believed to be involved in $\text{Pd}(\text{II})$ - or $\text{Hg}(\text{II})$ -catalyzed rearrangements (see Scheme 1).^{4,12,32} This mechanism is closely related to the mechanism originally proposed by Henry^{33,34} for $\text{Pd}(\text{II})$ -catalyzed allylic acetate rearrangements and subsequently by Overman for PdCl_2 -catalyzed Cope rearrangements.³⁵

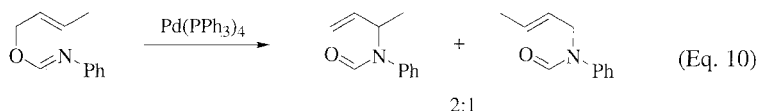


Scheme 1

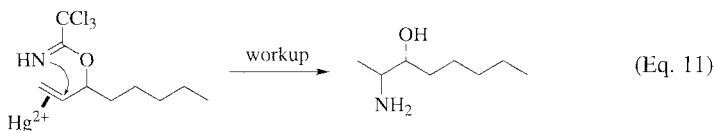
A cyclization-induced rearrangement mechanism rationalizes the complete 1,3 oxygen-to-nitrogen transfer that is observed in $\text{Hg}(\text{II})$ - and $\text{Pd}(\text{II})$ -catalyzed rearrangements such as depicted in Eq. 9.²⁸ In contrast, rearrangements of allylic *N*-phenylformimidates and *N*-phenylbenzimidates catalyzed by $\text{Pd}(0)$ complexes provide mixtures of products resulting from formal [1,3]- and [3,3]-sigmatropic



rearrangements that undoubtedly involve the formation of Pd- π -allyl intermediates (Eq. 10).³⁶

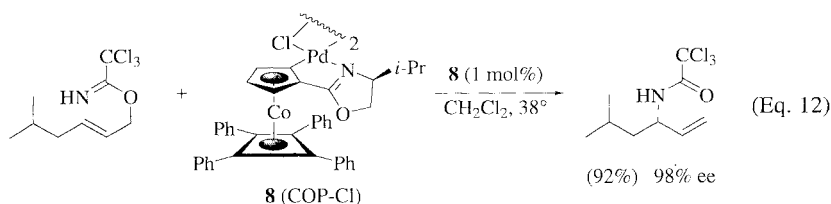


Reactivity trends also support the cyclization-induced rearrangement mechanism for metal-catalyzed allylic trichloroacetimidate rearrangements. For example, substitution at the internal carbon of the allyl double bond (C2) slows the rate of the Pd(II)-catalyzed rearrangement, presumably as a result of the difficulty of generating a tertiary carbon-palladium sigma bond.³² The limited scope of the Hg(II)-catalyzed process also provides support for a cyclization-induced rearrangement mechanism. Allylic substrates in which alkene substitution does not strongly favor intramolecular nucleophilic attack by the imino nitrogen at the allyl terminus (C3) fail to rearrange or rearrange in low yields under Hg(II) catalysis. Thus, for trichloroacetimidates containing terminal vinyl units, the 2-amino alcohol can be obtained after basic hydrolysis (Eq. 11).⁴ This latter limitation is also seen in Pd(II)-catalyzed rearrangements as no reports exist of successful catalyzed rearrangements of allylic imidates containing terminal vinyl units.



The suprafacial nature and high E stereoselectivity of Pd(II)-catalyzed rearrangements also implicate a cyclization-induced mechanism. Collapse of the most stable chair conformation of intermediate **7** of Eq. 9 predicts the observed stereochemical outcome, just as in corresponding thermal rearrangements. For example, palladium-catalyzed rearrangement of dioxolane **6** gives the trichloroacetamide product with exclusive E geometry and complete transfer of chirality (Eq. 9).²⁸

Given the direct involvement of the metal, the potential exists for asymmetric induction by a chiral metal complex in the rearrangement of prochiral allylic imidates. Not surprisingly, the development of suitable chiral metal catalysts has been a focus of intensive recent research in this area. Early results suggest that allylic trichloroacetimidates are generally unsuitable substrates for palladium-catalyzed asymmetric rearrangements, either resulting in poor yields, poor stereoselectivity or both.³⁷⁻³⁹ However, recent reports demonstrate that di- μ -chlorobis[(η^5 -(S)-(*p*-R)-2-(2'-(4'-isopropyl)oxazoliny)cyclopentadienyl)-1-C, 3'-N)]-(η^4 -tetraphenylcyclobutadiene)-cobalt[dipalladium (**8**, COP-Cl) and related Pd(II) complexes are excellent catalysts for asymmetric rearrangements of E allylic trichloroacetimidates and N-aryl trifluoroacetimidates, e.g., Eq. 12.⁷⁻⁹



SCOPE AND LIMITATIONS

Preparation and Stability of Allylic Trihaloacetimidates

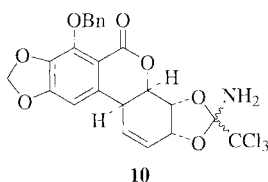
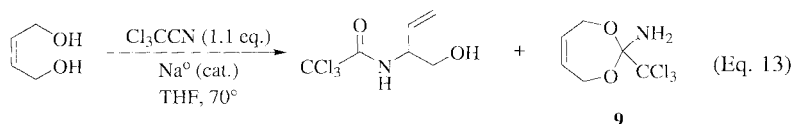
Preparation of Allylic Trichloroacetimidates. The ease of preparation of trichloroacetimidates is a major reason for the broad synthetic utility of the allylic trichloroacetimidate rearrangement. The Pinner synthesis of imidates, wherein an alcohol is condensed with a nitrile in the presence of one or more equivalents of a strong mineral acid, is not suitable for preparing allylic imidates because ionization to the allylic cation and subsequent Ritter reaction typically occurs.¹¹ However, allylic trihaloacetimidates can be prepared conveniently by a base-catalyzed method first presented by Cramer.^{40,41} Thus, addition of a mixture of the allylic alcohol and 5–20% of its alkoxide to an ether solution of trichloroacetonitrile at low temperature provides the trichloroacetimidate in isolated yields generally greater than 85%.^{4,6,42,43} Although many allylic trichloroacetimidates can be purified by silica gel chromatography or vacuum distillation, such purification is frequently bypassed as crude trichloroacetimidates commonly can be used directly in the subsequent rearrangement step.

A wide variety of bases can be used to generate the alkoxide, with alkali metal hydrides often selected.^{6,44–46} More recently, the addition of allylic alcohols to trichloroacetonitrile in dichloromethane or other aprotic solvents in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), employed either catalytically⁴⁷ or in excess,^{48–50} has been the method of choice for preparing allylic trichloroacetimidates. A direct comparison of potassium hydride to DBU in the preparation of aromatic trichloroacetimidates showed that catalytic DBU gave improved yields.⁵⁰

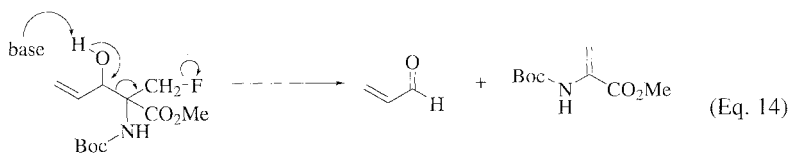
Limitations to the preparation of allylic trichloroacetimidates are rare. Primary allylic alcohols are converted readily to the corresponding trichloroacetimidates at or below room temperature. Although these conditions also succeed with many secondary and tertiary alcohols, some hindered alcohols require more forcing conditions. For example, the reaction of (*R,E*)-4-methylhexa-3,5-dien-2-ol with trichloroacetonitrile requires the addition of 18-crown-6 to the potassium hydride/alcohol mixture and long reaction times.⁵¹ The synthesis of trichloroacetimidate derivatives of cyclic tertiary alcohols, for example 1-vinylcyclopentanol and 1-vinylcyclohexanol, is reported to be problematic,⁵² however such imidates have been successfully prepared and rearranged.^{6,52–54}

An unusual obstruction to the preparation of the trihaloacetimidate is seen when a nucleophilic functional group is proximal to the alcohol. For example, attempted

formation of the monotrichloroacetimidate of *cis*-2-butene-1,4-diol by reaction with 1.1 equivalents of trichloroacetonitrile provides instead the dioxepin **9** in 84% yield (Eq. 13). Although heating **9** in *tert*-butylbenzene at 175–180° for 1.5 hours gives the desired rearrangement product in 80% yield,⁵⁵ rearrangement of such orthoamides is not always successful. For example, efforts to force the [3,3]-sigmatropic rearrangement of orthoamide **10** (formed in 85% yield from the precursor diol) failed to produce the product of allylic rearrangement.⁵⁶



The presence of fluoro functionality in the allylic alcohol can prevent successful formation of the trichloroacetimidate, although only in rare situations where the fluoro substituent is suitably positioned. For example, efforts to prepare the trichloroacetimidate of fluoro alcohol **11** led to either Grob fragmentation (Eq. 14) or no reaction.⁵⁷ Likewise, 1,1,1-trifluoro-2-phenylbut-3-en-2-ol failed to react with trichloroacetonitrile, presumably because of low nucleophilicity of the alkoxide.⁵⁸

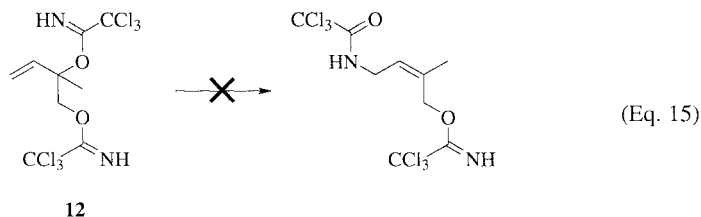


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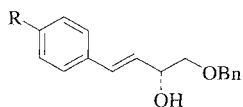
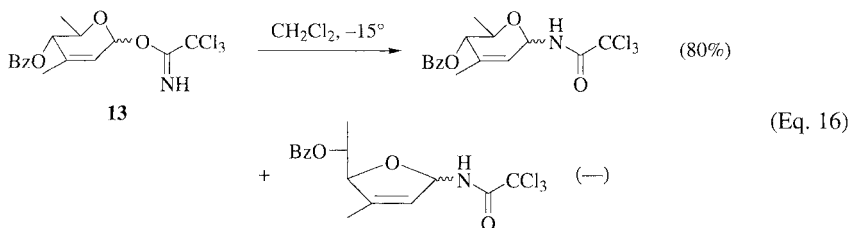
Preparation of Allylic Trifluoroacetimidates. The preparation of allylic trifluoroacetimidates is complicated by the fact that trifluoroacetonitrile is a gas at room temperature and pressure.¹ Initial procedures for preparing allylic trifluoroacetimidates involved deprotonation of a THF solution of the allylic alcohol with 20 mol% of *n*-butyllithium followed by addition of an excess of a freshly-prepared THF solution of trifluoroacetonitrile at –78°. ⁶⁰ More recently, a “one-pot” procedure was developed in which trifluoroacetonitrile is generated in situ by the reaction of trifluoroacetamide with oxalyl chloride, dimethyl sulfoxide, and triethylamine.⁶¹ A mixture of DBU and the allylic alcohol is then added to the crude trifluoroacetonitrile solution, providing the trifluoroacetimidates in good yields (54–92%).⁶²

¹ The trifluoroacetonitrile can be generated from trifluoroacetamide by dehydration with phosphorus pentoxide.⁵⁹

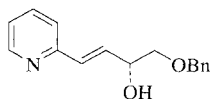
Stability of Allylic Trihaloacetimidates. Primary allylic trihaloacetimidates are quite robust. However, if the alcohol is more substituted, trihaloacetimidate derivatives become susceptible to acid-catalyzed ionization at elevated temperatures to form trihaloacetamide and, initially, the corresponding allylic cation. For example, the bis-trichloroacetimidate **12** failed to undergo rearrangement, with imidate cleavage taking place instead (Eq. 15).⁵² As will be discussed in more detail subsequently, addition of an acid scavenger such as potassium carbonate can minimize this decomposition pathway, allowing some rearrangements to take place that were previously unsuccessful.⁶³



The [1,3]-rearrangement product arising from dissociation-recombination is rarely observed, however such products are formed exclusively upon attempted Overman rearrangement of pyranoside **13** (Eq. 16).⁶⁴ The failed rearrangements of the trichloroacetimidates of aromatic allylic alcohols **14** and **15** are also attributed to the instability of the trichloroacetimidate,⁶⁵ although other cinnamyl substrates have been rearranged in high yields.^{20,65,66}



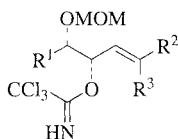
14 R = Me, MeO



15

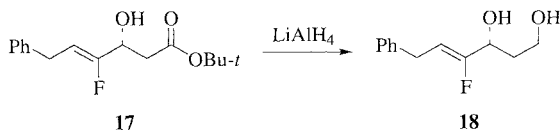
In some cases, the stability of the imidate can be enhanced by manipulation of the structural features of the allyl substrate. Thus, while trichloroacetimidate **16a**²¹ is unstable and fails to rearrange, replacement of the terminal methyl group (R^1) with a sterically more demanding phenyl or isopropyl group apparently enhances the imidate stability to a level that the rearrangement takes place in good yields

(60–98%).²¹ The tendency of the trichloroacetimidate of β -hydroxy ester **17** to eliminate to form a dienyl ester is overcome by reduction to diol **18** followed by formation of the bis-trichloroacetimidate and rearrangement to give the desired acetamide (Eq. 17).⁶⁷ However, such an alternative route generally appears not to be required. For example, the series of structurally similar alcohols **19** are converted to the corresponding trichloroacetimidates and rearrange without incident.²² Moreover, the rearrangement of the trichloroacetimidate derived from the unsaturated β -hydroxy ester **20** is reported to proceed in 100% yield.²³

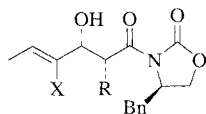
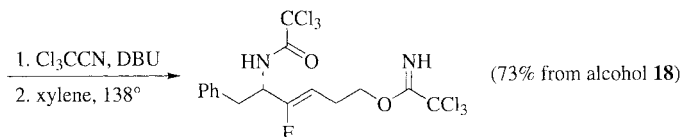
**16**

$R^1 = \text{Me (a), Ph, } i\text{-Pr}$

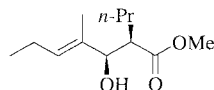
$R^2, R^3 = n\text{-Bu, Me, Ph, Et}$



(Eq. 17)

**19**

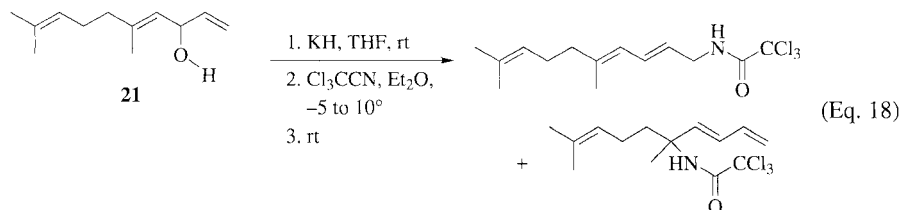
$X = \text{F, Cl, Me}$
 $R = \text{Me, } i\text{-Pr, Bn}$

**20**

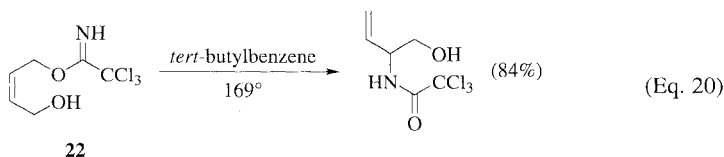
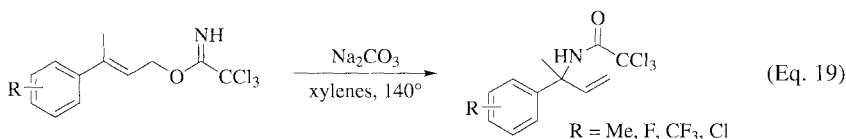
Thermal Rearrangements of Allylic Trihaloacetimidates

Reaction Conditions: Temperature, Solvent, and Additives. Thermal rearrangements of allylic trihaloacetimidates are carried out conveniently by dissolving the imidate in an aprotic solvent at ~ 0.1 M and heating the solution at reflux. Typically, trichloroacetimidates of primary allylic alcohols rearrange at $138\text{--}140^\circ$ (refluxing xylene) in the range of 4–24 hours. Trichloroacetimidates derived from secondary alcohols rearrange at lower temperatures (110° , refluxing toluene) or in shorter reaction times (often in 1–5 hours). Tertiary trichloroacetimidates typically rearrange within a few hours at 80° (refluxing benzene). As noted previously, rearrangements of trichloroacetimidates of doubly allylic alcohols take place at tem-

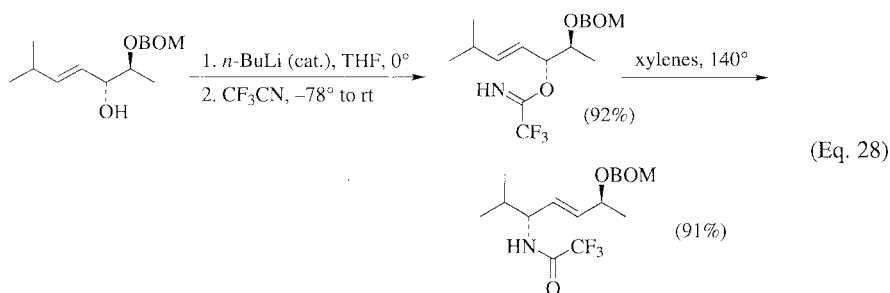
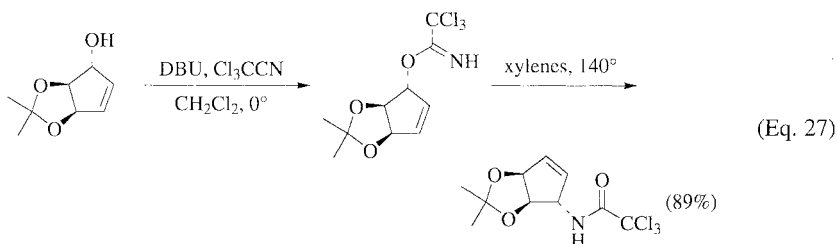
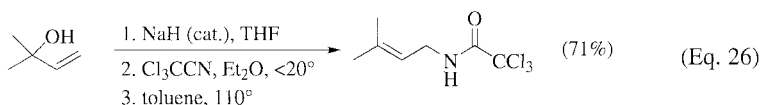
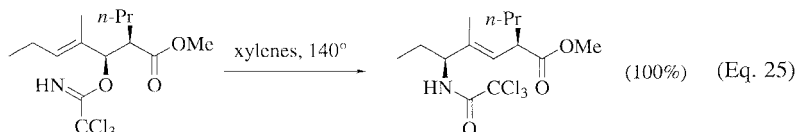
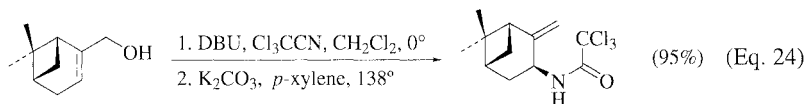
peratures at or below 0°. For example, the preparation of trichloroacetimidate **21** under normal conditions (addition of the alkoxide/alcohol mixture to trichloroacet-nitrile at -5° to 0°) yields the trienylamide rearrangement product directly (Eq. 18).⁶ In general, rearrangements of allylic trifluoroacetimidates are carried out under similar conditions (see later discussion).



Although allylic trichloroacetimidate rearrangements can be effected under solvent-free conditions by preadsorbing the alcohol onto KF-alumina, reacting this mixture with trichloroacetoneitrile, and then allowing the rearrangement to take place at room temperature,⁶⁸ the vast majority of thermal rearrangements are run in a solvent at reflux. Frequently the impact of the solvent is related to its reflux temperature. Thus, various cinnamyl trichloroacetimidates do not rearrange at a convenient rate in refluxing chloroform, toluene or THF, whereas refluxing xylenes give the rearrangement products in good to high yields (Eq. 19).¹⁹ Similarly, *tert*-butylbenzene (bp 169°) proved to be a convenient solvent for the rearrangement of imidate **22**; in refluxing xylene the reaction failed to go to completion in a convenient time span (Eq. 20).⁶⁹

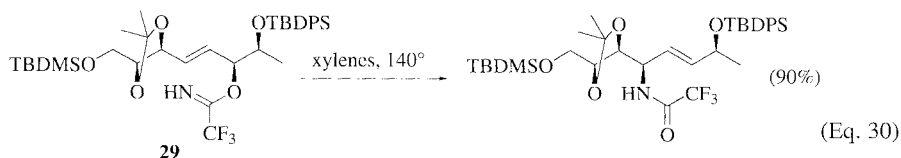
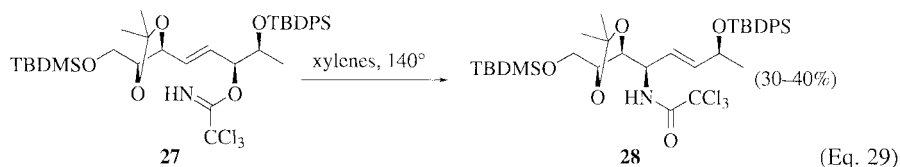


In some cases the polarity of the solvent appears to play an important role. For example, attempted rearrangement of dissaccharide trichloroacetimidate **23** in refluxing xylenes at 140° for 5.5 hours gives the allylic trichloroacetamide product in only a 27% yield, whereas switching to *N,N*-dimethylformamide (with the reaction run at essentially the same temperature) increases the yield to 80% (Eq. 21).⁷⁰ The increase in yield in this example likely reflects a faster rate of rearrangement in the

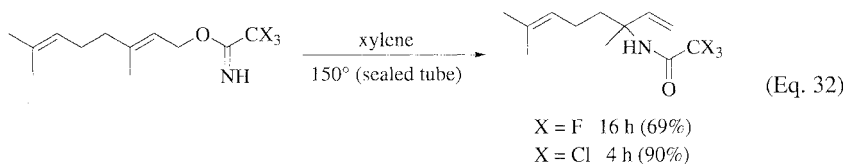
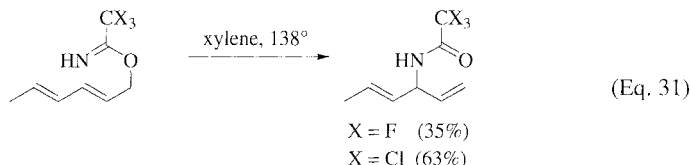


The Halogen Substituents. The halogen substituent on the imide plays an important role, not only in facilitating the synthesis of the rearrangement precursor, but also in increasing the rate of rearrangement. While thermal allylic rearrangements of several types of imides are known, the presence of the electron-withdrawing CCl_3 or CF_3 group on the imide leads to a more facile rearrangement. For example, formimides and benzimides require higher temperatures and/or longer reaction times than trihaloacetimidates to effect their allylic transposition.¹⁰

Trifluoroacetimidates in some cases rearrange slightly faster than the corresponding trichloroacetimidates. This rate enhancement, found to be approximately two-fold in one study,⁷⁵ can result in increased product yields. For example, the rearrangement of trichloroacetimidate **27** proceeds slowly in refluxing xylenes, with accompanying decomposition of the imidate under these conditions resulting in a poor yield of allylic trichloroacetamide **28** (Eq. 29). Switching to trifluoroacetimidate **29** results in doubling the yield of the allylic amide product (Eq. 30).⁷⁶



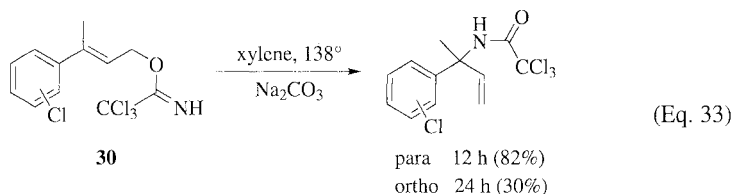
However, higher rearrangement yields are not universally observed when trifluoroacetimidates are employed. For example, rearrangement of the trifluoroacetimidate of 2,4-hexadien-1-ol proceeds under thermal conditions to provide the dienyl trifluoroacetamide in low yield (Eq. 31),⁶⁰ whereas thermal rearrangement of the trichloro analogue gives the analogous rearrangement product in 63% yield (73% in the presence of K_2CO_3).⁶³ In another recent study, several trifluoroacetimidates were found to rearrange more slowly and in lower yields than their trichloro congeners. Results obtained for the geranyl to linalyl conversion are shown in Eq. 32.⁶²



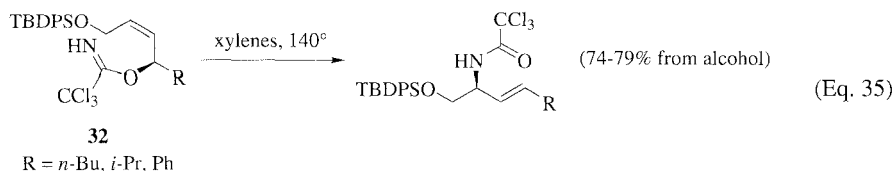
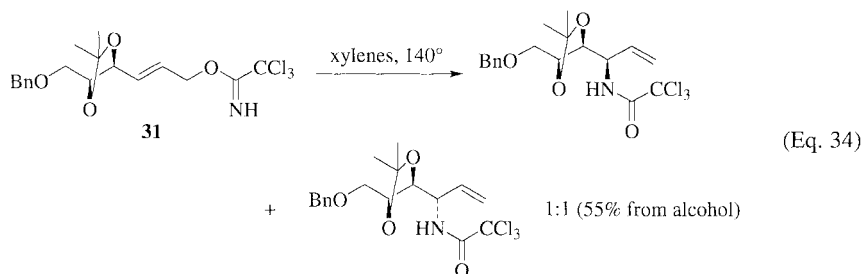
Carbon Skeleton. The allylic carbon skeleton, particularly substitution at the α carbon, plays a large role in determining what temperature is required for allylic trihaloacetimidate rearrangements. However, there are only a few reports where structural features present insurmountable difficulties in carrying out the rearrangement.

In most cases, difficulties can be overcome by increasing the reaction temperature. We have already discussed the fact that higher reaction temperatures are required as electron-releasing α substituents are replaced by hydrogen, with 130–160° typically being required for primary allylic imidates and 80° or less for tertiary allylic analogues.

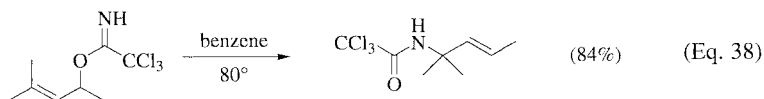
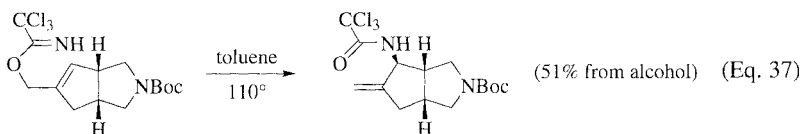
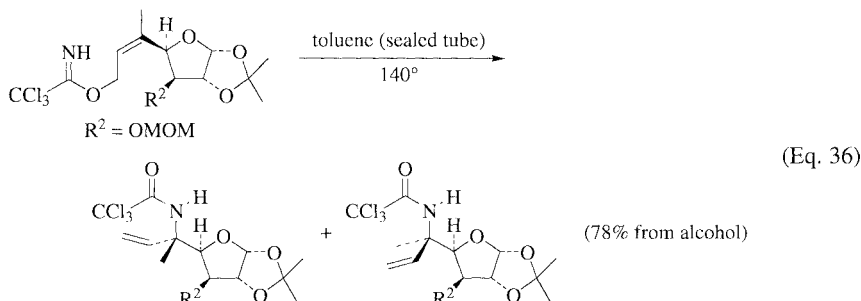
Steric effects at the imidate γ carbon can also play a role. In comparing the rearrangement of the *ortho*- and *para*-substituted aromatic imidates **30**, the *para*-substituted substrate is found to rearrange more quickly, and in higher yield, than the *ortho* isomer. This outcome is attributed to steric encumbrance to C–N bond formation in the latter case (Eq. 33).¹⁹



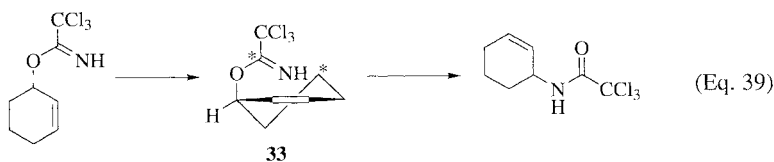
The geometry of the alkene affects both the temperature required for trihaloacetimidate rearrangements and the yields observed. Allylic trihaloacetimidates having a *Z* 1,2-disubstituted double bond typically require slightly higher temperatures to promote their allylic reorganization than their *E* counterparts.^{24,25} Presumably in part for this reason, many fewer examples of allylic trihaloacetimidate rearrangements are reported in the *Z* series. For example, the *E* trichloroacetimidate **31** rearranges in useful yield (Eq. 34), whereas the *Z* stereoisomer is noted to rearrange with “significantly more byproducts”.⁷⁷ However, a few *Z* disubstituted allylic trichloroacetimidates are reported to rearrange in high yield. For example, the rearrangement of the secondary trichloroacetimidates **32** proceeds in good yields in refluxing xylenes (Eq. 35).⁷⁸



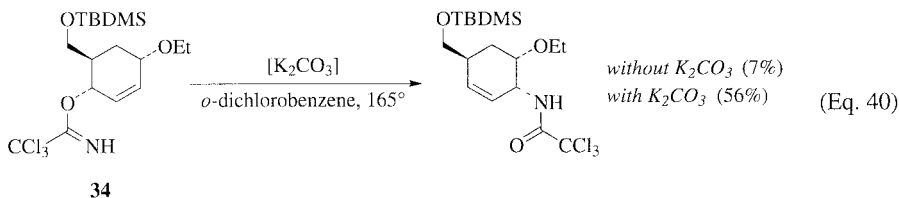
Numerous trisubstituted allylic trihaloacetimidates having a second substituent at either the β or γ carbon undergo thermal rearrangement in useful yields. Three representative examples are shown in Eq. 36–38.^{79–81}



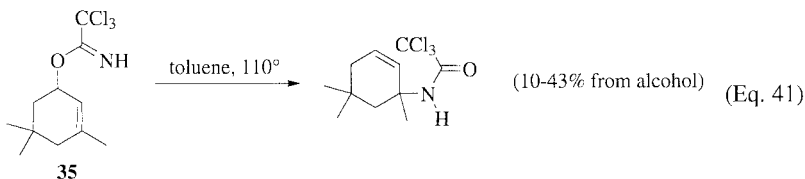
Cyclic Substrates. Rearrangements of allylic trihaloacetimidates in which the allyl unit is embedded in a ring can be challenging as the transition state conformation required for rearrangement is higher in energy than that of acyclic counterparts. If the ring is not large, the oxygen of the imidate must adopt a quasi-axial orientation to bring the imidate nitrogen and distal alkene carbon within bonding distance. This feature is illustrated in the cyclohexenyl series in Eq. 39. Moreover, in a half-chair transition structure, a destabilizing syn-pentane interaction would exist between the starred atoms in **33**. This interaction would be avoided in a twist-boat transition structure.



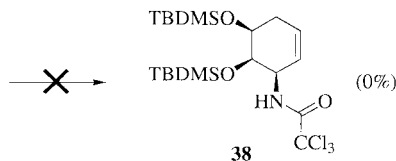
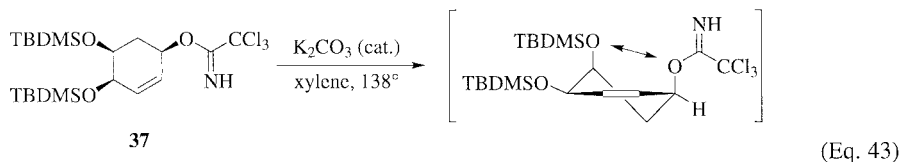
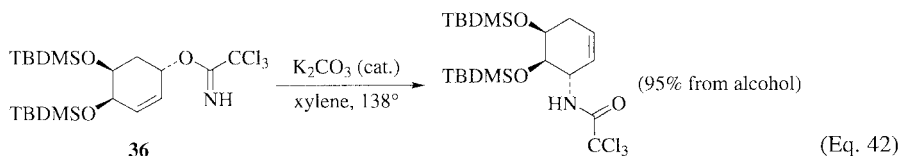
Because the trihaloacetimidate must adopt a high-energy conformation to undergo rearrangement, cyclic allylic imidates are particularly prone to decompose at the elevated temperatures required to promote their sigmatropic rearrangement. The addition of K_2CO_3 to thwart acid-catalyzed decomposition of the allylic imidate can be particularly critical in these cases as illustrated in the rearrangement of imidate **34** (Eq. 40).⁶³



If additional steric impediments exist, rearrangements of six-membered cyclic substrates can be low-yielding. For example, the additional 1,3-diaxial interaction (between O and C) brought about by the gem dimethyl group in trichloroacetimidate **35** is believed to be responsible for the low rearrangement yields realized in this case (Eq. 41);⁶ this situation is not improved by adding K_2CO_3 .⁶³

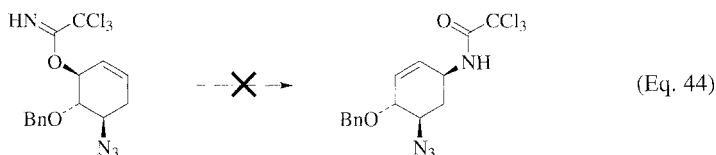


The deleterious effect of adding an additional 1,3-diaxial interaction is also seen in the rearrangements shown in Eq. 42 and Eq. 43. Thus, while cyclohexenyl tri-

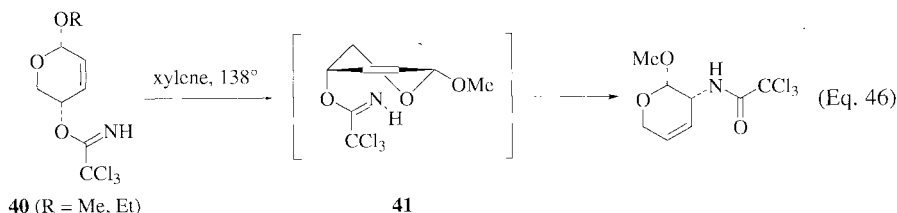
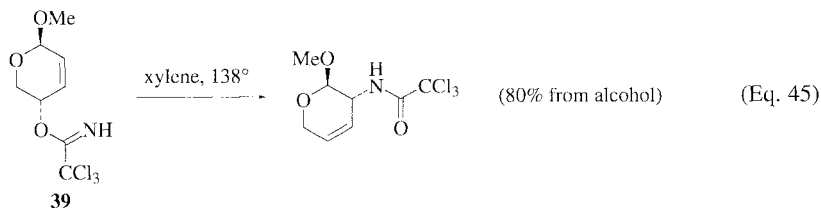


chloroacetimidate **36** rearranges in high yield at 138° , the attempted rearrangement of stereoisomeric imideate **37**, which would suffer a 1,3-diaxial O—O interaction if the imideate is oriented quasi-axially,⁹⁶ yields none of the rearrangement product **38**.

Instead, the starting imidate is recovered in 35% yield.⁸² Under some circumstances, interactions of this type can completely subvert the rearrangement process (Eq. 44).⁸³

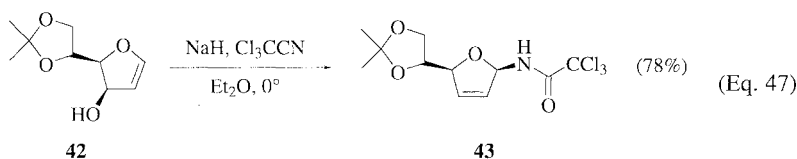


Many pyranose^{45,64,70,84–86} and furanose^{18,53,54,87} substrates have been subjected to the Overman rearrangement with good success, but rearrangements of unsaturated pyranose substrates having the $1\alpha,4\alpha$ configuration are problematic. For example, the $2\beta,5\alpha$ -trichloroacetimidate **39** rearranges stereospecifically in refluxing xylenes in 80% yield, whereas the $2\alpha,5\alpha$ isomer **40** ($R = \text{Me}$) rearranges much more sluggishly (Eqs. 45, 46).⁸⁶ Although these results are ascribed to a more sterically congested transition state in the reaction of isomer **40**, the loss of anomeric stabilization in transition structure **41** is more likely the origin of this difference. However, examples exist where pyranose substrates having the $1\alpha,4\alpha$ configuration do rearrange in moderate yield. For example, heating **40** ($R = \text{Et}$) at 165° in *ortho*-dichlorobenzene in the presence of K_2CO_3 gives the trichloroacetamide in 56% yield.⁶³

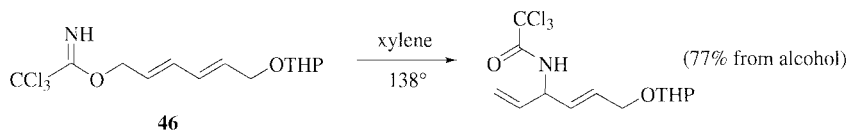
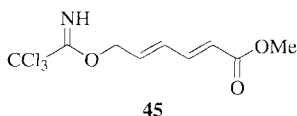
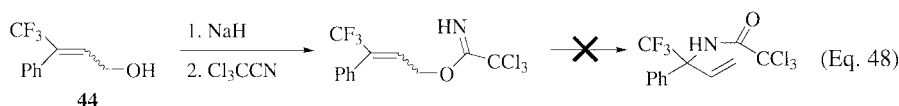


Successful Overman rearrangements of disaccharides have been reported, particularly in cases where the energetically favored half-chair conformation of the unsaturated pyranose places the trichloroacetimidate in an axial orientation. Such an example is shown in Eq. 21.⁷⁰

Substituent Effects and Problematic Substituents. Allylic trihaloacetimidate rearrangements are impacted by the electronic effects of substituents attached to carbons 2 and 3 of the allylic system. Electron-releasing substituents can favor the rearrangement. For example, reaction of the secondary dihydrofuryl alcohol **42** with trichloroacetonitrile at 0° leads directly to the rearranged trichloroacetamide **43** in 78% yield (Eq. 47); the intermediate imidate derivative is not observed.⁸⁸

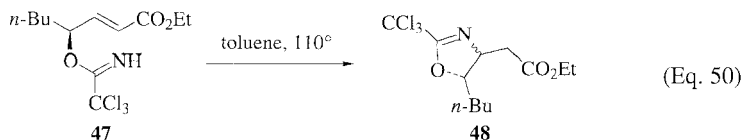


The presence of electron-withdrawing groups at the distal alkene carbon can be problematic. For example, the trifluoromethylated allylic alcohol **44** undergoes imidate formation without incident, however allylic rearrangement fails (Eq. 48).⁵⁸ Some allylic trichloroacetimidates in which the double bond is part of an α,β -unsaturated carbonyl system fail to undergo Overman rearrangement, for example, dienyl ester **45**. The presence of the electron-withdrawing ester is shown to be the problem, as the structurally similar THP-protected dienol **46** rearranges without incident (Eq. 49).⁸⁹



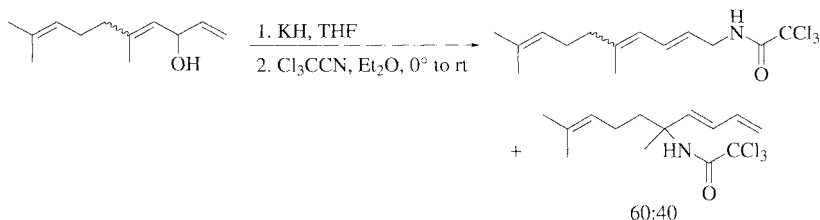
(Eq. 49)

The problem in these examples is likely competitive 1,4-addition of the imidate nitrogen to the α,β -unsaturated carbonyl functionality. For example, when unsaturated ester **47** is heated in refluxing toluene, [3,3]-sigmatropic rearrangement is not observed, but instead oxazoline **48** is formed (Eq. 50). As in the previous example, this side reaction is circumvented by reducing the ester to the alcohol, protecting the alcohol, then carrying out the rearrangement with the protected alcohol congener.²⁹

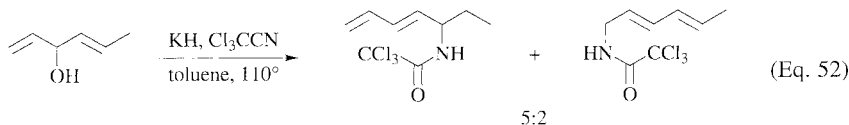


Regioselectivity

If the trihaloacetimidate is positioned proximal to two different double bonds, two regioisomeric dienyl trichloroacetamides can be formed. In cases of this type, little selectivity is observed. For example, conversion of 5,9-dimethyl-1,4,8-decatriene-3-ol to its trichloroacetimidate derivative results in a 60:40 mixture of regioisomeric trichloroacetamides upon rearrangement (Eq. 51).⁶ In the case of the trichloroacetimidate derived from 1,4-hexadien-3-ol, a slight preference for reaction at the more highly substituted alkene is observed (Eq. 52).⁹⁰

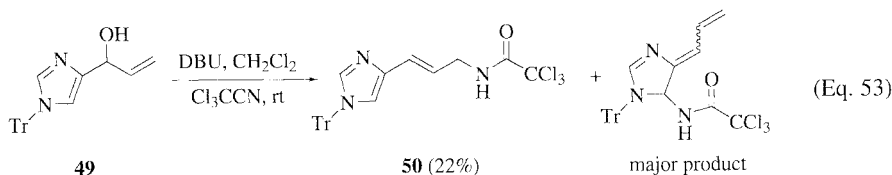


(Eq. 51)



(Eq. 52)

An interesting example in which regioisomers result from participation of the double bond of a heteroaromatic system is known. Thus, attempted rearrangement of the imidazole trichloroacetimidate **49** leads to the desired product **50** in relatively low yield, with the major product arising from competitive rearrangement at the 4,5 double bond of the imidazole ring (Eq. 53).⁹¹ This limitation is not seen with related aromatic substrates and may arise in the imidazole case by an ionization-recombination pathway as the trityl-protected nitrogen is perfectly situated to stabilize the derived allyl cation.



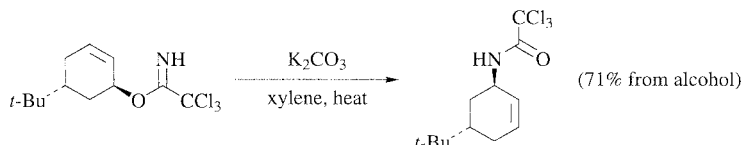
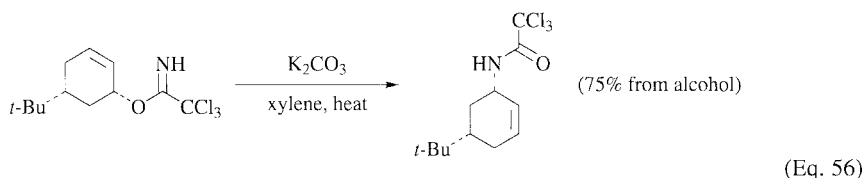
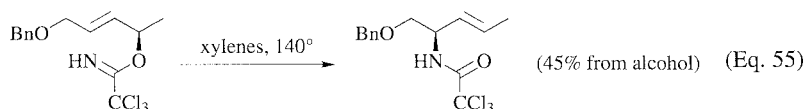
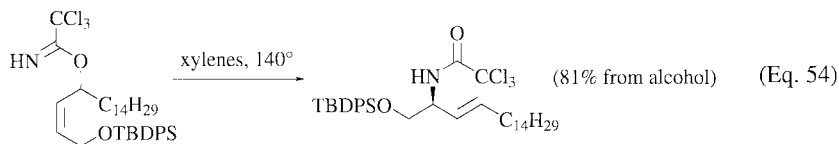
(Eq. 53)

Stereochemistry

Chiral Secondary Imidates: Chirality Transfer. High stereoselection is a hallmark of the trihaloacetimidate rearrangement. Self-immolative⁹² transfer of chirality was first demonstrated in the rearrangement of (*R*)-1-methyl-3-phenyl-2*E*-

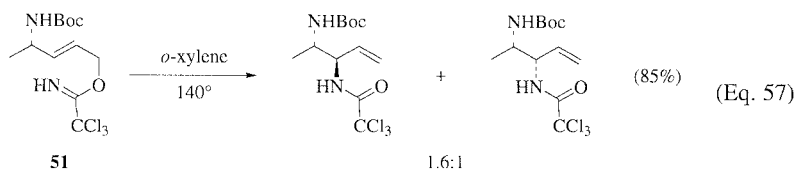
propenyl trichloroacetimidate, which proceeds smoothly to give the corresponding secondary benzylic trichloroacetamide with complete transfer of chirality (Eq. 5).²⁰

There are numerous other examples of this reliable transposition of chirality. Three are shown in Eqs. 54–56.^{24,26,93}

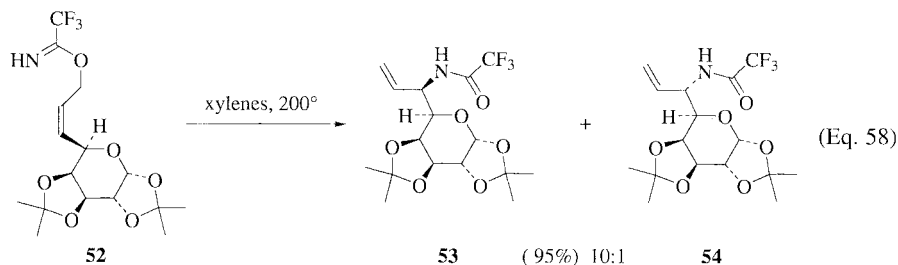


Diastereoselectivity Arising from Stereocenters Outside the Pericyclic Arena.

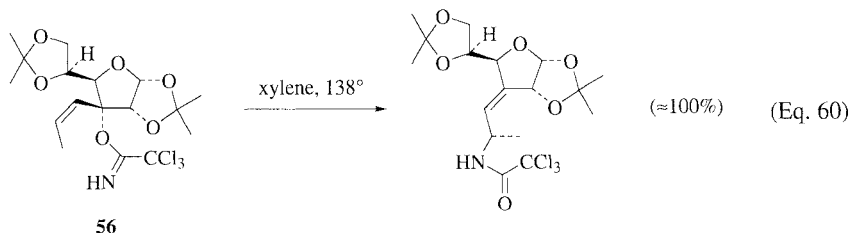
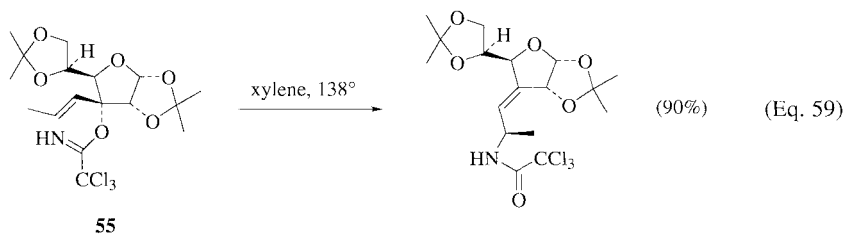
The impact of chirality external to the six-centered electrocyclic framework varies widely. The conformational flexibility of the substrate and the temperature for the rearrangement influence the observed degree of diastereoselection. For example, no stereocontrol is achieved in the rearrangement of the chiral allylic dioxolane **31** in refluxing xylenes (Eq. 34).⁷⁷ Likewise, rearrangement of trichloroacetimidate **51** at 140° yields a 1.6:1 mixture of diastereomeric amides (Eq. 57).³⁰ As will be discussed later, Pd(II)-catalyzed rearrangements of substrates of this type typically proceed with high stereoselectivity.^{30,94}



Allylic trihaloacetimidate rearrangements of more conformationally constrained systems often proceed with substantial diastereoselectivity, however. Thus, trifluoroacetimidate **52** rearranges to give an excellent yield of epimeric amides **53** and **54** with 10:1 diastereoselectivity (Eq. 58). The trichloroacetimidate analogue of **52** is reported to rearrange over a period of 30 hours in 47% yield with no diastereoselectivity.⁹⁵ No explanation for this surprising difference has been advanced.

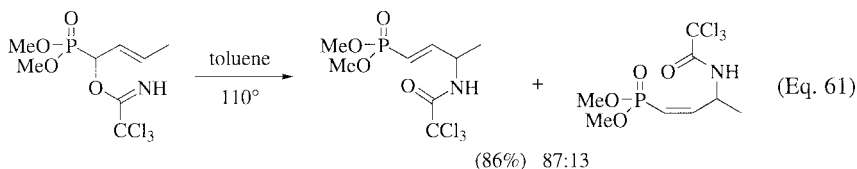


Rearrangement of the *exo*-allylic trichloroacetimidate **24** takes place selectively from the face opposite the dioxolane substituent, which would be oriented quasi-axially⁹⁶ to give amide **25** as a single stereoisomer in excellent yield on a 20 gram scale (Eq. 22).⁴⁹ This product is a key intermediate in the synthesis of (–)-5,11-dideoxytetradotoxin. Excellent stereoselectivity also is observed in the rearrangement of the *E* and *Z* propenyl trichloroacetimidates **55** and **56** (Eqs. 59 and 60). In both reactions, rearrangement occurs from the same alkene face to provide opposite epimers at the new nitrogen-bearing stereocenter.⁵³

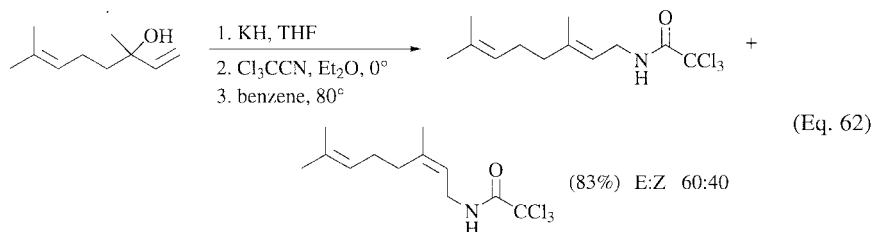


Geometry of the New Double Bond. As discussed earlier in the context of favored chair transition structures for allylic trihaloacetimidate rearrangements, a common feature of the [3,3]-sigmatropic rearrangement of secondary allylic trihalo-

acetimidates is transposition to generate a new E double bond. Although extremely high E stereoselectivity is typically seen, some examples of moderate stereoselection have been reported. For example, in the rearrangement of a series of trichloroacetimidates of alkyl-substituted α -hydroxyphosphonates, the product is obtained as a mixture of E and Z isomers, with the Z isomer typically accounting for $\sim 13\%$ of the product mixture (Eq. 61).⁹⁷



Low stereoselectivity is seen in allylic trichloroacetimidate rearrangements of chiral tertiary allylic alcohols when the two α substituents are of similar size, as the two possible chair transition structures are of similar energy. For example, rearrangement of the trichloroacetimidate of linalool at 80° provides a 60:40 mixture of geranyl and neryl trichloroacetamides (Eq. 62).⁶



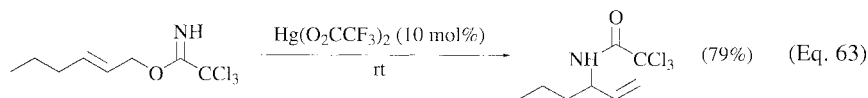
Catalyzed Rearrangements of Allylic Trihaloacetimidates

Catalysis of trichloroacetimidate rearrangements by mercuric trifluoroacetate was disclosed in the inaugural report of this transformation.⁴ Whereas the thermal rearrangement of the trichloroacetimidate of (*E*)-2-hexen-1-ol requires refluxing *meta*-xylene (138°) for nine hours to give the allylically rearranged trichloroacetamide in 81% yield, this allylic amide is formed in similar yield within minutes in THF at 0° in the presence of 10 mol% of mercuric trifluoroacetate. This mercury(II) complex is estimated to increase the rate of the rearrangement by a factor greater than 1×10^{12} .⁶ Similar rate accelerations are realized in the presence of soluble complexes of PdCl_2 , which have emerged as the most generally useful catalysts for allylic trihaloacetimidate rearrangements. An early example was reported in 1980,¹¹ although Pd(II)-catalysis of allylic trihaloacetimidate rearrangements was not studied in detail until several years later.²⁸

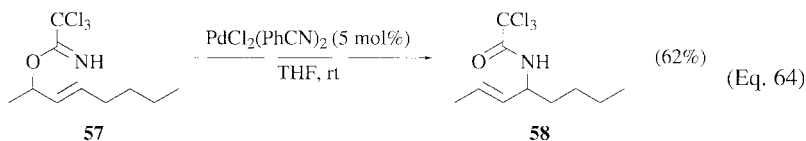
The utility of the metal-catalyzed rearrangement is limited by the propensity of the catalyst to promote elimination to form dienes and trichloroacetamide, occasioned by competitive coordination of the catalyst to the allylic trichloroacetimidate

nitrogen. In general, primary allylic trihaloacetimidates containing *trans* 1,2-disubstituted double bonds rearrange in good yields in the presence of Hg(II) or Pd(II) catalysts. Fewer examples exist of successful rearrangements of secondary allylic trihaloacetimidates; however, several high-yielding examples are known with Pd(II) catalysts.^{25,28,29} Complete suprafacial transfer of chirality is a hallmark of catalyzed versions of the rearrangement, as it is of the thermal variant. Diastereoselection in rearrangements of chiral, δ -substituted, allylic trihaloacetimidates can be significantly enhanced in the presence of PdCl₂ catalysts. Of potentially greater significance, useful asymmetric Pd(II) catalysts have been developed quite recently.⁷⁻⁹

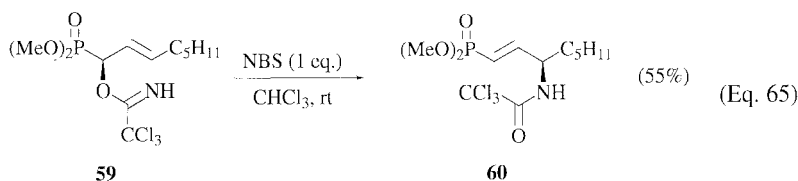
General Conditions. The rearrangement of allylic trichloroacetimidates with mercuric trifluoroacetate is carried out using 10–30 mol% of this catalyst in THF, e.g., Eq. 63. Hg(II)-catalyzed rearrangements can take place at temperatures as low as -60° , with yields often being high for primary substrates.⁶



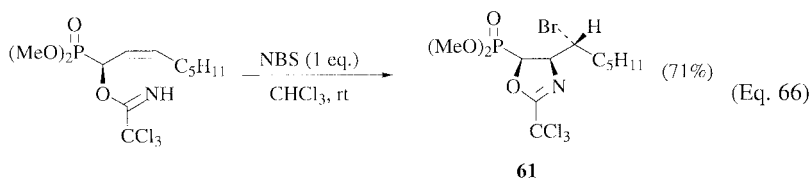
More recently, Pd(II) complexes have been the catalysts of choice, with excellent outcomes being achieved at room temperature using 4–8 mol% of the soluble bis(acetonitrile) or bis(benzonitrile) complexes of PdCl₂ in aprotic solvents such as THF or toluene. Palladium acetate and palladium trifluoroacetate have also been employed, although rarely.²⁵ Pd(II)-catalyzed allylic trichloroacetimidate rearrangements typically take place in a few hours at or below room temperature, as exemplified by the conversion of trichloroacetimidate **57** to amide **58** (Eq. 64).²⁸



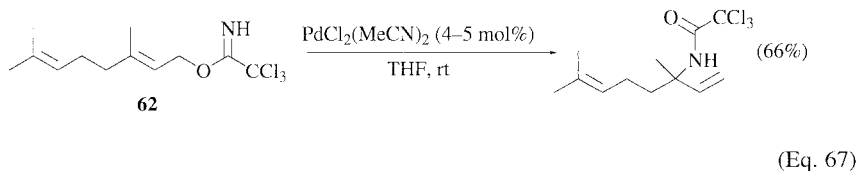
There is a single report of trichloroacetimidate rearrangements being promoted by halogen electrophiles, specifically *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide. For example, the *E* allylic phosphonate trichloroacetimidate **59** is transformed to the rearrangement product **60** in moderate yield at room temperature in the presence of one equivalent of NBS (Eq. 65). In contrast, the *Z* isomer reacts slowly under identical conditions to give oxazoline **61** (Eq. 66).^{66,2}



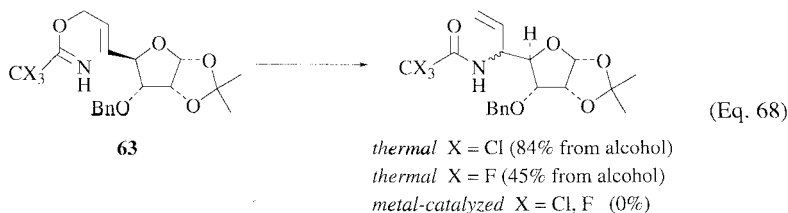
² The reported yield in Eq. 66 is after hydrolysis to the hydroxamide.

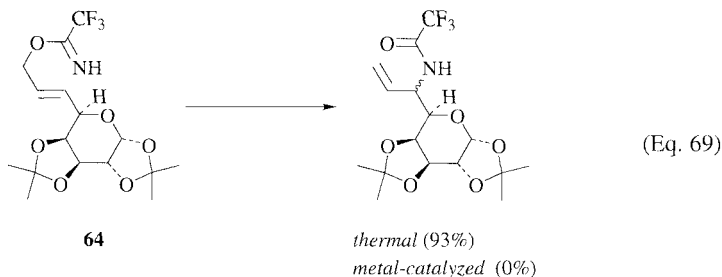


Scope. Although metal-catalyzed allylic trihaloacetimidate rearrangements take place under milder conditions than their thermal counterparts, the scope of the catalyzed rearrangement is much more limited. Trichloroacetimidates are typically used and give higher yields than the less nucleophilic trifluoroacetimidates,⁶² a result expected for a cyclization-induced rearrangement mechanism. Primary trichloroacetimidates containing *trans* 1,2-disubstituted double bonds are the best substrates for metal-catalyzed rearrangements, typically undergoing rearrangement in good yields using either $\text{PdCl}_2(\text{RCN})_2$ or $\text{Hg}(\text{O}_2\text{CCF}_3)_2$ catalysts.^{6,27,62,94} Substitution on the allylic double bond impedes the metal-induced rearrangement. For example, the rearrangement of the trichloroacetimidate of geraniol (**62**, Eq. 67) under thermal conditions provides linalyl trichloroacetamide in 90% yield (Eq. 32), whereas this product is formed in only 66% yield in the presence of $\text{PdCl}_2(\text{MeCN})_2$.⁶² There have been no reports of successful metal-catalyzed rearrangements of substrates having a substituent on the internal allylic alkene carbon.

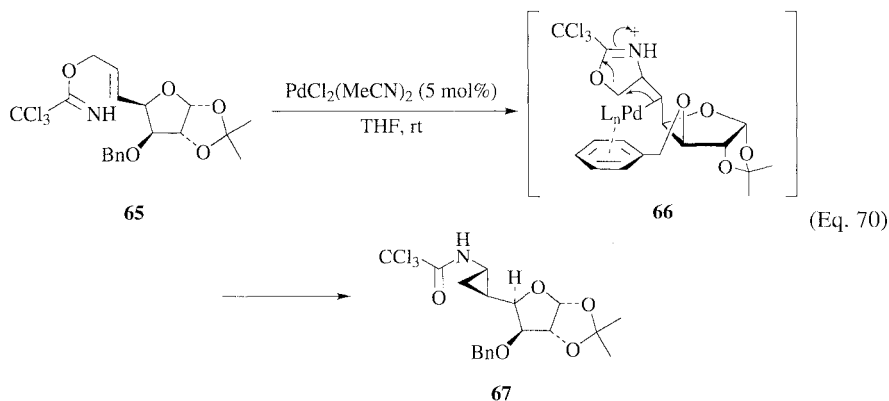


More highly functionalized primary allylic trichloroacetimidates often have proven to be resistant to metal catalysis. For example, the ribose-derived imide **63** fails to yield any rearrangement product in the presence of $\text{PdCl}_2(\text{MeCN})_2$ or $\text{Hg}(\text{O}_2\text{CCF}_3)_2$.⁹⁸ This result should be contrasted with the successful rearrangement of this imide under thermal conditions (xylene at 137° in the presence of two per cent di(*tert*-butyl)-*para*-cresol; Eq. 68). Similarly, xylose derivative **64** (Eq. 69) fails to rearrange under catalysis by either Pd(II) or Hg(II) species, although again its rearrangement is successfully realized thermally (xylene at 200°).⁹⁵

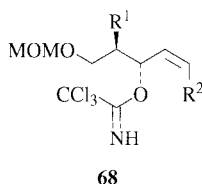




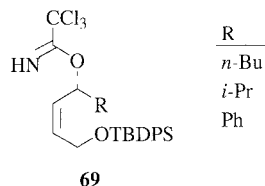
An interesting example is shown in Eq. 70, where failure to observe [3,3]-sigmatropic rearrangement arises from an alternate reaction pathway of a Pd(II)-olefin complex. In this case, attempted rearrangement of **65** using $\text{PdCl}_2(\text{MeCN})_2$ gives a 58% yield of cyclopropane derivative **67**. This product is postulated to derive from **66**, which would arise if intramolecular attack by the imidate on the nascent Pd(II)-olefin complex took place at the proximal alkene carbon (5-exo, rather than 6-endo cyclization).⁹⁸



Although there are no examples of high-yielding rearrangements of secondary allylic trichloroacetimidates using $\text{Hg}(\text{O}_2\text{CCF}_3)_2$ as the catalyst, several successful PdCl_2 -catalyzed rearrangements of secondary allylic trichloroacetimidates containing trans 1,2-disubstituted double bonds are known (see the following section). However, this catalyzed transformation is limited to secondary substrates of this specific type. For example, attempted PdCl_2 -catalyzed rearrangement of the cis secondary trichloroacetimidates **68** failed due to competing elimination to form the corresponding dienes and trichloroacetamide,²⁵ an outcome also observed with Z trichloroacetimidates **69**.⁷⁸ Low yields (<30%) were also reported for rearrangements of secondary allylic trichloroacetimidates containing trans 1,2-disubstituted double bonds using $\text{Pd}(\text{OAc})_2$ as the catalyst; elimination was again the major reaction pathway.²⁵ Consistent with these observations, there are no reports of successful catalytic rearrangements of cyclic secondary allylic trichloroacetimidates nor secondary allylic trichloroacetimidates containing trisubstituted double bonds.

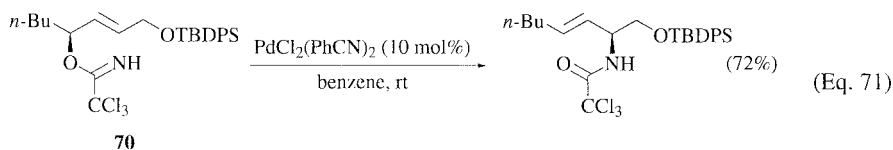


R ¹	R ²
Me	<i>n</i> -Bu
<i>i</i> -Pr	<i>n</i> -Bu
<i>i</i> -Bu	<i>i</i> -Bu

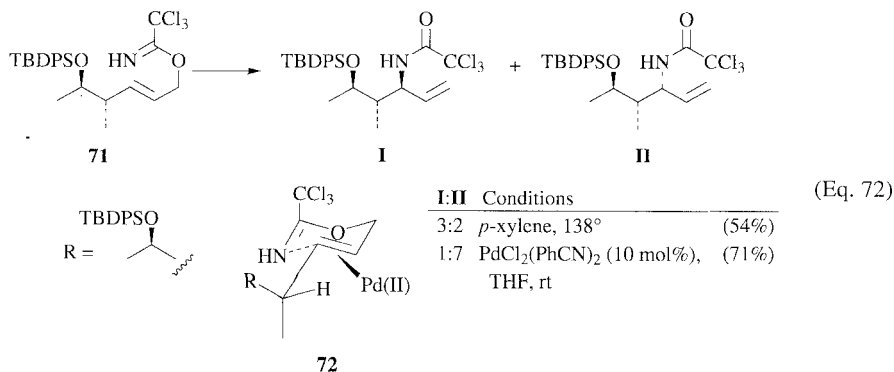


R
<i>n</i> -Bu
<i>i</i> -Pr
Ph

Stereoselectivity. *Chiral Secondary Imidates: Chirality Transfer.* Although metal-catalyzed rearrangements of secondary allylic trihaloacetimidates are limited to substrates containing *trans* 1,2-disubstituted double bonds, such rearrangements of chiral imidates proceed with excellent transfer of chirality. For example, Pd(II)-catalyzed rearrangement of trichloroacetimidate **6** proceeds with complete suprafacial diastereoselection to give the trichloroacetamide in high yield (Eq. 9).²⁸ In one reaction, the milder conditions associated with Pd(II) catalysis lead to enhanced selectivity when compared to the thermal counterpart. For example, thermal rearrangement of chiral trichloroacetimidate **70** (Eq. 71) at 110° (refluxing toluene) takes place with 7% loss of enantiomeric purity.²⁹ In contrast, the Pd(II)-catalyzed version of this rearrangement occurs with no loss of enantiomeric purity. As is seen in analogous thermal rearrangements, high *E* stereoselectivity is observed in forming the new 1,2-disubstituted double bond of the allylic trichloroacetamide products, see, e.g., Eqs. 64 and 71.

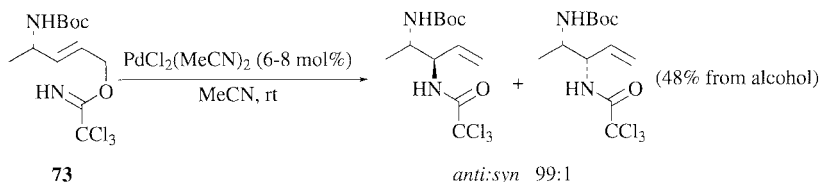


Chiral Primary Imidates: Diastereoselectivity. A number of examples of chiral, δ -substituted trichloroacetimidates rearranging with enhanced stereoselectivity in the presence of PdCl₂ catalysts have been reported. For example, thermal rearrangement of trichloroacetimidate **71** in refluxing xylene provides the *anti* and *syn* stereoisomeric allylic amides in moderate yield and a mediocre 3:2 ratio (Eq. 72).⁹⁹ In

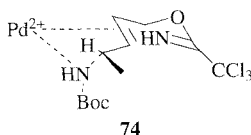


contrast, rearrangement of **71** with either $\text{PdCl}_2(\text{MeCN})_2$ or $\text{PdCl}_2(\text{PhCN})_2$ takes place with much improved diastereoselectivity, providing the 3,4-anti isomer as the major product. This product results from preferential cyclization of the imidate nitrogen from the si face of the alkene. The authors suggest that this transition structure is favored because it allows coordination of the Pd(II) catalyst to the double bond to occur away from the bulky *tert*-butyldiphenylsilyl protecting group, as depicted in **72**.^{99,3}

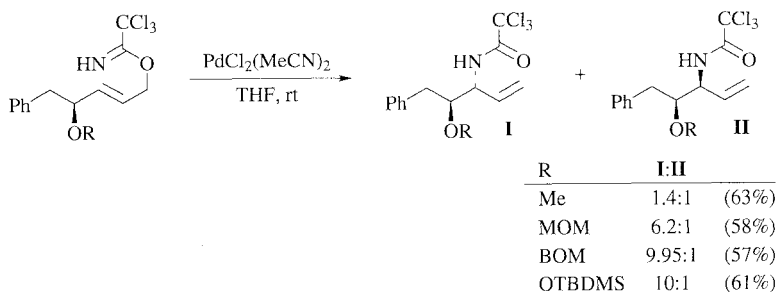
Several examples show high stereoselectivity in the synthesis of anti vicinal diamines by diastereoselective Pd(II)-catalyzed rearrangements of allylic trichloroacetimidates having a Boc-protected amine substituent at the δ position. For example, rearrangement of **73** in the presence of $\text{PdCl}_2(\text{MeCN})_2$ gives exclusive formation of the anti isomer (the syn isomer was undetected; Eq. 73). In contrast, thermal rearrangement of the same substrate gives a 62:38 mixture of the anti:syn products.³⁰ Coordination of the palladium to the adjacent Boc-protected nitrogen, as depicted in **74**, is invoked to rationalize the stereoselection.



(Eq. 73)



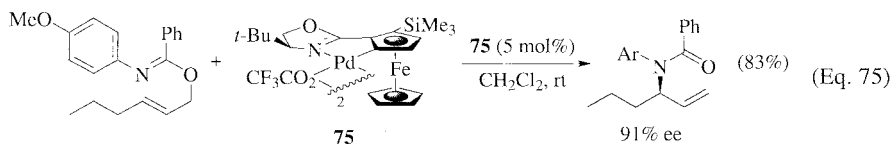
In a related example, potential chelation of a Pd(II) catalyst to a δ -alkoxy or δ -siloxy substituent was examined and found to have no impact. The rearrangement results summarized in Eq. 74 lead to the conclusion that diastereoselection, which can be as high as 10:1, results solely from steric effects.¹⁰⁰



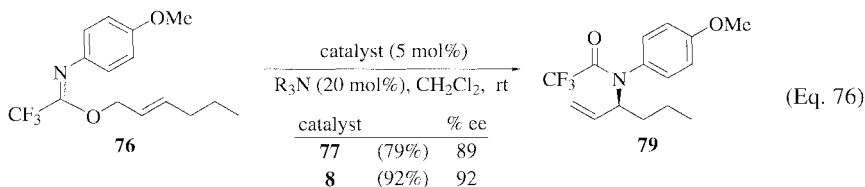
(Eq. 74)

³ This intermediate is drawn incorrectly in the original paper; i.e. the configuration shown at C4 is incorrect.

Asymmetric Catalysis. The success of Pd(II) catalysis for allylic trichloroacetimidate rearrangements naturally has led to research on the development of asymmetric Pd(II) catalysts. Early studies employing cationic Pd(II) complexes suggested that allylic trichloroacetimidates were not viable substrates for asymmetric catalysis, as attempts to carry out such transformations were plagued by competing elimination reactions, slow reaction rates, and low enantioselectivities.¹⁰¹ The first two of these difficulties were ascribed to competitive strong complexation of the small, basic trichloroacetimidate nitrogen to the hard palladium center.¹⁰² Consequently, success in developing asymmetric Pd(II) catalysts for allylic imidate rearrangements was realized initially with less strongly coordinating *N*-arylimidates.¹⁰¹ Whereas high enantioselectivities can be realized with substrates of this type, for example Eq. 75,³⁹ transformation of the amide products to the corresponding allylic amines is not high yielding. A wide variety of chiral, enantiopure Pd(II) complexes have been shown to catalyze allylic rearrangements of *N*-arylimidates,^{8,37,39,101,103–105} although a survey of these studies is outside the scope of this review. Reviews of early developments in this area have appeared.^{14,102}

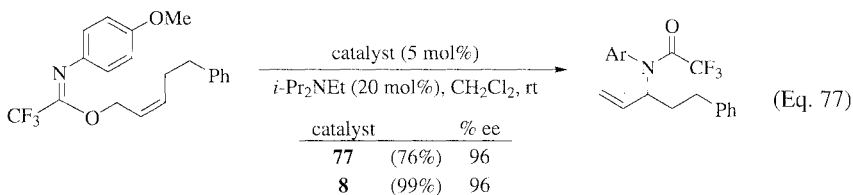
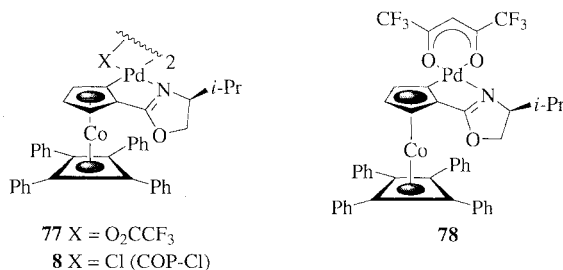


N-Anisyltrifluoroacetimidates are more attractive substrates for catalytic asymmetric allylic imidate rearrangements as their allylic *N*-anisyltrifluoroacetamide products can be converted to the parent allylic amines in good yield. An initial survey of six asymmetric Pd(II) complexes for catalyzing the rearrangement of **76** to **79** identified the cationic ferrocenyl oxazoline palladacyclic complex **75** (Eq. 75),

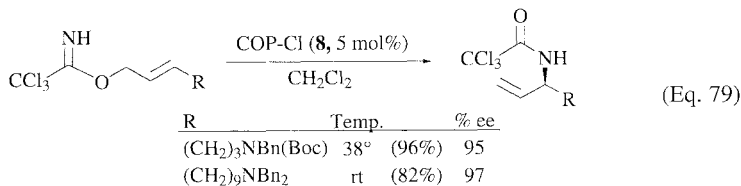
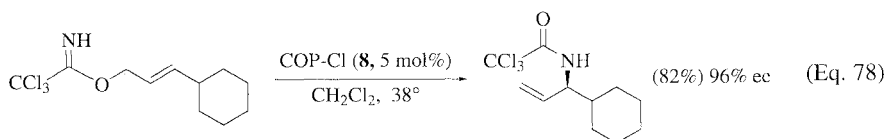


and the related cationic and neutral palladacyclic catalysts **77**, **78**, and **8** (COP-Cl) containing a chiral oxazoline substituent and a planar chiral cyclopentadienyl(η^4 -*m*-tetraphenylcyclobutadiene)cobalt fragment, as effective catalysts for this transformation (Eq. 76).⁸ Subsequent deprotection of the *N*-anisyltrifluoroacetamide **79** to form (*R*)-3-amino-1-hexene is accomplished in 73% yield. Cis allylic *N*-anisyltrifluoroacetimidates are converted also in good yield and high ee to the corresponding secondary *N*-anisyltrifluoroacetamides using the cobalt oxazoline palladacycle (COP) catalysts (Eq. 77). Incorporation of small amounts of tertiary amines, typically *i*-Pr₂NEt, minimizes acid-catalyzed decomposition of the starting imidates in rearrangements that employ the trifluoroacetate-bridged catalysts **75** and **77**, which are

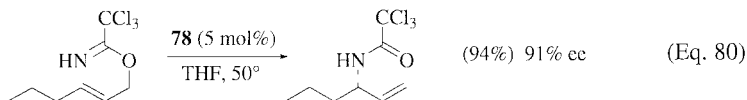
generated in situ by reaction of the corresponding halide-bridged dimers with excess silver trifluoroacetate.



In a recent publication, the neutral chloride-bridged dimer COP-Cl (**8**) was shown to be an excellent catalyst for asymmetric rearrangement of trans 1,2-disubstituted allylic trichloroacetimidates, thus providing the first truly useful catalytic asymmetric method for transforming prochiral allylic alcohols to enantioenriched allylic amines and their analogues, e.g., Eq. 78.⁷ Although the scope and limitations of this method are not well explored at this point, a variety of oxygen functionality is well tolerated. Some nitrogen functional groups appear to be also well tolerated, e.g. Eq. 79. However, the allylic rearrangement is prevented (at least at 38°) by tertiary amine functionality at C6, secondary amine functionality at either C6 or C12, or a thio ether substituent at C6 of the (*E*)-2-alkenyl trichloroacetimidate starting material. This method is limited to the rearrangements of allylic trichloroacetimidates containing trans 1,2-disubstituted double bonds as analogous *cis* substrates rearrange only slowly in the presence of COP-Cl.



The more soluble monomeric COP-hexafluoroacetylacetonate complex **78** allows a wider variety of solvents to be employed and higher catalyst concentrations, and correspondingly higher catalysis rates, to be achieved.⁹ One example is shown in Eq. 80.



APPLICATIONS TO SYNTHESIS

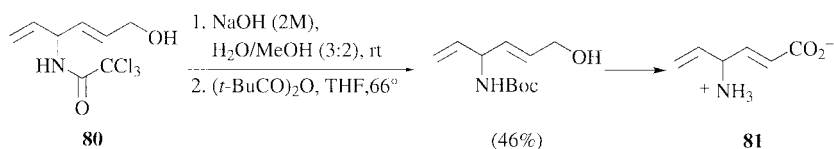
Overview

The chief significance of the allylic trihaloacetimidate rearrangement lies in the many uses of the allylic trichloroacetamide products. Foremost among these uses is ready access to allylic amines. The trichloroacetyl group is typically removed from allylic trichloroacetamides using either NaOH in mixed organic–aqueous solvent systems, strong mineral acids, or methanolic NaBH₄. One potential advantage of employing trifluoroacetimidates in this allylic rearrangement is the ready cleavage of the trifluoroacetyl group under mildly basic conditions.¹⁰⁶

The trichloroacetyl group has also been exploited to accomplish subsequent elaborations of rearrangement products. For example, the trichloroacetyl group has been used to initiate radical cyclizations; as a precursor of guanidines, carbodiimides, and ureas; and to regulate facial selectivity in the addition of various reagents to the allylic double bond.

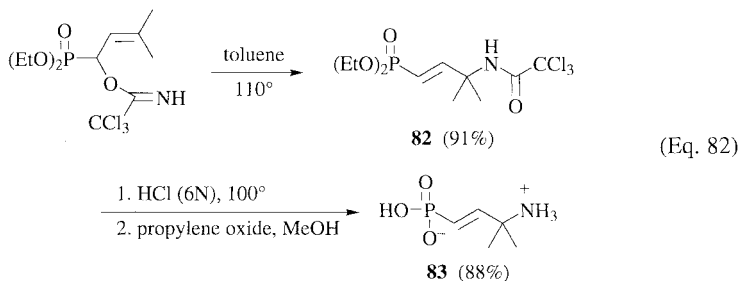
Preparation of Allylic Amines

Overman rearrangements have been employed to prepare a broad range of allylic amines for many diverse uses. For instance, a number of selective enzyme inhibitors have been prepared in this way. Examples include a variety of 2-(2-thienyl)allyl-amines, synthesized for studies of the inhibition of dopamine β -hydroxylase,¹⁰⁷ and dienyl amino acid **81**, an inhibitor of 4-aminobutyrate-2-oxoglutarate aminotransferase.⁸⁹ This latter agent is prepared in four steps from dienyl trichloroacetamide **80** (Eq. 81), whose synthesis by allylic trichloroacetimidate rearrangement is summarized in Eq. 49.

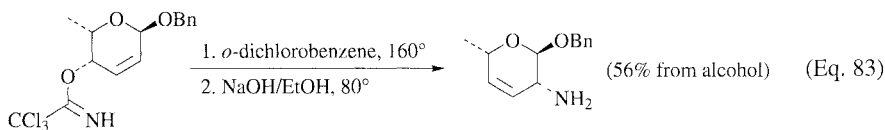


An example of the application of this rearrangement to the preparation of novel classes of biologically important nitrogen compounds is seen in the synthesis of

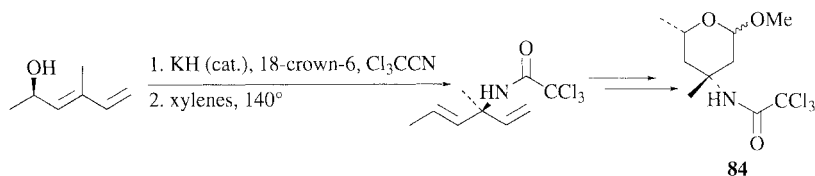
γ -aminophosphonic acids, for example **83** (Eq. 82).⁹⁷ Refluxing 6N HCl was employed to hydrolyze the trichloroacetamide and phosphonic ester functionalities of **82** in good yield.

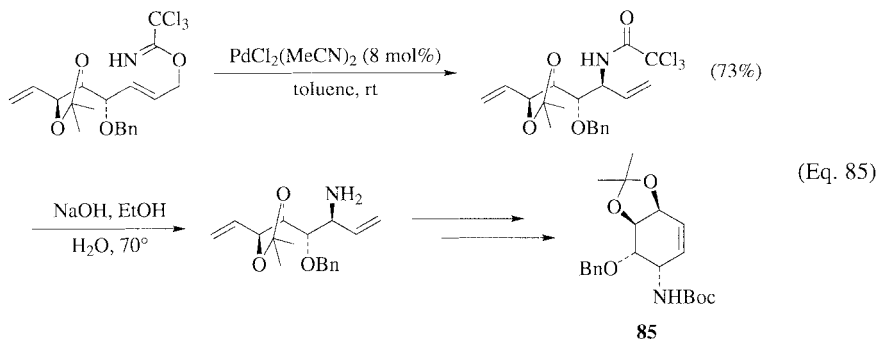


A variety of amino sugars, including both monosaccharides and disaccharides, has been prepared using the Overman rearrangement as the key step. In many of these syntheses, the trihaloacetimidate rearrangement is employed to install the amino functionality with high stereocontrol.^{45,70,85,108,109} In one approach, the trihaloacetimidate rearrangement is carried out on a carbohydrate framework, as exemplified by the example shown in Eq. 83. This tactic has been employed widely, with several examples of the rearrangement stage of these amino sugar constructions being highlighted earlier in Scope and Limitations (cyclic substrates).

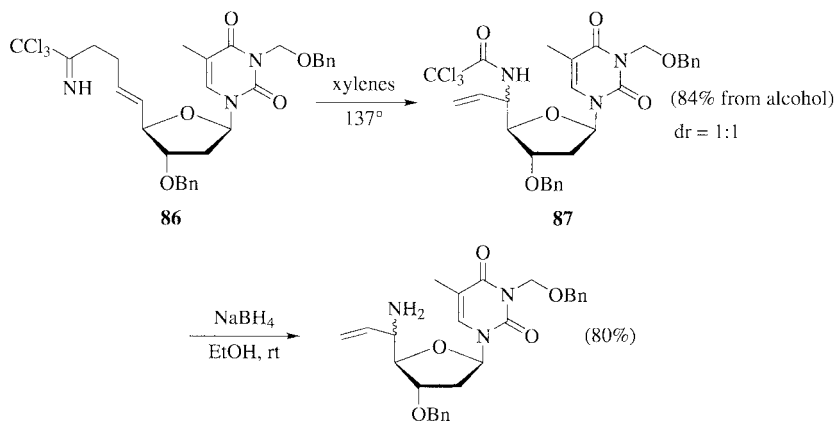


In another construction of amino sugars, the rearrangement step is carried out on an acyclic substrate, with cyclization to form the carbohydrate occurring at a later stage. An early example, the preparation of (\pm)-*N*-(trichloroacetyl)vancosamine (**84**), is shown in Eq. 84.⁵¹ This strategy has been applied also to the synthesis of several aminocarbasugar derivatives,^{27,110} as in preparation of the conduramine analogue **85** (Eq. 85).²⁷

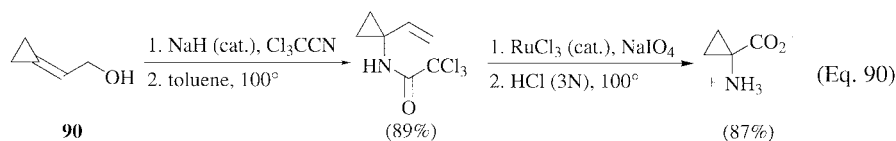




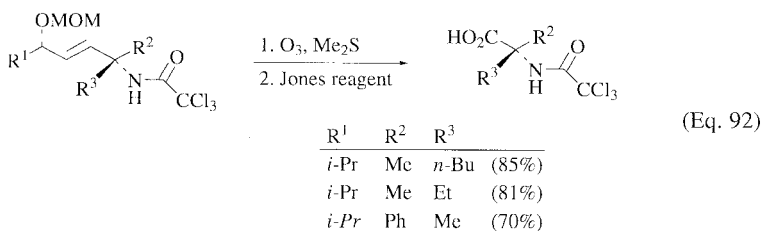
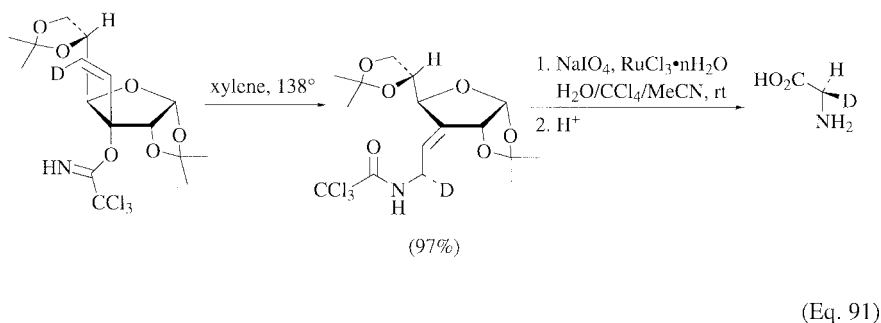
Given the promise of nucleoside analogues as therapeutic agents, much effort has been devoted to their synthesis, with trihaloacetimidate rearrangements being central steps in several approaches. For example, the dideoxyribose **43** has been prepared in 78% yield from the allylic alcohol precursor, placing the amino group in the correct position for subsequent construction of the appropriate heterocyclic substituent (Eq. 47).⁸⁸ Allylic rearrangement of trichloroacetimidate **86** is a central step in the synthesis of a series of 5'-branched 5'-aminothymidines (Eq. 86).⁹⁸ This example illustrates the mild removal of the trichloroacetyl group by reaction of allylic trichloroacetamide **87** with ethanolic NaBH₄ at room temperature.



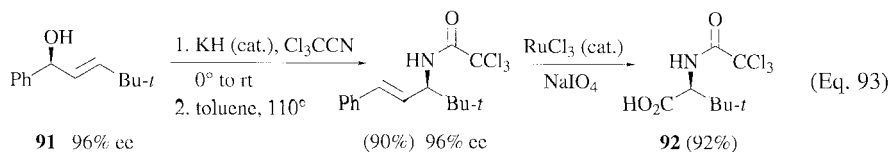
Allylic trichloroacetimidate rearrangements have been central to the synthesis of several peptide analogues. For example, a range of dipeptide olefin isosteres has been synthesized in a study of parathyroid hormone receptor activation by analogues of the *N*-terminal fragment of the natural hormone. These dipeptide isosteres were accessed by the sequence exemplified in Eq. 87.²² Numerous other dipeptide isosteres have been prepared using allylic trichloroacetimidate rearrange-



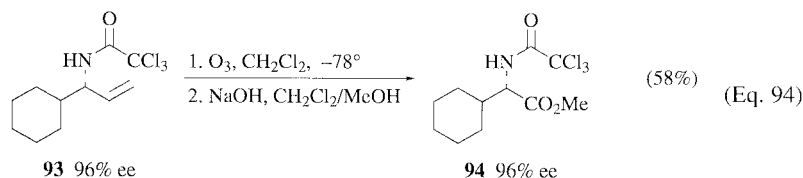
Enantiopure amino acids have been accessed in this way using several strategies. In one method, a diastereoselective allylic imide rearrangement is orchestrated on a chiral, enantiopure template. An example that employs a carbohydrate scaffold to synthesize (*S*)-(2-²H)glycine is shown in Eq. 91.⁵³ A second example, where a δ -methoxymethyl substituent regulates face selectivity in the key allylic imide rearrangement, is summarized in Eq. 92.²¹



Another tactic couples direct construction of enantioenriched, chiral secondary allylic alcohols with oxygen-to-nitrogen chirality transfer. In the example shown in Eq. 93, catalytic asymmetric vinylation of benzaldehyde provides **91**, which is transformed in 83% overall yield without loss of enantiomeric purity into trichloroacetyl-protected amino acid **92**.¹¹⁴

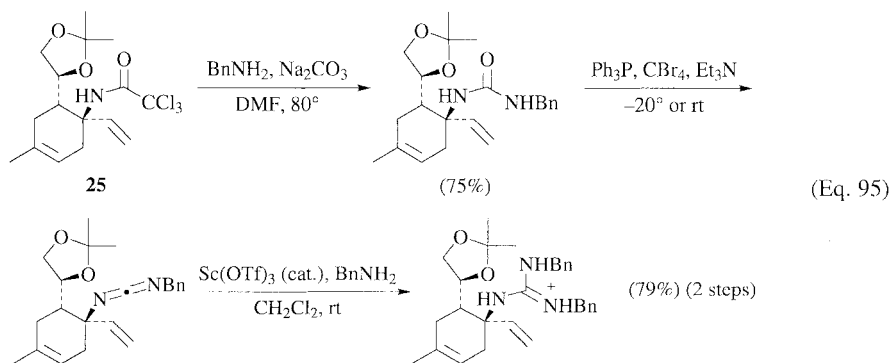


A third appealing strategy exploits asymmetric catalysis to access directly the chiral, enantioenriched allylic trichloroacetamide. For example, the differentially protected *S* α -amino ester **94** is prepared without loss of enantiopurity from allylic trichloroacetamide **93** (Eq. 94), which in turn is prepared by a COP-Cl catalyzed allylic trichloroacetimidate rearrangement (see Eq. 78).⁷

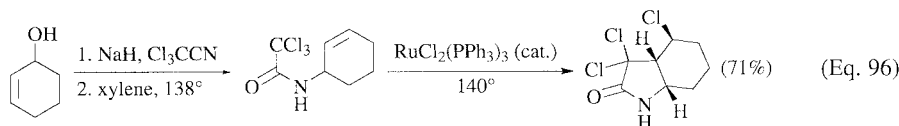


Other Direct Uses of Allylic Trihaloacetamides

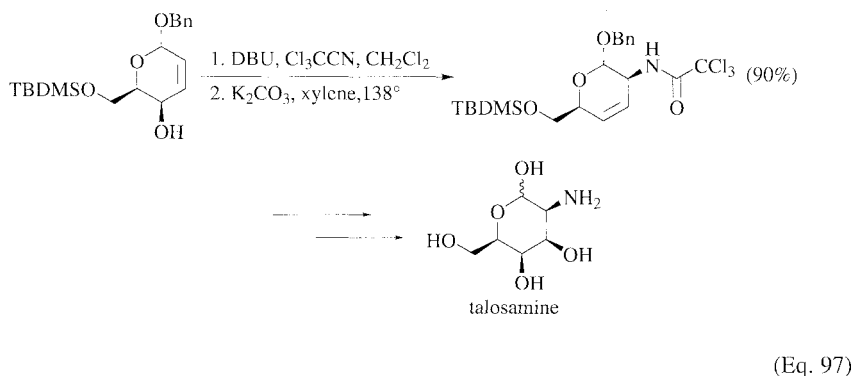
Because trichloromethyl is a competent leaving group, allylic trichloroacetamides can be directly converted to congeneric ureas, carbodiimides, and guanidines.¹¹⁵ One example of this chemistry, which was developed by Isobe and co-workers during their studies of the total synthesis of tetrodotoxin and analogues, is illustrated in Eq. 95; see Eq. 22 for the preparation of the starting allylic trichloroacetamide **25**.



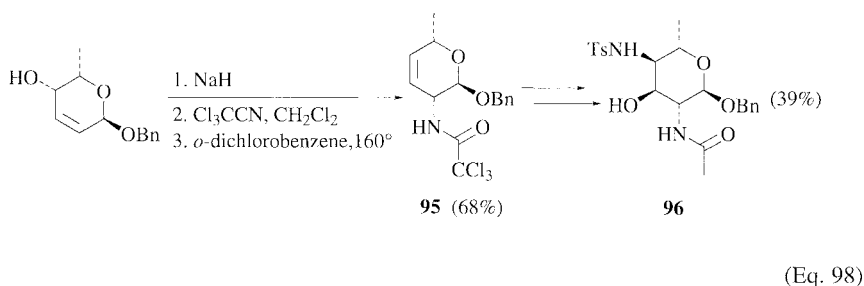
A variety of heterocycles have been assembled from products of allylic trihaloacetimidate rearrangements, employing the double bond as a partner in ring-closing metatheses,¹¹⁶ or involving the double bond in other C–C bond-forming ring constructions.^{90,117–122} A clever strategy of this type which requires no additional manipulation of the allylic trichloroacetamide functionality has been used to prepare a series of γ -lactams.⁷² In this case, ring construction is accomplished by an atom transfer radical cyclization (Eq. 96).



The potential for functionalization of the double bond to be directed by the nearby trichloroacetamide group has also been exploited. The trichloroacetamide group is particularly effective in promoting syn dihydroxylation as a result of the strong propensity of the N-H bond to participate in hydrogen bonding.^{93,123,124} This strategy has been employed in syntheses of several amino sugars as exemplified in the preparation of talosamine (Eq. 97).^{125,126}

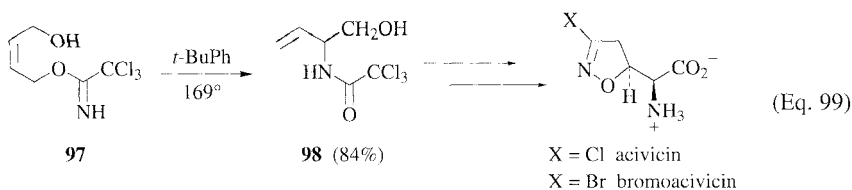


However, the trichloroacetyl group proves to be a hindrance in attempted Sharpless oxyamination of allylic trichloroacetamide **95**, a finding attributed to the “suppressing influence of an electronegative substituent”.⁴⁵ Conversion of the trichloroacetyl group to the acetate followed by oxyamination with chloramine T and osmium tetroxide yields the desired product **96** in 39% yield from the precursor allylic amide (Eq. 98).⁴⁵

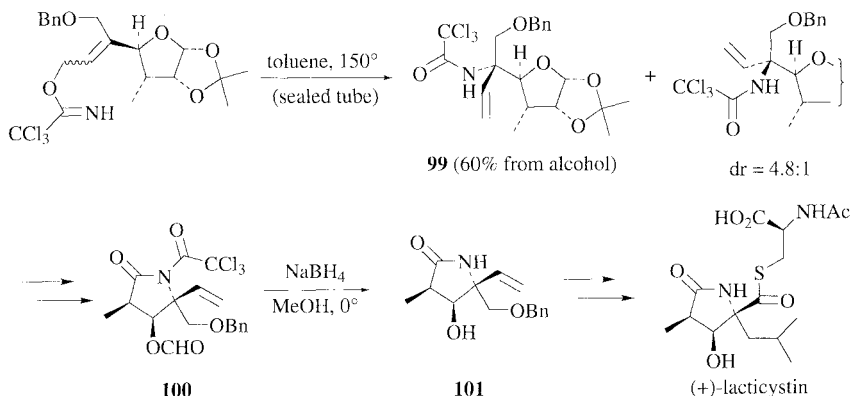


Applications in the Total Synthesis of Natural Products

(±)-Acivicin. Syntheses of the antitumor, antimetabolites (±)-acivicin and (±)-bromoacivicin take advantage of the trichloroacetimidate rearrangement’s residual allylic functionality to elaborate the heterocyclic acivicin framework through a 1,3-dipolar cycloaddition. The crucial building block in this synthesis is vinyl glycine, for which, at the time, no other efficient preparation was available. Thermal rearrangement of the trichloroacetimidate derivative **97** of *cis*-2-butene-1,4-diol is used to prepare the vinyl glycine fragment **98** (Eq. 99).^{55,69}

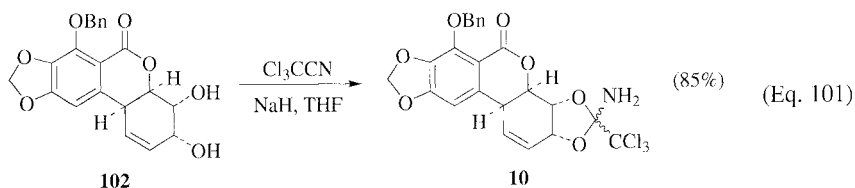


(+)-Lactacystin. The application of the trichloroacetimidate rearrangement to the synthesis of (+)-lactacystin exemplifies the utility of this reaction for constructing tertiary carbinyl amine stereocenters. The starting material for the synthesis, D-glucose, provides the chiral template for the rearrangement, giving allylic trichloroacetamides **99** as a 4.8:1 mixture of diastereomers in 60% yield from the starting allylic alcohol (Eq. 100). After acidic cleavage of the acetone, these epimers are separated and the major stereoisomer is processed in two steps to pyrrolidine imide **100**. Treatment of intermediate **100** with NaBH_4 in methanol at 0° removes both the *N*-trichloroacetyl and *O*-formyl groups to provide late stage lactacystin precursor **101**.¹²⁷ A similar strategy is employed to synthesize (–)-sphingofungin E.^{47,128}

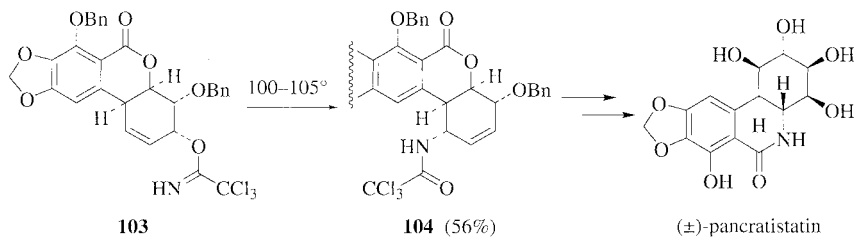


(Eq. 100)

(±)-Pancratistatin. The reliable suprafacial transfer of chirality of trichloroacetimidate rearrangements was exploited in the synthesis of (±)-pancratistatin. Although it was initially hoped that diol **102** would react with trichloroacetimidate at the less-hindered allylic oxygen center, orthoamide **10**, formed as a mixture of diastereomers, was the only product produced. Unfortunately, this intermediate stubbornly refused to undergo thermal [3,3]-sigmatropic rearrangement (Eq. 101).⁵⁶



However, benzyl-protected congener **103** is converted to the late-stage (\pm)-pancratistatin precursor **104** upon heating at 100–105° under high vacuum (Eq. 102).



(Eq. 102)

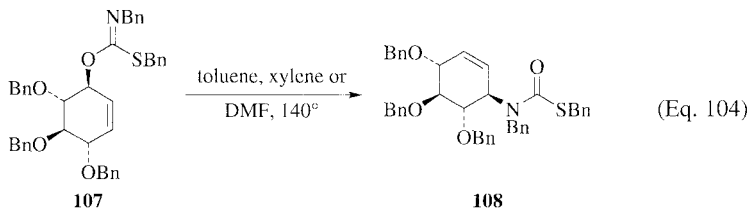
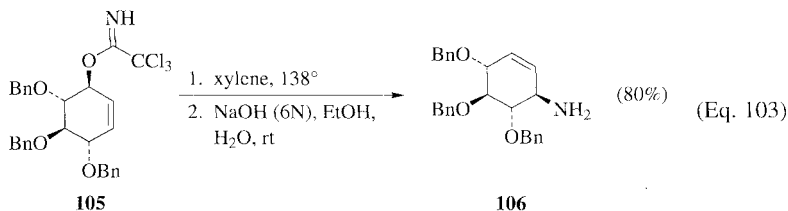
COMPARISON WITH OTHER METHODS

The importance of allylic amines in synthesis has led to the development of many methods for their synthesis, several of which take advantage of allylic alcohols as starting materials. Although various attractive methods have been developed, few match the breadth, regiocontrol, and stereocontrol of the trihaloacetimidate rearrangement. The ease by which the trihaloacetyl group can be removed to release the free allylic amine further distinguishes the trihaloacetimidate rearrangement from related methods. A recent review summarizes some of these methods as well as other syntheses of allylic amines.¹⁵ This section covers the more significant developments since that review, including other rearrangement methods, aminolysis of allylic electrophiles, allylic amination of alkenes, hydroamination of alkynes and dienes, and addition of vinyl nucleophiles to imine derivatives.

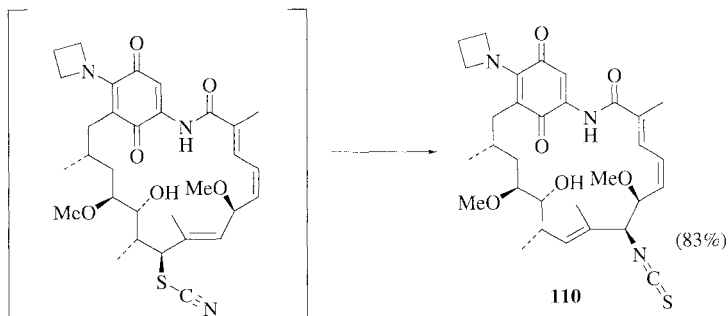
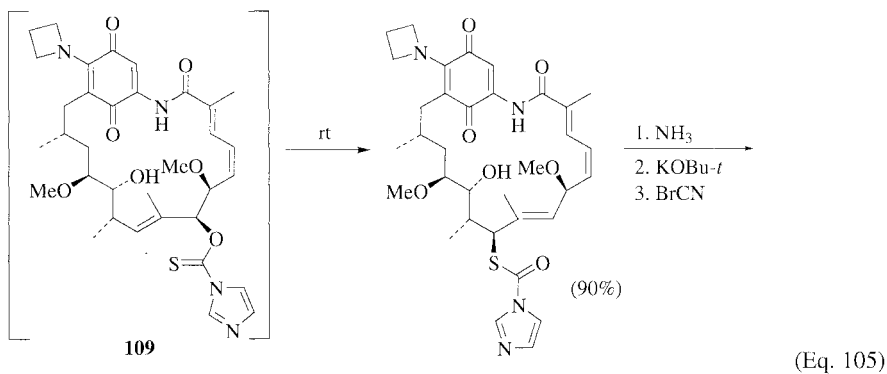
Other Allylic Rearrangements

In addition to the imidate group, several functional groups are suitable for preparation of allylic amines by [3,3]-sigmatropic rearrangement. Allylic urethanes,¹²⁹ isourcas,¹³⁰ cyanates,¹³¹ thioimidates,^{132,133} and sulfamates¹³⁴ were explored early on as potential candidates for the sigmatropic transformation of allylic alcohols into allylic amines.¹⁰ More recently, rearrangements of allylic *N*-benzoyl benzimidates and allylic phosphorimidates have been studied.^{101,135} Each of these methods exhibits some limitations, either in the preparation of the rearrangement precursors, conditions required for the rearrangement, scope of the rearrangement, or difficulties encountered in subsequent hydrolysis of the protected amine products. At this point, none of the aforementioned alternatives to the trihaloacetimidate rearrangement has been developed into a broadly useful method for preparing allylic amines.

Thioiminocarbonates have found some application in the synthesis of allylic nitrogen derivatives.¹³⁶ However, in a direct comparison, trichloroacetimidate rearrangement of **105** is found to be the preferred method for preparation of the amine **106** (Eq. 103). Rearrangement of thioiminocarbonate **107** gives rearrangement product **108** in low yield (Eq. 104), whereas heating **105** in refluxing xylene provides the desired amine in high yield after mild hydrolysis to remove the trichloroacetyl group.¹³⁷

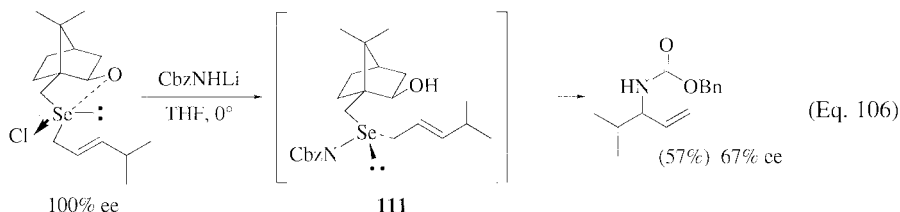


A method for converting an allylic alcohol to the corresponding amine with retention of configuration that involves two sequential [3,3]-sigmatropic rearrangement steps is used in the synthesis of an ansamycin.¹³⁸ In this study, thionocarbamate **109** is not isolated, but rearranges spontaneously upon its formation at room temperature to give the allylically-transposed thiocarbamate product in 90% yield from the starting allylic alcohol (Eq. 105). This intermediate is then transformed in two

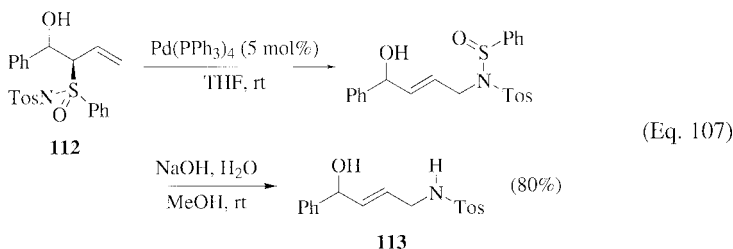


steps to the allylic thiocyanate, which also rearranges spontaneously providing allylic isothiocyanate **110** in 83% yield.

Allylic amine derivatives are also available from allylic alcohols by [2,3]-sigmatropic rearrangements of allylic selenimides^{139,140} and allylic selenonium ylides.¹⁴¹ These promising methods also exhibit the potential for asymmetric induction. For example, rearrangement of chiral, enantioenriched allylic selenimide **111** takes place in situ to yield the allylic carbamate (Eq. 106). Enantiomeric excesses of up to 93% are achieved in some related reactions when the substituent on nitrogen is a *para*-toluenesulfonyl group.¹⁴⁰



Allylic sulfoximines undergo either thermal or Pd(II)-catalyzed rearrangement to yield *N*-protected allylic amines. Although the thermal process gives a mixture of isomers, presumably by a dissociation-recombination mechanism,¹⁴² Pd(II)-catalyzed rearrangement of allylic sulfoximine **112** takes place readily with transposition of the double bond to give rearrangement product **113** in 80% overall yield (Eq. 107).^{143,144}

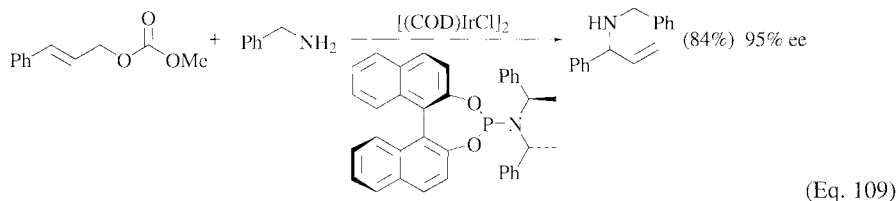
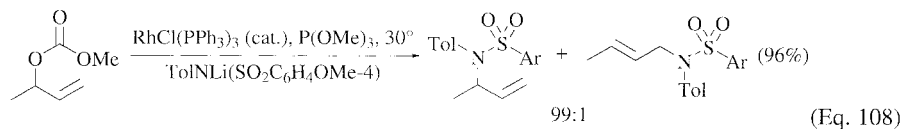


Other Routes to Allylic Amines

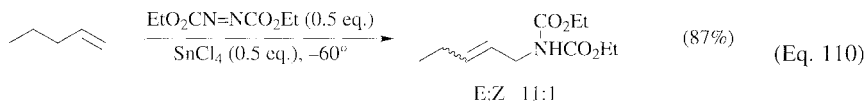
Amination of Allylic Electrophiles. The most straightforward preparation of allylic amines is unquestionably direct allylation of nitrogen with an allylic electrophile. However, this approach is often compromised by the propensity for di- and triallylation. This problem can be circumvented by delivery of the nitrogen atom in protected form as in the Gabriel synthesis.

An area of intense recent study is the transition-metal-catalyzed reaction of amines with allylic electrophiles.¹⁵ A variety of allyl acetates, carbonates, halides, and even allylic alcohols are converted to allylic amines in this way, with the most widely used catalysts to date being complexes of palladium. When a π -allyl palladium intermediate is unsubstituted at one end, the amine generally attacks

at this terminus to give a trans unbranched allylic amine. Recently, complexes of rhodium,^{145–147} ruthenium,^{148,149} iridium,^{150–153} and palladium¹⁵⁴ have been shown to catalyze allylic aminations favoring reaction at the more hindered allyl terminus to give the branched allylic amine product (Eq. 108).¹⁴⁷ However, regioselectivity is typically diminished when there is branching α to the leaving group. These discoveries open up the opportunity to accomplish such aminations in enantioselective fashion,^{150,153–156} providing a highly attractive route to enantioenriched allylic amines (Eq. 109).^{150,155,156}

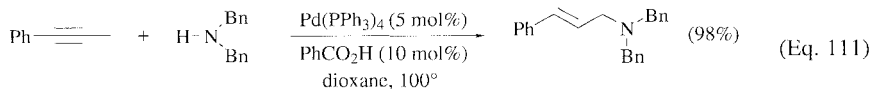


C–H Activation. Direct substitution of an allylic C–H bond of an alkene by nitrogen is a very attractive route to allylic amines. This chemistry is generally associated with ene reactions of N=N species¹⁵⁷ or nitrene addition followed by rearrangement to the allylic amine.¹⁵⁸ Several approaches of these types have met with success, although yields are generally moderate and these methods at present are limited in scope. Thus, the ene reaction of diethyl-azodicarboxylate with alkenes provides good yields (77–95%) of allylic amine adducts (Eq. 110).¹⁵⁷ Efforts to introduce asymmetry into the reaction using di-(–)-menthyl diazodicarboxylate meet with moderate success; however, removal of the menthol chiral auxiliary is difficult.¹⁵⁹ Iron^{160,161} and manganese¹⁵⁸ complexes have also been used to successfully introduce nitrogen at the allylic position of alkenes, although yields are modest.

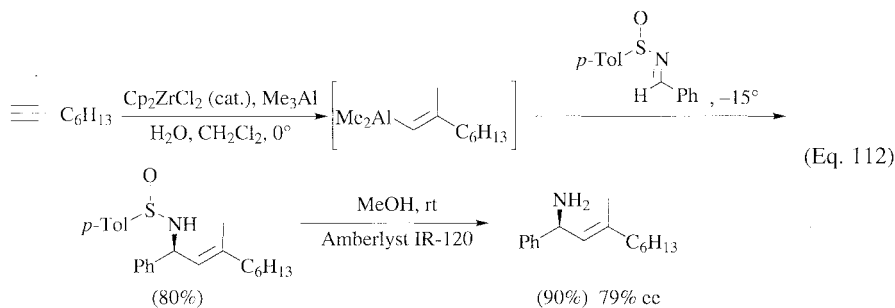


Hydroamination. The application of transition metal catalysis to the synthesis of allylic amines by hydroamination of dienes¹⁶² and alkynes (Eq. 111)¹⁶³ holds considerable promise. At this point, the scope of this approach is largely unexplored. Mixtures of regioisomeric products are not uncommon in the hydroamination of dienes, including variable trans/cis ratios of the allylic amine product, depending

upon the reaction conditions.



Addition of Vinyl Nucleophiles to Imine Derivatives. Much progress has been recorded in recent years in the synthesis of amines by the addition of organometallic reagents to imines and their derivatives, with several recent reviews summarizing this progress.^{164,165} When the nucleophile is vinylic, an allylic amine or a derivative results. An example, illustrating the synthesis of enantioenriched allylic amines, is shown in Eq. 112.¹⁶⁶



EXPERIMENTAL CONDITIONS

General Comments

An attractive aspect of the Overman rearrangement is its experimental simplicity. Typically the intermediate allylic trichloroacetimidate is not purified, but rearranged directly under either thermal or metal-catalyzed conditions. Despite the progress that has been made in the area of metal catalysis, the thermal rearrangement of allylic trihaloacetimidates is so reliable and convenient that most applications employ these conditions. A wide variety of non-nucleophilic solvents can be used in the imidate preparation and rearrangement steps. Dry solvents (commercial quality) are typically acceptable, and should be employed to minimize hydrolysis of the trichloroacetimidate intermediate.

Preparation of Allylic Trichloroacetimidates

Bases promote the addition of alcohols to trichloroacetonitrile. Two general conditions are commonly employed for preparing allylic trichloroacetimidates: catalytic or stoichiometric amounts of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU),^{91,108} or catalytic quantities of a metal alkoxide that is generated in situ by reaction of the allylic alcohol with 5–20 mol% of NaH, KH, sodium metal, or *n*-BuLi. Sodium hydride is employed most commonly in the latter procedure with diethyl ether or

THF being used as the solvent and deprotonation being carried out at temperatures from 0° to -15°. If the alkoxide is generated, it is important to use only catalytic quantities: although the equilibrium constant for generating trichloroacetimidates from the addition of alcohols to trichloroacetonitrile is high, the corresponding equilibrium of an alkoxide and trichloroacetonitrile to form the trichloroacetimidate conjugate base is much less favorable. Dichloromethane has commonly been the solvent when DBU is used as a base, although other dry aprotic solvents could likely be utilized. When DBU is used, it is employed catalytically (10 mol%) or used in excess.

In the alkoxide-catalyzed procedure, the order of addition of the reagents is variable. For secondary and tertiary alcohols, the preferred order of addition is to slowly transfer the alcohol/alkoxide solution by cannula into a solution of trichloroacetonitrile,⁶ although the reverse order of addition has been employed without adverse effects.^{137,167} The formation of trichloroacetimidates from primary alcohols is best carried out by adding trichloroacetonitrile to the alcohol/alkoxide mixture.

In the DBU-promoted process, the order of addition of the base does not play a critical role: DBU can be pre-mixed with the alcohol,^{26,49} added to the alcohol as a mixture with the trichloroacetonitrile,^{47,108} or added sequentially with trichloroacetonitrile (first DBU, followed by trichloroacetonitrile). Use of DBU allows unhindered allylic trichloroacetimidates to be formed at low temperatures (down to -78°), although temperatures around -35° to 0° are most common.

Allylic trichloroacetimidates are reasonably stable to standard purification methods, such as either vacuum distillation or silica gel chromatography. Nonetheless, they are almost always used with minimal purification. For example, after extractive workup and quick passage through a plug of silica gel, the solvent is removed and the crude imidate is redissolved in the rearrangement solvent for heating to reflux. Allylic trichloroacetimidates often undergo partial hydrolysis during slow chromatography on silica gel; this is not observed if Davisil grade silica gel (W.R. Grace & Co.) is used.

Preparation of Allylic Trifluoroacetimidates

The preparation of allylic trifluoroacetimidates first requires generation of trifluoroacetonitrile, a colorless gas (bp = -64°). In early studies, trifluoroacetonitrile was generated by the vigorous dehydration of trifluoroacetamide using phosphoric pentoxide.⁷⁵ After passing gaseous trifluoroacetonitrile through a sequence of traps and scrubbers, an excess of trifluoroacetonitrile is condensed to prepare an ethereal solution for subsequent addition to a solution of the alcohol/alkoxide at -78°. The alkoxide is typically generated by the action of *n*-BuLi (20 mol%) on the alcohol in THF at 0° or below. A more convenient "one-pot" procedure for preparing allylic trifluoroacetimidates generates trifluoroacetonitrile in situ from trifluoroacetamide by reaction with oxalyl chloride and DMSO.¹⁶⁸

Thermal Rearrangements of Allylic Trihaloacetimidates

As discussed in the Scope and Limitations section, the thermal rearrangement is somewhat faster in solvents of higher polarity. Nevertheless, high-boiling hydrocarbon solvents such as toluene and xylenes have been employed most widely. The crude allylic trichloroacetimidate typically is dissolved in the solvent of choice and

the rearrangement carried out at reflux. Some substrates require higher temperatures and these rearrangements can be carried out in a sealed tube. Alternatively, *ortho*-dichlorobenzene (bp 180°), decalin (bp 190°), *tert*-butylbenzene (bp 169°), or diphenyl ether (bp 259°) can be used to bring about the rearrangement. The concentration at which the thermal rearrangement is conducted appears to be of little importance: most rearrangements are run at about 0.1 M, although some have even been effected at high concentration or neat.

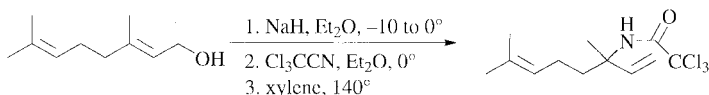
Unwanted decomposition of the allylic trichloroacetimidate by ionization to form trichloroacetamide and the corresponding allylic cation (and eventually diene byproducts) can be problematic when ionization of the allylic C–O σ -bond produces a particularly stable allylic cation, for example with tertiary allylic trichloroacetimidates. This side reaction is likely promoted by acidic impurities. A significant improvement to the rearrangement procedure is the inclusion of powdered anhydrous K_2CO_3 , which scavenges acids and prevents the decomposition of the imidate.⁶³ The amount of K_2CO_3 added varies from a small amount (20 mol% relative to the crude allylic imidate) to a slight excess. Improvements in yield of up to 50% are reported;⁶³ in some cases, previously nonviable rearrangements are made possible.

Rearrangements of allylic trifluoroacetimidates are carried out under similar conditions. The time required for the rearrangement to proceed to completion may be reduced and/or the yield improved when trifluoroacetimidates, rather than their trichloro congeners, are employed.^{75,95}

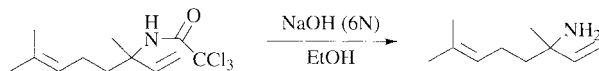
Metal-Catalyzed Rearrangements of Allylic Trichloroacetimidates

After the initial report that mercuric trifluoroacetate catalyzes the rearrangement of allylic trichloroacetimidates,⁴ the catalysts that have been most successfully applied are Pd(II) complexes. The commercially available, or readily prepared,¹⁶⁹ bis(acetonitrile) and bis(benzonitrile) complexes of $PdCl_2$ are employed widely. These complexes are used at 4–10 mol% to effect the rearrangement of primary and secondary allylic trichloroacetimidates; reports of successful Pd(II)-catalyzed rearrangements of secondary imidates are rare. Tetrahydrofuran, toluene, and dichloromethane have been used as solvents, with rearrangements taking place at room temperature in a matter of hours.^{27,28,30,62} Catalytic asymmetric rearrangements employing the catalyst COP-Cl (**8**) generally are carried out with catalyst loadings of 1–5 mol% in CH_2Cl_2 .⁷ The recently introduced COP-hexafluoroacetylacetonate complex **78** is more soluble allowing a wider variety of solvents to be employed and the reactions to be conducted at high substrate concentration (up to 2.6 M).⁹ Catalytic asymmetric rearrangements of allylic trichloroacetimidates with the COP catalysts can be conducted at temperatures up to 60° without loss of enantioselectivity.

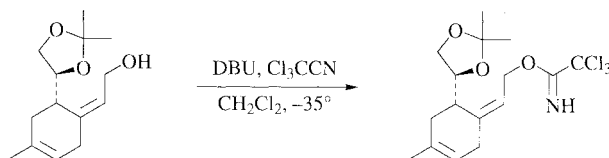
EXPERIMENTAL PROCEDURES



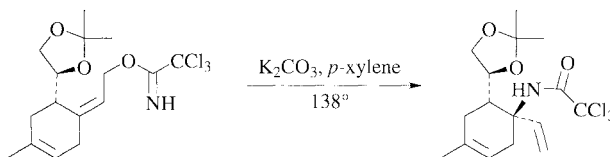
2,2,2-Trichloro-*N*-(3,7-dimethylocta-1,6-dien-3-yl)acetamide (Alkoxide-Catalyzed Procedure for Preparing Allylic Trichloroacetimidates and Thermal Rearrangement of the Crude Imidate Intermediate).⁴³ This preparation is described in *Organic Synthesis*.⁴³



3,7-Dimethylocta-1,6-dien-3-amine (Basic Hydrolysis of an Allylic Trichloroacetamide to Form the Allylic Amine).⁴³ This preparation is described in *Organic Synthesis*.⁴³

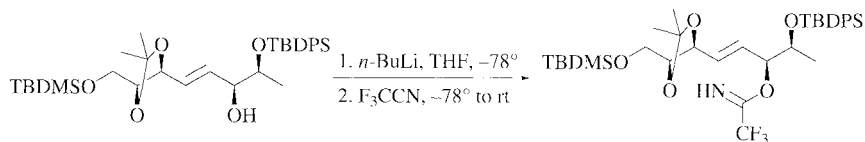


(*Z*)-2-[(6*S*)-6-(2,2-Dimethyl-1,3-dioxolan-4-yl)-4-methylcyclohex-3-enyl]-2,2,2-Trichloroacetimidate (Preparation of a Trichloroacetimidate using DBU).⁴⁹ To a cooled (-35°) solution of the allylic alcohol (18.5 g, 77.7 mmol) in dry CH_2Cl_2 (370 mL) was added DBU (13.9 mL, 93.2 mmol) followed by the dropwise addition of Cl_3CCN (9.35 mL, 93.2 mmol) over a period of 10 minutes. The reaction mixture was stirred at -35° for 1 hour, then was quenched with NH_4Cl (saturated aqueous, 300 mL) and extracted with CH_2Cl_2 . The combined organic extracts were washed with saturated NH_4Cl solution, dried (Na_2SO_4) and concentrated. The residue was dissolved in Et_2O and passed through a short column packed with anhydrous Na_2SO_4 and silica gel 60. The Et_2O was evaporated to yield the imidate as a light yellow oil: IR (KBr) 3345, 2983, 2931, 1661, 1455, 1370, 1289, 1072 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 1.33 (s, 3H), 1.41 (s, 3H), 1.64 (br s, 3H), 1.72 (br d, $J = 18$ Hz, 1H), 2.33 (br d, $J = 18$ Hz, 1H), 2.67 (br d, $J = 19$ Hz, 1H), 2.94–3.10 (m, 2H), 3.71 (dd, $J = 8, 6.5$ Hz, 1H), 4.10 (dd, $J = 8, 6$ Hz, 1H), 4.23 (dt, $J = 10, 6.5$ Hz, 1H), 4.77 (ddd, $J = 12, 6, 2$ Hz, 1H), 5.00 (ddd, $J = 12, 8, 1$ Hz, 1H), 5.38 (br s, 1H), 5.71 (ddd, $J = 8, 6, 2$ Hz, 1H), 8.25 (br s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 23.2, 25.3, 26.7, 32.3, 33.3, 39.8, 65.3, 68.6, 75.7, 91.5, 109.0, 118.2, 120.2, 131.1, 142.5, 162.7.

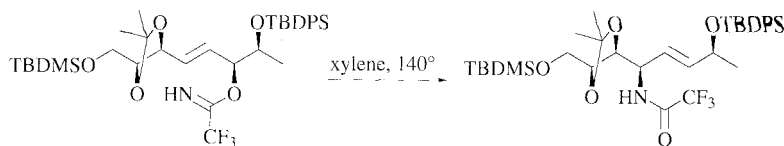


2,2,2-Trichloro-*N*-(1*R*,6*S*)-6-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-methyl-1-vinylcyclohex-3-enyl]acetamide (Thermal Rearrangement of a Trichloroacetimidate in the Presence of K_2CO_3).⁴⁹ Powdered K_2CO_3 (1.2 g) was added to a

solution of the crude imidate (prepared as described in the previous procedure) in *para*-xylene (600 mL) and the mixture was heated at reflux with vigorous stirring for 20 hours. After cooling to room temperature, the mixture was filtered through a pad of Super-Cel and the precipitate was washed with toluene. The combined filtrates were concentrated and the residue was purified by column chromatography (SiO₂, 550 g, ether in hexane, 1:10 to 1:5) to yield the amide as colorless crystals (27.4 g, 92% from the alcohol): mp 100–102°; $[\alpha]_D^{27} = +70.2^\circ$ (*c* 0.97, CHCl₃); IR (KBr) 3313, 2987, 2924, 1727, 1542, 1261, 1067 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.39 (s, 3H), 1.42 (s, 3H), 1.64–1.71 (m, 5H), 2.08 (td, *J* = 9, 7.5 Hz, 1H), 2.27 (d quintet, *J* = 17.5, 2.5 Hz, 1H), 3.37 (ddq, *J* = 17.5, 6, 1.5 Hz, 1H), 3.63 (dd, *J* = 9, 7.5 Hz, 1H), 4.03 (td, *J* = 9, 5.5 Hz, 1H), 4.10 (dd, *J* = 7.5, 5.5 Hz, 1H), 5.30 (dd, *J* = 17, 1 Hz, 1H), 5.32 (dd, *J* = 11, 1 Hz, 1H), 5.39 (m, 1H), 5.82 (dd, *J* = 17, 11 Hz, 1H), 9.21 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 22.5, 26.2, 26.5, 30.0, 35.8, 44.3, 59.9, 68.8, 76.3, 93.8, 109.9, 116.0, 119.0, 130.8, 133.7, 160.4; HRMS (FAB) calcd for C₁₆H₂₂NO₃Cl₃ (*M*+*H*), 382.0743, found 382.0721.

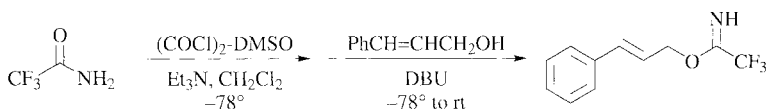


(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(3*S*,4*S*,1*E*)-4-*tert*-butyldiphenylsiloxy-3-(2,2,2-trifluoroacetimidoyloxy)pentenyl]-2,2-dimethyl-1,3-dioxolane (Preparation of an Allylic Trifluoroacetimidate).⁷⁵ To a solution of the alcohol (0.25 g, 0.43 mmol) in THF (6 mL) at -78° was added *n*-butyllithium (1.6M in hexane; 0.29 mL, 0.46 mmol). The resulting solution was stirred for 1 hour whereupon a stream of trifluoroacetonitrile was allowed to bubble through the reaction mixture for five minutes. [The trifluoroacetonitrile was prepared by mixing powdered trifluoroacetamide (10 g, 88 mmol) with phosphorus pentoxide (24 g, 148 mmol) in a round-bottomed flask fitted with a nitrogen inlet and condenser. A polytetrafluoroethylene tube fitted to the condenser led to a trap cooled in an ice–salt mixture, then to a trap cooled in an ether–N₂ (liquid) mixture, and finally to a bath containing aqueous sodium hydroxide via a tube packed with calcium chloride. The reaction mixture was slowly heated to 150° and held at this temperature for 3 hours under a gentle stream of nitrogen gas. The trifluoroacetonitrile distilled out and was collected as a colorless liquid in the -100° ether/N₂ (liquid) trap.] The reaction was allowed to warm to room temperature over a period of 1 hour, then NH₄Cl (0.2 g, 3.6 mmol) was added and the reaction mixture was concentrated under reduced pressure. The product was purified by column chromatography (silica gel 60; petroleum ether in ether, 9:1): 81%; $[\alpha]_D^{23} = -5.7^\circ$ (*c* 0.5, CHCl₃); IR (CHCl₃) 3360, 1680, 1470, 1430, 1380, 1200, 1170, 1112, 840 cm⁻¹; ¹H NMR (CDCl₃) δ 0.1 (s, 6H), 0.9 (s, 9H), 1.0 (d, *J* = 7 Hz, 3H), 1.1 (s, 9H), 1.45 (s, 6H), 3.74 (m, 3H), 4.2 (quintet, *J* = 6 Hz, 1H), 4.44 (m, 1H), 5.5 (t, *J* = 6 Hz, 1H), 5.85 (dd, *J* = 5, 6 Hz, 1H), 5.9 (dd, *J* = 16, 5 Hz, 1H), 7.3–7.8 (m, 10H), 8.2 (s, 1H).



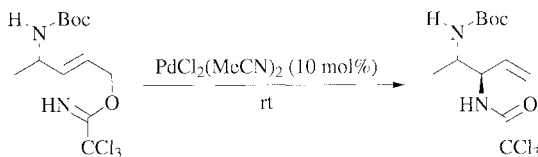
(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-5-[(1*R*,4*S*,2*E*)-4-*tert*-butyldiphenylsiloxy-1-(2,2,2-trifluoroacetyl-amino)pent-2-enyl]-2,2-dimethyl-1,3-dioxolane (Thermal Rearrangement of an Allylic Trifluoroacetimidate).⁷⁵

A solution of a portion of the trifluoroacetimidate prepared in the previous procedure (90 mg, 0.13 mmol) in xylene (2 mL) was degassed with argon and heated at reflux for 20 hours. The reaction mixture was then concentrated under reduced pressure and the residue was purified by column chromatography (silica gel 60, petroleum ether in ether, 15:1) to give the amide (74 mg, 82%): $[\alpha]_{\text{D}}^{23} = -50.6^\circ$ (*c* 1.1, CHCl_3); IR (CHCl_3) 3420, 1730, 1530, 1480, 1470, 1430, 1370, 1170, 1110, 1080, 840 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.1 (s, 6H), 0.9 (s, 9H), 1.1 (s, 9H), 1.2 (d, $J = 6$ Hz, 3H), 1.4 (s, 6H), 3.7 (m, 2H), 3.85 (m, 1H), 4.0 (dd, $J = 8, 2$ Hz, 1H), 4.3 (quintet, $J = 6$ Hz, 1H), 4.67 (t, $J = 7.5$ Hz, 1H), 5.5 (dd, $J = 16, 7$ Hz, 1H), 5.75 (dd, $J = 16, 6$ Hz, 1H), 6.85 (d, $J = 9$ Hz, 1H), 7.3–7.8 (m, 10H). Anal. Calcd for $\text{C}_{35}\text{H}_{52}\text{F}_3\text{NO}_5\text{Si}_2$: C, 61.8; H, 7.7. Found: C, 61.5; H, 8.05.

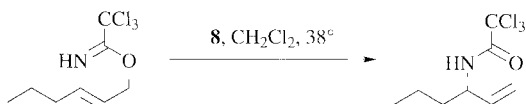


Cinnamyl 2,2,2-Trifluoroacetimidate (“One-Pot” Procedure for the Preparation of an Allylic Trifluoroacetimidate).⁶²

Into a flame-dried three-necked round-bottomed flask was placed 2,2,2-trifluoroacetamide (734 mg, 3 mmol), DMSO (1.36 mL, 8.7 mmol), and CH_2Cl_2 (30 mL). The mixture was cooled to -75° whereupon oxalyl chloride (0.51 mL, 5.9 mmol) and triethylamine (2.5 mL, 18 mmol) were slowly added. The mixture was stirred at -78° for 30 minutes, then DBU (0.6 mL, 4 mmol) and cinnamyl alcohol (296 mg, 2.2 mmol) were added slowly by syringe. The reaction mixture was allowed to warm to room temperature over 10 hours, then the reaction was quenched by the addition of water. The aqueous layer was extracted (EtOAc), the combined organic layers washed with brine, dried (Na_2SO_4) and filtered. Purification by column chromatography (SiO_2 , hexane in ethyl acetate, 10:1) and then Kugelrohr distillation afforded the product as a colorless oil (384 mg, 76%): bp $100\text{--}105^\circ/0.9$ mm; IR (neat) 3347, 3087, 3063, 3031, 2950, 2887, 1686, 1356, 1202, 1167, 1117, 1076, 967, 847, 747, 735, 693 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.94 (d, $J = 6.3$ Hz, 2H), 6.37 (td, $J = 6.3, 16.1$ Hz, 1H), 6.73 (d, $J = 16.1$ Hz, 1H), 7.26–7.29 (m, 1H), 7.32–7.36 (m, 2H), 7.40–7.43 (m, 2H), 8.23 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 68.2, 115.6 (q, $J = 280$ Hz), 121.9, 126.7, 128.4, 128.6, 135.0, 136.0, 157.8 (q, $J = 38.0$ Hz); EI-HRMS: $[\text{M}^+]$ calcd for $\text{C}_{11}\text{H}_{10}\text{F}_3\text{NO}$, 229.0714; found 229.0689.



(3*R*,4*S*)-4-*tert*-Butoxycarbonylamino-3-(trichloroacetyl)amino-1-pentene (Pd(II)-Catalyzed Rearrangement of an Allylic Trichloroacetimidate).³⁰ To a solution of the crude allylic trichloroacetimidate, prepared from 4.25 g (21 mmol) of the corresponding allylic alcohol, in THF was added $\text{PdCl}_2(\text{MeCN})_2$ (552 mg, 2.13 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 3 hours, whereupon the solvent was removed and the product (3.48 g, 48% from the alcohol) was isolated by column chromatography (silica gel 60, 4:1 toluene–ethyl acetate): ^1H NMR (CDCl_3) δ 1.21 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H), 4.02 (m, 1H), 4.28 (m, 1H), 4.49 (d, $J = 7$ Hz, 1H), 5.34 (m, 2H), 5.73 (m, 1H), 8.73 (s, 1H); ^{13}C NMR (CDCl_3) δ 18.6, 28.7, 49.7, 60.2, 80.9, 93.3, 119.6, 131.7, 157.5, 161.9.



(*S*)-2,2,2-Trichloro-*N*-(1-propylallyl)acetamide (Catalytic Asymmetric Rearrangement of an Allylic Trichloroacetimidate).¹⁷⁰ A round-bottomed flask fitted with a stirring bar was charged with (*E*)-2-hexenyl trichloroacetimidate (6.81 g, 28 mmol, prepared from (*E*)-2-hexenol in 99% yield using the DBU procedure and purified by filtration through a short column of Davisil-grade silica gel using 2% ethyl acetate–hexanes as eluent), (*S*)-COP-Cl (816 mg, 0.56 mmol), and dry methylene chloride (9.3 mL). The flask was sealed with a polyethylene stopper, the stopper secured to the flask with Parafilm, and placed in an oil bath preheated to 38°. After 24 hours, the solution was cooled to room temperature and concentrated using a rotary evaporator to yield a brown oil. This oil was purified by flash chromatography (Davisil-grade silica gel, 0.5% ethyl acetate:hexanes) to give after concentration 6.50 g (95%, 94% ee) of the *S* allylic trichloroacetamide product as a pale yellow oil: IR (neat) 3329, 2966, 2873, 1699, 1522, 1460, 1251 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.96 (t, $J = 7.4$ Hz, 3H), 1.35–1.47 (m, 2H), 1.55–1.69 (m, 2H), 4.39–4.47 (m, 1H), 5.19 (d, $J = 10.5$ Hz, 1H), 5.23 (d, $J = 17.2$ Hz, 1H), 5.80 (ddd, $J = 17.0, 10.4, 5.6$ Hz, 1H), 6.50 (broad s, 1H); ^{13}C NMR (CDCl_3) δ 13.7, 18.8, 36.6, 53.3, 92.8, 116.0, 136.7, 161.2; HRMS (CI-NH_3): ($M-n\text{-Pr}$) calcd for $\text{C}_5\text{H}_5\text{Cl}_3\text{NO}$, 199.9437; found 199.9436.

TABULAR SURVEY

The tabular survey in this chapter covers allylic trihaloacetimidate rearrangements reported from 1974 through April, 2004. [3,3]-Sigmatropic rearrangements of

other imidates are not included, nor are the [3,3]-sigmatropic rearrangements of propargylic alcohols. The tables are organized by substrate structure (the starting allylic alcohol) and are arranged on the basis of increasing carbon count of the alcohol, exclusive of protecting groups.⁴ Secondary alcohols are separated into acyclic (Table 2A) and cyclic (Table 2B) substrates. Both thermal and metal-catalyzed conditions are included in the individual tables with the exception of Table 4, which presents examples of metal-catalyzed asymmetric trihaloacetimidate rearrangements.

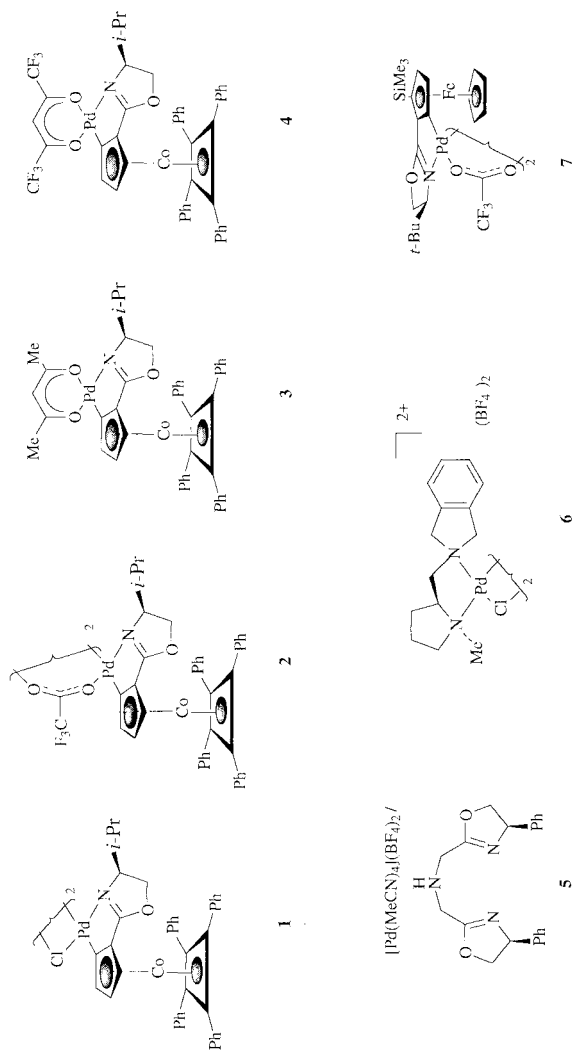
For Tables 1–3 the yield presented is the overall yield for the two-step process (preparation of the imidate and subsequent rearrangement) unless otherwise noted. For Table 4 the yield is for the rearrangement step only. The highest yield is generally given in the case of multiple reports for the same rearrangement. A “(—)” entry indicates that no yield was reported.

The following abbreviations are used in the tables:

OAc	Acetate
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
BOM	Benzyloxymethyl
Bz	Benzoyl
Cbz	Carbobenzyloxy
DBPC	Di(<i>tert</i> -butyl)- <i>para</i> -cresol
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
MOM	Methoxymethyl
MPM	<i>para</i> -Methoxybenzyl
NIS	<i>N</i> -Iodosuccinimide
NBS	<i>N</i> -Bromosuccinimide
TBDMS	<i>tert</i> -Butyldimethylsilyl
TBDPS	<i>tert</i> -Butyldiphenylsilyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
Tr	Trityl (triphenylmethyl)
Ts	<i>para</i> -Toluenesulfonyl

⁴ Generally, the methoxy group was not considered as a protecting group, hence anisole, for example, would be categorized as a C7 compound.

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CHAPTER 2

ASYMMETRIC DIHYDROXYLATION OF ALKENES

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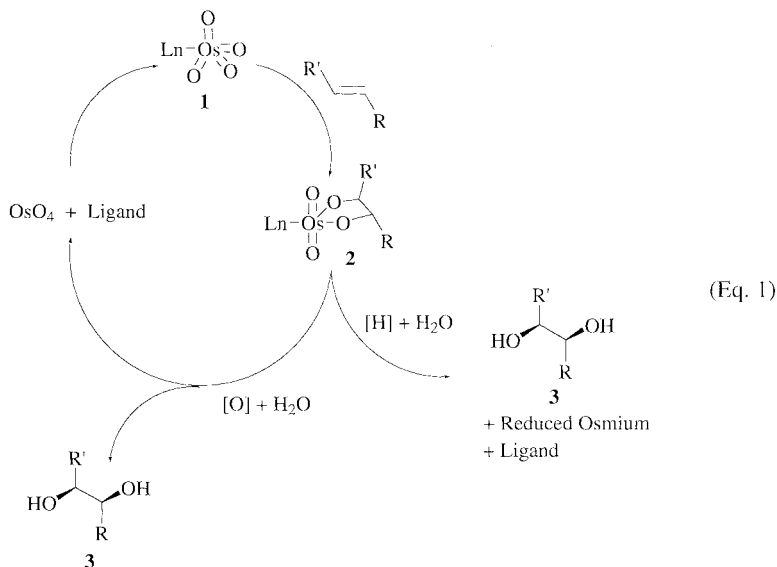
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INTRODUCTION

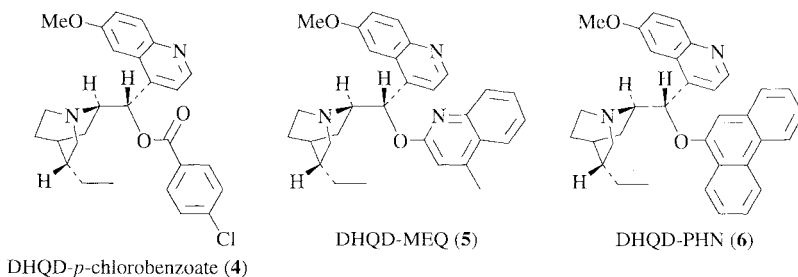
The oxidation of alkenes to vicinal diols using osmium tetroxide (OsO_4) is one of the most selective and reliable transformations in organic synthesis. The reaction stereospecifically produces a cis-1,2-glycol and is tolerant of a wide array of functional groups.¹ Methods have been developed to oxidize alkenes stoichiometrically, as well as in the presence of catalytic amounts of OsO_4 when a suitable secondary oxidant is present. The latter process is particularly useful considering the expense and toxicity of OsO_4 . The utility of dihydroxylation in organic synthesis is enhanced by the availability of facile transformations of the cis-1,2-diol products into other synthetically useful intermediates. Among the most versatile intermediates are the corresponding cyclic sulfates, which serve as reactive epoxide equivalents that can be singly or doubly displaced with amine-, oxygen-, sulfur-, or carbon-based nucleophiles.^{2–5}

The reaction of OsO_4 with alkenes is accelerated by several orders of magnitude in the presence of coordinating amine ligands such as triethylamine, quinuclidine, or diazabicyclooctane (DABCO).^{6,7} These ligands form complexes (**1**) with OsO_4 that subsequently react with the alkene to produce Os(VI) ester intermediate **2** (Eq. 1). When ligand binding to the Os(VI) ester is tight, a reductive quench and workup affords the 1,2-diol product **3** along with reduced osmium species and recoverable ligand. In certain cases, the Os(VI) ester can be oxidatively cleaved, allowing catalytic turnover of the ligand and osmium.

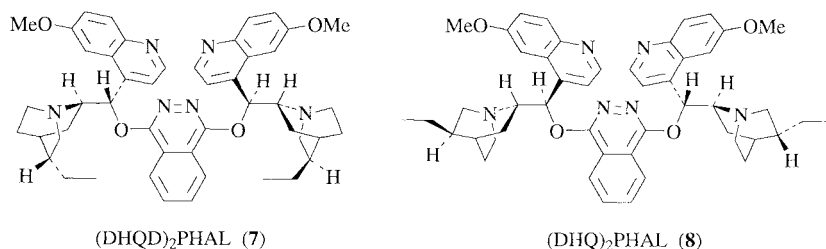


The logical extension to asymmetric osmylation of alkenes in the presence of chiral amine bases spurred the study of asymmetric dihydroxylation. In 1980 the first asymmetric dihydroxylation of alkenes was reported using a cinchona alkaloid as the ligand coordinated to OsO_4 .⁸ This initial report detailed the stoichiometric dihydroxylation of various alkene substrates using dihydroquinidyl acetate resulting in modest to good levels of enantioselection. The availability of the pseudo-enantiomeric alkaloids quinine and quinidine allows for convenient preparation of either enantiomer of the product glycol using the appropriate ligand. Chiral 1,2-diamine ligands have also been used successfully, and ligands derived from 1,2-diaminocyclohexane,^{9,10} 1,2-diphenylethylenediamine,¹¹ *N,N'*-dineohexyl-2,2'-bipyrrrolidine,^{12,13} and 1,2-*bis*-(pyrrolidinyl)ethane^{14–17} provide high levels of enantioselectivity. The tight binding of these diamine ligands to the Os(VI) ester intermediate precludes oxidative catalytic turnover, requiring the use of stoichiometric amounts of the chiral ligand and OsO_4 .

The observation of catalytic turnover in the cinchona alkaloid- OsO_4 system was a breakthrough discovery that revolutionized the field of asymmetric dihydroxylation. The first highly enantioselective catalytic asymmetric dihydroxylation using *N*-methylmorpholine *N*-oxide (NMO) as the secondary oxidant was reported in 1988.¹⁸ Subsequent process improvements and changes in ligand design dramatically extended the scope and utility of the reaction. The use of $\text{K}_3\text{Fe}(\text{CN})_6$ as the secondary oxidant in the presence of aqueous potassium carbonate further enhanced the generality of the process and obviated the requirement of gradual addition of the alkene substrate in cases where hydrolysis of the osmate ester intermediate was slow. By 1991, the *p*-chlorobenzoate (DHQD-*p*-chlorobenzoate) (**4**), the methylquinoline ether (DHQD-MEQ) (**5**), and the 9-phenanthryl ether (DHQD-PHN) (**6**) of dihydroquinidine and dihydroquinine were the most commonly used ligands for catalytic asymmetric dihydroxylation.



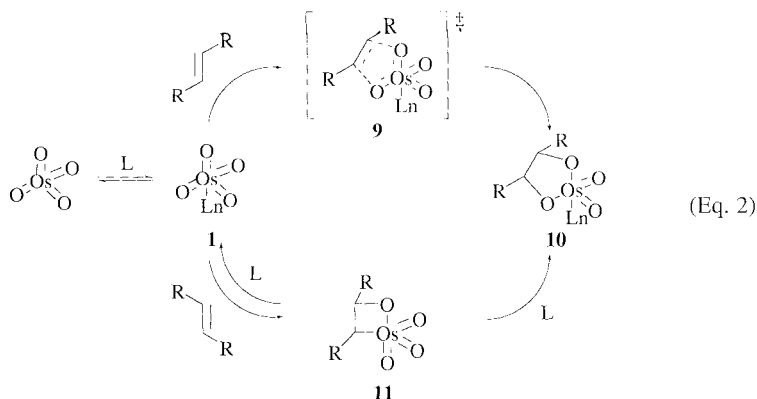
The discovery of bis-cinchona alkaloid ligands that afford higher enantioselectivity and increased generality with regard to alkene substitution was reported in 1992.¹⁹ Since then, specialized ligands have been developed that provide position selectivity in the dihydroxylation of polyenes, efficient kinetic resolution of racemic substrates, and high levels of enantioselectivity for each of the six alkene classes (terminal, 1,1-disubstituted, *cis*-1,2-disubstituted, *trans*-1,2-disubstituted, trisubstituted, and tetrasubstituted). The most commonly used ligands for catalytic asymmetric dihydroxylation are (DHQD)₂PHAL (7) and (DHQ)₂PHAL (8). These ligands are commercially available and can be purchased pre-mixed with potassium osmate, potassium ferricyanide, and potassium carbonate as AD-mix α [containing (DHQ)₂PHAL (8)] or AD-mix β [containing (DHQD)₂PHAL (7)] for added convenience.



Several reviews have appeared covering various aspects of asymmetric dihydroxylation, the most extensive being that of Kolb, VanNieuwenhze, and Sharpless in 1994.^{20–29} This review provides a comprehensive treatment of enantioselective dihydroxylation in the presence of a chiral ligand coordinated to OsO₄. The subject of diastereoselective dihydroxylation under substrate control has been covered extensively elsewhere and is not treated here.³⁰

MECHANISM AND STEREOCHEMISTRY

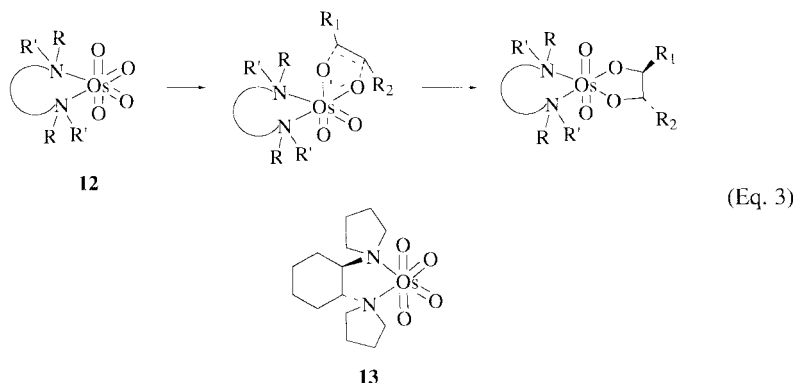
The mechanism of the reaction of OsO₄ with alkenes has been a matter of debate for several decades. At the heart of the controversy is the mechanism of cycloaddition of OsO₄ (or one of its complexes) to the substrate double bond (Eq. 2). Criegee proposed a concerted [3+2] cycloaddition that directly produces the observed



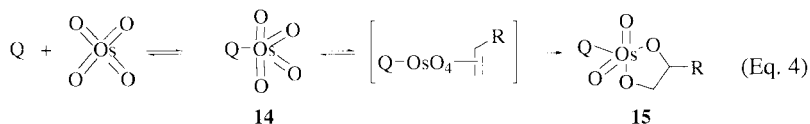
Os(VI) intermediate **10** via transition state **9**.^{31–33} Many of these ligand-bound Os(VI) esters are stable, colored solids that have been characterized by NMR spectroscopy. In some cases, crystal structures have been determined by X-ray methods.^{34–38} The presence of a chiral ligand on osmium affects the stereochemical course of the reaction, and the enantioselectivity of the dihydroxylation is determined by the relative energies of the diastereomeric transition states for the cycloaddition. An understanding of the substrate and catalyst features that are important in determining the relative energies of these diastereomeric transition states is essential for designing more efficient catalysts and for predicting the direction and amount of enantioselectivity that can be expected in the dihydroxylation of a given substrate. An alternative model has been proposed involving an initial [2+2] cycloaddition of one of the Os=O bonds across the substrate double bond to produce an unstable intermediate (**11**) that subsequently rearranges to afford the observed Os(VI) ester.³⁹ In this model the chiral ligand can be involved either in the initial [2+2] cycloaddition or in the subsequent rearrangement to produce the Os(VI) ester.⁸ The proposed [2+2] cycloadduct has never been observed experimentally, and while the [2+2] cycloaddition reaction is consistent with frontier molecular orbital theory, the latest computational studies favor the Criegee [3+2] cycloaddition pathway.^{40–44}

The origin of enantioselectivity in the reaction of 1,2-diamine-OsO₄ complexes with alkenes has been postulated to be governed by steric interactions between the OsO₄ complex and the substituents of the double bond of the substrate. The chelated 20-electron species **12** resulting from coordination of the 1,2-diamine ligand to OsO₄ has been proposed as the active species in these reactions.¹¹ Both kinetic and structural studies provide support for this hypothesis. Kinetic studies show that the dihydroxylation of alkenes in the presence of one equivalent of a 1,2-diamine ligand is several orders of magnitude faster than the corresponding reaction using two equivalents of a monoamine ligand. Moreover, a crystal structure of 1,2-bis(pyrrolidinyl)cyclohexane coordinated to OsO₄ (**13**) has been reported, providing evidence of the existence of these 20-electron species.⁴⁵ A mechanism involving concerted

[3+2] cycloaddition of the alkene across one axial and one equatorial oxygen atom of the bidentate complex **12** predicts the correct stereochemical outcome of the reaction for each of the known reaction systems (Eq. 3).



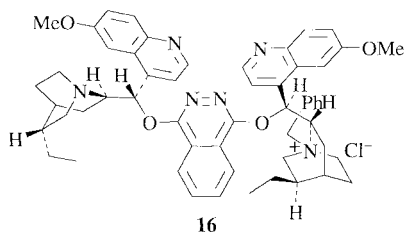
The origin of enantioselectivity in catalytic asymmetric dihydroxylation has been a topic of intense study and debate throughout much of the last decade.^{28,29} Critical to the understanding of the reaction mechanism are kinetic studies that show that the reaction proceeds through a monomeric ligand-osmium complex (**14**; Q = cinchona alkaloid) and point to the existence of a rapid pre-equilibrium that precedes the rate-determining formation of the Os(VI) ester (**15**) (Eq. 4).⁴⁶⁻⁴⁹



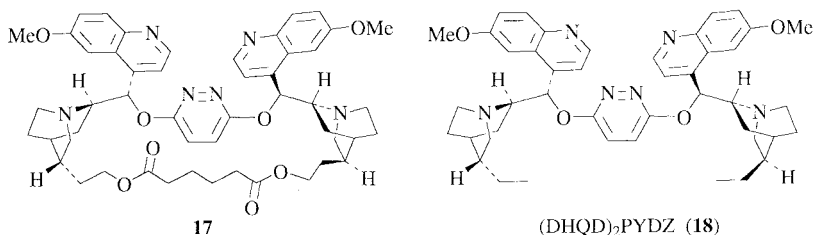
Because of the sterically demanding environment around the quinuclidine nitrogen atom, the equilibrium constant for formation of the cinchona alkaloid-OsO₄ complex **14** is relatively small. Both enantioselectivity and reaction rate are dependent on cinchona alkaloid ligand concentration, and saturation behavior is observed for both parameters at high ligand concentration.⁴⁶ The reaction is first order in both ligand and OsO₄ and exhibits a dramatic ligand acceleration effect relative to the corresponding reaction using quinuclidine as ligand.⁵⁰ Moreover, the extent of ligand acceleration directly parallels the level of enantioselectivity generally observed with each of the alkene classes. The observation of Michaelis-Menten kinetics in the catalytic asymmetric dihydroxylation suggests the existence of a rapid pre-equilibrium step prior to the rate-determining formation of the Os(VI) ester **15**.⁴⁹ The observed inversion phenomenon in Eyring plots of enantioselectivity as a function of temperature is consistent with this observation and suggests the existence of more than one enantioselectivity-determining process in the reaction.^{51,52} Recently

reported kinetic isotope effects on the rate of dihydroxylation are more consistent with theoretical calculations for the [3+2] cycloaddition process than for current proposals of a stepwise [2+2] cycloaddition and subsequent rearrangement of a metallaoxetane intermediate to the observed Os(VI) ester **15**.^{53,54}

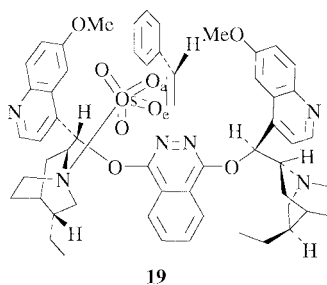
Structural and kinetic studies suggest the formation of a monomeric complex of OsO₄ with the quinuclidine nitrogen of the cinchona alkaloid ligand as the catalytically active species.^{55,56} The observation that reactions using the mono-quaternary ammonium salt **16** as ligand behave identically with respect to enantioselectivity and rate to those employing the corresponding free base **7** establishes that a single ligand-OsO₄ complex is involved in the reaction.^{47,57}



The observation that the tethered bis-cinchona alkaloid ligand **17** behaves identically with regard to rate and enantioselectivity to the corresponding non-tethered ligand **18** rigorously establishes the active conformation of the bis-cinchona alkaloid catalyst.^{58,59} X-ray crystallographic and computational modeling studies suggest that the nitrogen atoms of the phthalazine and pyridazine linker groups are critical to enforcing this active conformation through stereoelectronic effects.⁶⁰



Attractive interactions between the cinchona alkaloid ligand and the alkene substrate influence enantioselectivity in the catalytic asymmetric dihydroxylation. It has been proposed that the high levels of enantioselectivity and rate accelerations observed in the cinchona alkaloid catalyzed asymmetric dihydroxylation are the result of attractive interactions between the alkene substrate and a U-shaped binding pocket established by the methoxyquinoline “walls” and the pyridazine or phthalazine linker “floor” of the catalyst.⁵⁸ The proposed transition state for the dihydroxylation of styrene is depicted in complex **19**.



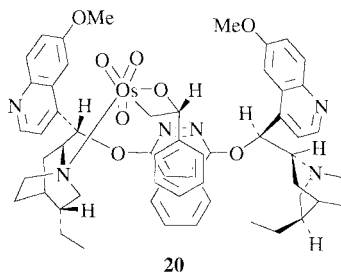
Binding of the substrate in this pocket positions the double bond of the substrate in a perfect orientation for the [3+2] cycloaddition across the axial and one of the equatorial oxygen atoms of the coordinated OsO_4 molecule. According to this model, the rate acceleration for the observed enantioselective pathway relative to other modes is due to the favorable free energy of activation for the reaction from the complex **19** in a manner that is ideal for the formation of the thermodynamically more stable osmate ester. Dihydroxylation of the opposite alkene face to that shown in **19** is unfavorable, as there is no three-dimensional arrangement for π -facial approach of the alkene to the oxygens labeled O_a and O_e while maintaining favorable Van der Waals interactions with the binding pocket. The observation of Michaelis-Menten kinetics and inversion phenomena in Eyring plots of enantioselectivity vs. temperature can be understood in terms of rapid, reversible formation of the complex **19**, followed by irreversible formation of the Os(VI) ester. The sense and magnitude of enantioselectivity for a given dihydroxylation reaction can be anticipated as follows:

- (1) Orient the substrate and catalyst such that the alkene substituent with the greatest potential for binding (usually an aromatic or aliphatic substituent with little steric demand) is positioned within the U-shaped pocket.
- (2) Allow the carbon atoms of the reacting double bond to overlap with the oxygen atoms of the coordinated OsO_4 molecule as illustrated in **19**.
- (3) Assess the degree of unfavorable steric interactions that remain between the catalyst and the substrate.

This model for the asymmetric dihydroxylation reaction has been successfully used to predict the highly enantioselective dihydroxylation of allylic 4-methoxybenzoates,⁶¹ to design a ligand for enantioselective and regioselective dihydroxylation of terpenes,⁶² to optimize catalyst and substrate pairs in kinetic resolutions,⁶³ and to incorporate appropriate hydroxy protecting groups for the regioselective dihydroxylation of dienyl alcohols.⁶⁴

An alternative mechanistic model was proposed that invokes a different mode of cycloaddition of the substrate double bond across one of the $\text{Os}=\text{O}$ bonds as well as a different catalytic binding pocket that governs enantioselectivity. According to

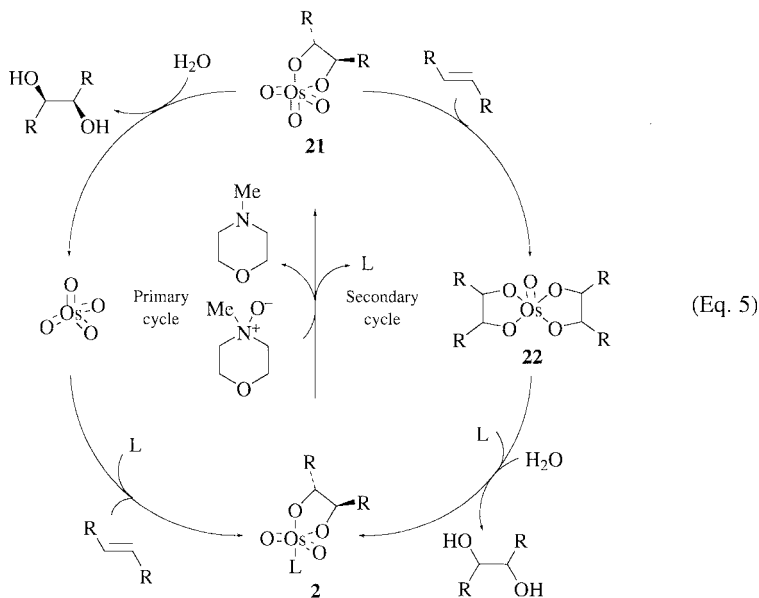
this model, ligand-accelerated catalysis occurs through reduction of the activation energy required for either the formation of the putative metallaoxetane intermediate **20** or its subsequent rearrangement to the Os(VI) ester. Enantioselectivity in the asymmetric dihydroxylation is determined by the difference in transition-state energies for either the formation or rearrangement of the diastereomeric metallaoxetanes. The differential stabilization of these diastereomeric intermediates is thought to occur through favorable Van der Waals interactions between one of the substrate substituents and an L-shaped domain composed of the phthalazine linker group and one of the methoxyquinoline rings of the catalyst.^{48,65} Computational models were developed to describe quantitatively the interactions between the ligand and substrate within the context of this model that lead to enantioselectivity in the reaction.⁴⁸



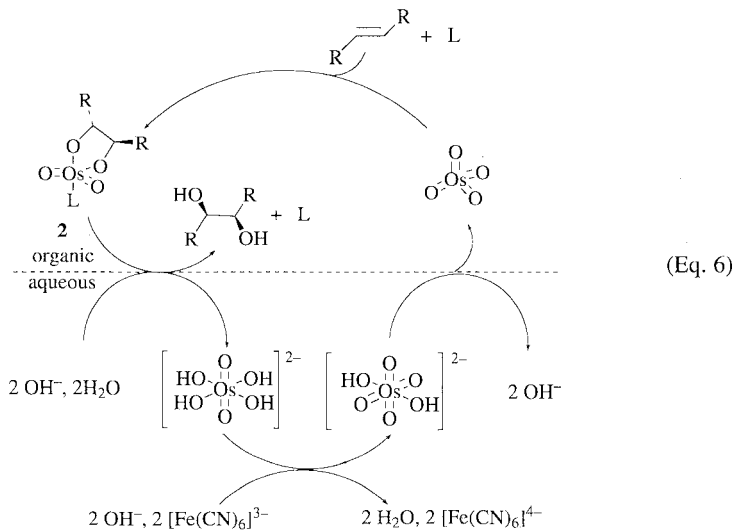
A comparison of the two models for dihydroxylation describes experimental observations of enantioselectivity, position selectivity, and efficiency of kinetic resolution that are more easily understood in the context of the U-shaped binding pocket model.⁶⁶ Computational studies using hybrid quantum mechanics/molecular mechanics (QM/MM) descriptors provide further support for the [3+2] model in the cinchona alkaloid catalyzed asymmetric dihydroxylation.^{67,68} Subsequent studies of kinetic isotope effects⁵³ were inconsistent with the intermediacy of a metallaoxetane intermediate that has been shown by low level computational studies to have higher transition state energies for its formation and rearrangement than the transition state energy for the [3+2] pathway.⁵⁴

Elucidation of the mechanism of catalytic turnover has been more straightforward and has resulted in several improvements in both process and scope for the cinchona alkaloid catalyzed asymmetric dihydroxylation. The Upjohn NMO-based secondary oxidant system was the first to be successfully applied to the reaction.¹⁸ After formation of the Os(VI) ester **2**, oxidation to the Os(VIII) ester **21** precedes the hydrolysis step that produces the product glycol and recycles OsO₄ (Eq. 5). In cases where this hydrolysis step is slow, the intermediate Os(VIII) ester **21** can undergo a second reaction with the alkene substrate, which produces a bis-glycolate ester **22**. Hydrolysis of the osmium bis-glycolate produces the diol product and regenerates the osmate ester **2**. This “second cycle” results in deterioration of both enantioselectivity and rate, as the second alkene addition occurs with poor facial selectivity, and the hydrolysis of the bis-glycolate ester **22** can be extremely slow.⁶⁹ The addition of tetraalkylammonium acetate salts can accelerate the hydrolysis of the Os(VIII) ester

21, but slow addition of substrate is often required to circumvent the second cycle for substrates in which each carbon atom of the double bond is substituted.



The Tsuji $\text{K}_3\text{Fe}(\text{CN})_6\text{--K}_2\text{CO}_3$ secondary oxidant system has also been used successfully for catalytic asymmetric dihydroxylation and is currently the preferred system (Eq. 6). Mechanistic studies indicate that hydrolysis of Os(VI) ester **2** occurs



prior to outer-sphere oxidation of Os(VI) to Os(VIII) by $[\text{Fe}(\text{CN})_6]^{3-}$, thereby precluding the possibility of a second catalytic cycle.⁷⁰ Where each carbon atom of the substrate double bond is substituted, hydrolysis of the corresponding Os(VI) esters can be accelerated by addition of methanesulfonamide, which presumably functions as a nucleophile at the moderately basic pH of the aqueous mixture, or by running the reaction under slightly more basic conditions (pH 12).^{19,71} In situations where Os(VI) salts are used as the osmium source in the reaction, oxidation to Os(VIII) precedes entry into the catalytic cycle.

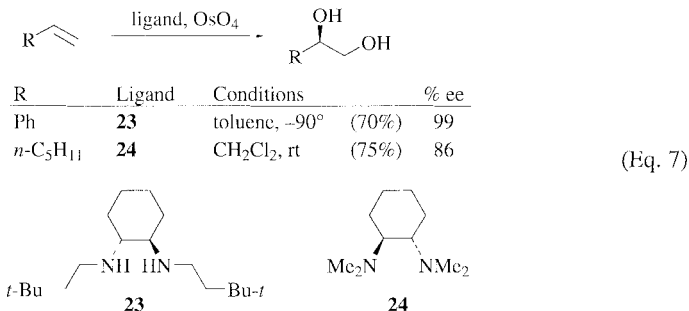
SCOPE AND LIMITATIONS

Asymmetric dihydroxylation of alkenes using either 1,2-diamine ligands or the cinchona alkaloid system is perhaps one of the most general asymmetric processes. The reaction is tolerant of a diverse array of functional groups that may be present on the substrate, and a number of specially developed ligands can be employed for special substrate classes and processes, such as: regioselective and enantioselective dihydroxylation of substrates containing more than one double bond, kinetic resolution of racemic substrates, and dihydroxylation of sterically hindered alkenes. Perhaps the main factor governing the success of an asymmetric dihydroxylation is the substitution pattern of the double bond undergoing transformation. It has long been recognized that the substitution pattern of a carbon-carbon double bond undergoing dihydroxylation by OsO_4 influences the rate of the initial addition of OsO_4 as well as the hydrolysis of the resultant osmate ester intermediate. Steric and electronic effects of substituents can influence both the rate and enantioselectivity of asymmetric dihydroxylation. In order to simplify the analysis, this section will discuss the scope of the reaction as defined for different alkene classes. The six basic alkene classes are: terminal, 1,1-disubstituted, cis-1,2-disubstituted, trans-1,2-disubstituted, trisubstituted, and tetrasubstituted. Within each section, both stoichiometric and catalytic asymmetric dihydroxylation will be addressed with the main focus on the latter process, as this is most general and useful to the synthetic chemist.

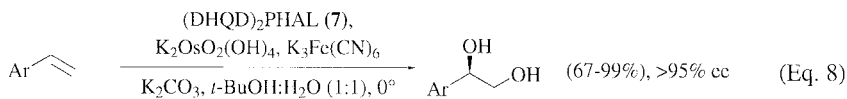
Terminal Alkenes

The enantioselectivity and rate of dihydroxylation of terminal alkenes is strongly influenced by the nature of the single substituent of the substrate double bond. There are few examples of highly enantioselective dihydroxylations of these substrates using 1,2-diamine- OsO_4 complexes. The most commonly examined substrates include styrene, 1-hexene, and 1-heptene. The dihydroxylation of styrene proceeds with generally high enantioselectivity (>90% ee), and the best reported case employed *N,N'*-bis(3,3-dimethylbutyl)-1,2-cyclohexanediamine (**23**) as the chiral ligand to afford styrene glycol with 99% ee and 70% yield (Eq. 7).⁹ Substrates bearing simple aliphatic substituents react with significantly lower enantioselectivity. The best reported case for the dihydroxylation of 1-heptene used a related ligand (*N,N'*-dimethyl-1,2-cyclohexanediamine) (**24**) and afforded the product glycol in 86% ee (Eq. 7).¹⁰ In general, these reactions are run in aprotic solvents (methylene

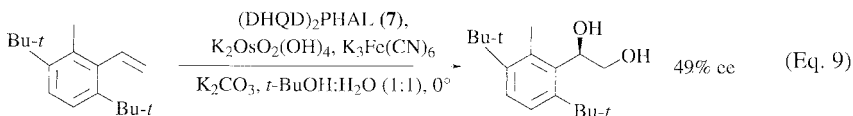
chloride, tetrahydrofuran, or toluene) at low temperatures (-78°) and require stoichiometric amounts of ligand and OsO_4 .



The asymmetric dihydroxylation of terminal alkenes using the catalytic system developed by Sharpless has the greatest synthetic utility due to its breadth of scope and the fact that high levels of enantioselectivity can be routinely obtained. Dimeric ligands, such as the commercially available $(\text{DHQD})_2\text{PHAL}$ (**7**) and $(\text{DHQ})_2\text{PHAL}$ (**8**), afford glycol products of very high enantiomeric purity in cases where the substrate bears an aromatic substituent (styrene-like alkenes) (Eq. 8).¹⁹ This enantioselectivity is attributed to the ability of the substrate to participate in π -stacking and hydrophobic interactions with the binding pocket of the catalyst. These dimeric ligands give substantially higher enantioselectivities than earlier monomeric ligands, such as DQHD-PHN (**6**).⁷² Enantioselectivities greater than 90% can be routinely obtained, and selectivity is largely unaffected by electronic effects imparted by substituents on the aromatic ring. Only substrates possessing unusually large substituents (e.g. 3,5-di-*tert*-butylstyrene)⁶⁰ are oxidized with modest enantioselectivity (Eq. 9), and this is attributed to their inability to interact effectively with the catalyst's binding pocket.

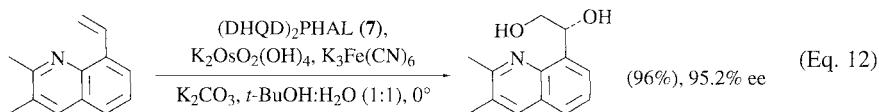
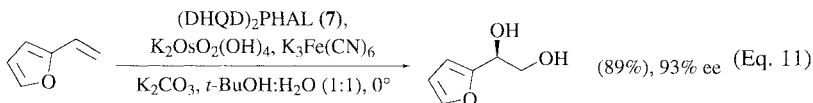
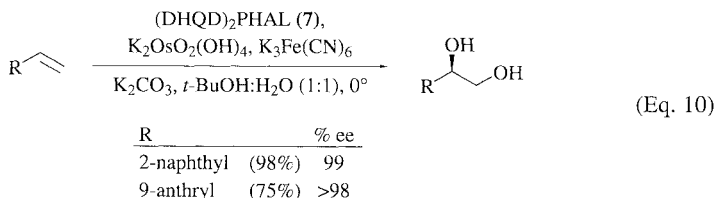


Ar = simple substituted phenyl



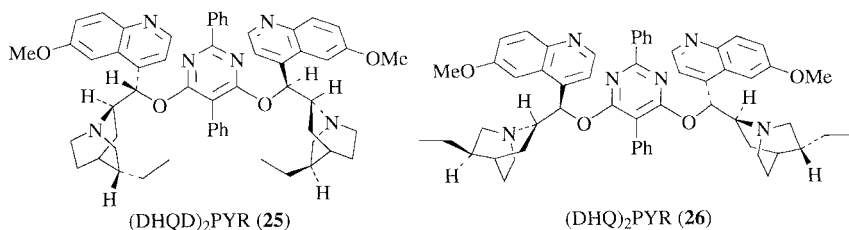
In addition to simple substituted styrenes, the reaction affords very high levels of enantioselectivity in the dihydroxylation of substrates bearing fused aromatic and heteroaromatic rings. Thus, vinylnaphthalene and 9-vinyanthracene are exceptionally good substrates (Eq. 10).^{66,73} Dihydroxylation of vinylheterocycles generally occurs with high enantioselectivity and produces synthetically useful products. The

dihydroxylation of 2-vinylfuran was used to establish a non-carbohydrate route to levoglucosenone, an important chiral building block,⁷⁴ and provides convenient access to carbohydrates (Eq. 11).⁷⁵ Like their carbocyclic counterparts, substrates possessing a fused heteroaromatic substituent are also oxidized with high enantioselectivity (Eq. 12), and the asymmetric dihydroxylation of these substrates has wide scope.⁷⁶



The asymmetric dihydroxylation of terminal alkenes bearing simple aliphatic substituents using (DHQD)₂PHAL (**7**) or (DHQ)₂PHAL (**8**) occurs with somewhat lower enantioselectivity. Some of the best results are obtained for substrates with a straight chain substituent, such as 1-hexene. For these substrates, enantioselectivity is a direct function of substituent chain length as shown in Figure 1.²⁰ This observation can be understood in terms of the increasing hydrophobic interactions between the substrate and the catalyst, which become saturated with substituent chains longer than C₅.

For substrates in which the double bond substituent is cyclic or branched, asymmetric dihydroxylation using the 2,5-diphenylpyrimidine-based ligands [(DHQD)₂PYR (**25**) or (DHQ)₂PYR (**26**)] affords better enantioselectivity than the corresponding phthalazine-linked ligands (Eq. 13).⁷⁷ These two sets of ligands are complementary in that the phthalazine-linked ligands are far superior for the dihydroxylation of terminal alkenes that bear an aromatic substituent such as styrene.



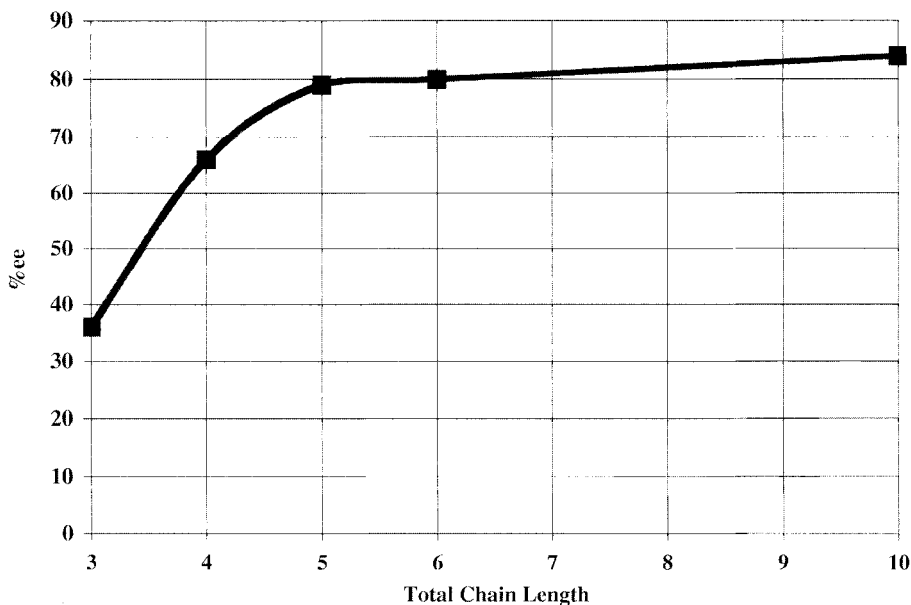
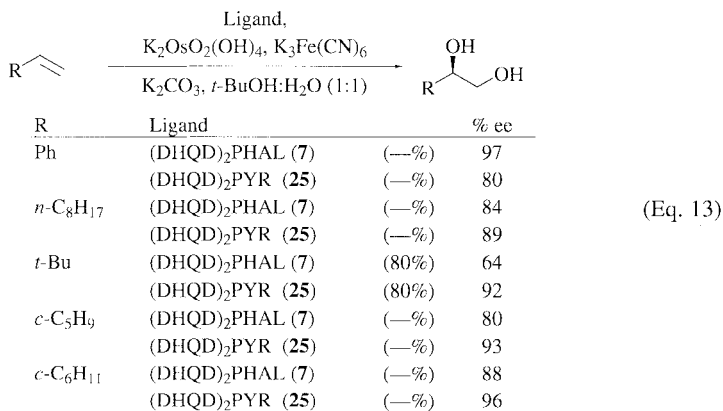


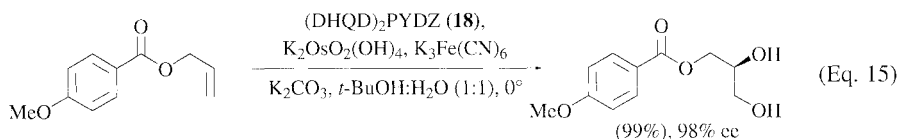
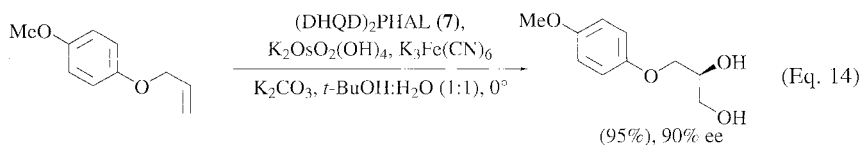
Figure 1. Enantioselectivity as a Function of Total Chain Length for the Asymmetric Dihydroxylation of *n*-Alkyl-substituted Terminal Olefins Catalyzed by (DHQD)₂PHAL.



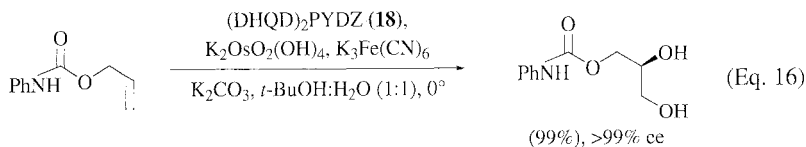
The asymmetric dihydroxylation of monosubstituted alkenes is largely tolerant of protected nitrogen or oxygen functionality on the substituent chain. Substrates containing azides, thioethers, amides, ethers, ketones, and imines can be oxidized without destruction of the additional functionality. Steric effects of alkene substitution on enantioselectivity are consistent with the trends outlined above. Dihydroxylation of hydroxyl-containing substrates proceeds with somewhat lower enantioselectivity, although several protecting groups have been discovered that

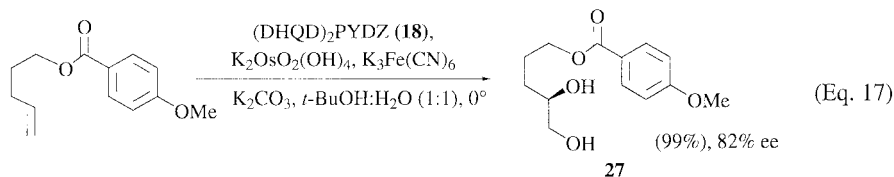
allow highly enantioselective dihydroxylation, and these are discussed below. Reactions where the substrate hydroxy group is protected as an ether or ester have been extensively evaluated.^{61,78,79}

Suitably protected allyl alcohols can be oxidized with very high levels of enantioselectivity, providing synthetically useful chiral glycerol equivalents. The dihydroxylation of allyl aryl ethers proceeds with good enantioselectivity and is largely unaffected by the presence of functional groups present at the 4-position of the aromatic ring.⁷⁹ The most synthetically useful example is the dihydroxylation of allyl 4-methoxyphenyl ether using (DHQD)₂PHAL (**7**), which affords the product glycol in 95% yield and 90% ee (Eq. 14).^{79,80} Significantly better enantioselectivities can be obtained in the dihydroxylation of allyl 4-methoxybenzoate [98% ee with (DHQD)₂PYDZ (**18**)], affording a chiral glycerol equivalent with a readily removed protecting group (Eq. 15).⁶¹ Under these conditions, the reaction time must be minimized, and the isolation of the product from the reaction must be carried out with

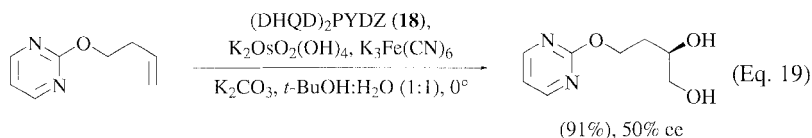
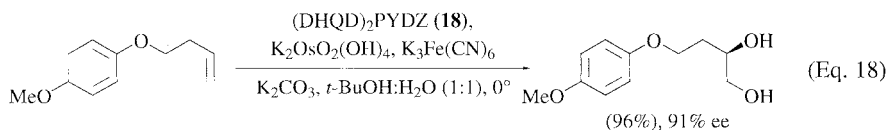


care (by washing the organic phase several times with brine) to remove traces of base that can cause racemization through intramolecular transesterification upon concentration in vacuo. The use of the 4-methoxybenzoyl protecting group as opposed to benzoyl retards transesterification by increasing the kinetic barrier to this side reaction. The enantioselective dihydroxylation of allyl *N*-phenyl carbamate also proceeds with very high enantioselectivity, and the reduced tendency of the carbamoyl group to undergo oxygen to oxygen acyl migration obviates the need to minimize reaction time (Eq. 16).⁸¹ Protection of the allylic alcohol as a bulky silyl or aliphatic ether results in dramatically reduced enantioselectivity, presumably resulting from the inability of the bulky silyl group to fit adequately in the catalyst binding pocket. The 4-methoxybenzoyl group is also the optimum protecting group for 4-pentenol in the asymmetric dihydroxylation, affording the chiral diol **27** with 82% ee (Eq. 17).^{61,82}

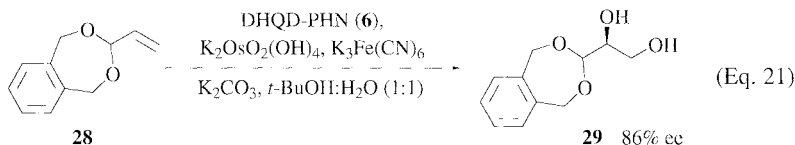
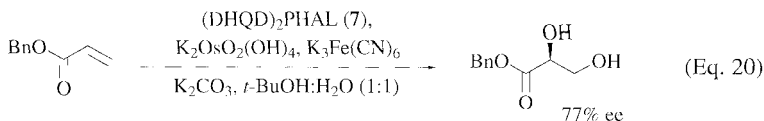




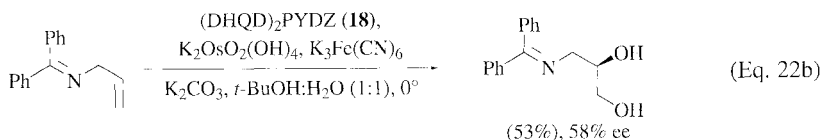
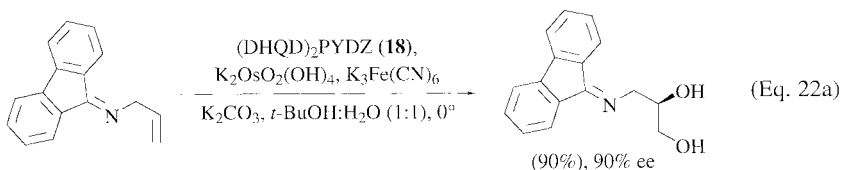
Selectivity in the dihydroxylation of protected homoallylic alcohol derivatives is highly sensitive to the nature of the protecting group.^{61,83} Unlike allylic and bis-homoallylic alcohols that afford products of high enantiomeric purity when protected as the corresponding 4-methoxybenzoates, homoallylic esters are poor substrates for (DHQD)₂PYDZ (**18**). For reactions using this ligand, protection of the substrate hydroxy group as its 4-methoxyphenyl ether is necessary for high enantioselectivity (Eq. 18).⁶¹ The 4-methoxyphenyl group is easily removed by oxidation with ceric ammonium nitrate or DDQ, allowing further elaboration of this useful synthetic piece. The poor enantioselectivity obtained in the reaction of homoallylic 4-methoxybenzoates is attributed to repulsive electronic interactions between the ester carbonyl group and the linker atom nitrogens of the catalyst, as these groups come in close proximity during the [3+2] cycloaddition transition state for the reaction. This inference was experimentally verified by the poor enantioselectivity obtained in the dihydroxylation of homoallyl 2-pyrimidyl ether (50% ee) (Eq. 19),^{61,83} as opposed to that observed with the corresponding 4-methoxyphenyl ether (91% ee) (Eq. 18).



The asymmetric dihydroxylation of acrolein acetals and acrylic esters has also been investigated. Modest levels of enantioselectivity are observed for reaction of acrylic esters catalyzed by (DHQD)₂PHAL (**7**) (Eq. 20); significantly lower enantioselectivity was obtained using (DHQD)₂PYR (**25**) as the chiral ligand.¹⁹ The asymmetric dihydroxylation of acrolein acetals affords synthetically useful glyceraldehyde acetals. The optimum substrate for this reaction is acrolein acetal **28**, which is oxidized to **29** in 86% ee (Eq. 21). The enantiomeric purity of this product can be enhanced by recrystallization, affording glyceraldehyde acetal **29** of 97% ee in 60% overall yield.⁸⁴

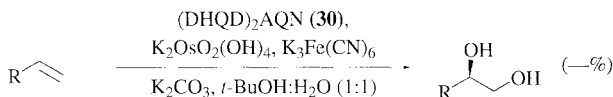
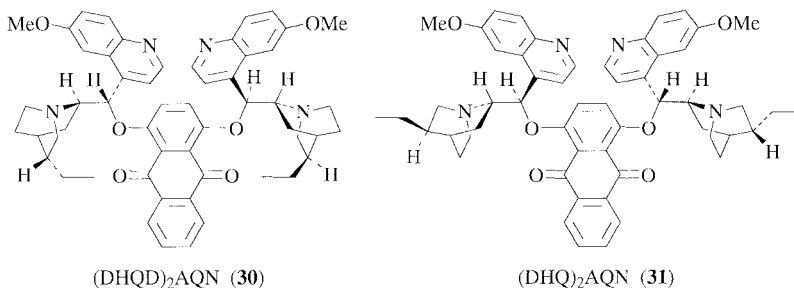


The asymmetric dihydroxylation of nitrogen-containing substrates has been studied with substrates possessing amide, imine, and azide groups.^{61,85} These non-basic substrates react in high yield, and enantioselectivity is strongly dependent on the nature of the nitrogen substituent(s). As observed for allylic alcohol derivatives, protection with flat, aromatic systems results in higher enantioselectivity than protection with bulkier or conformationally flexible groups. For allylic amines, the planar fluorenone imine (Eq. 22a) is superior to the non-planar, benzophenone imine (Eq. 22b) for high enantioselectivity and can be easily removed by treatment with aqueous acid or by hydrogenolysis. The product of this dihydroxylation is a useful synthetic building block for the preparation of cardiovascular β -blocker drugs and other medicinally active substances.



Whereas the majority of reported catalytic enantioselective dihydroxylation of terminal alkenes use the conventional PHAL and PYR based ligands, the anthraquinone ligands (DHQD)₂AQN (**30**) and (DHQ)₂AQN (**31**) afford higher enantioselectivities in reactions of many allylically substituted terminal alkenes (Eq. 23).⁸⁶ The diols that are derived from these substrates are enantiomerically enriched, functionalized chiral glycerol derivatives that are important building blocks for asymmetric synthesis. While the difference in enantioselectivity obtained in the dihydroxylation with the AQN ligands as compared with the PHAL ligands is typically on the order of 10%, it can be as high as 40% for the dihydroxylation of certain substrates such as allyl tosylate. The AQN ligands are not as effective as the

PHAL ligands in the dihydroxylation of substituted styrenes, but they do provide higher levels of enantioselectivity in the oxidation of allylbenzene (78% ee). The AQN ligands are thus complementary to the PHAL and PYR ligands for the enantioselective dihydroxylation of certain terminal alkenes.



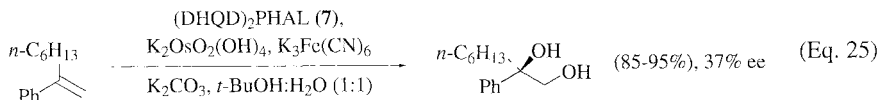
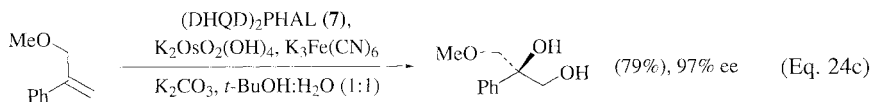
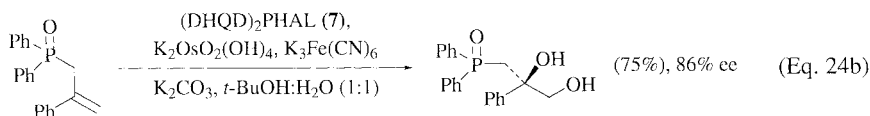
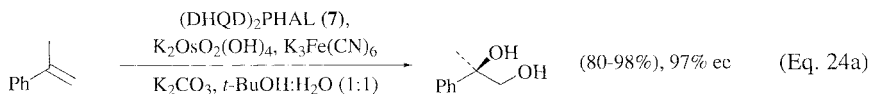
R	% cc
CH ₂ Cl	90
CH ₂ Br	89
CH ₂ I	83
CH ₂ OTs	83
CH ₂ OMs	84
CHCl ₂	72
CF ₃	81
CO ₂ Bn	88
Bn	78

(Eq. 23)

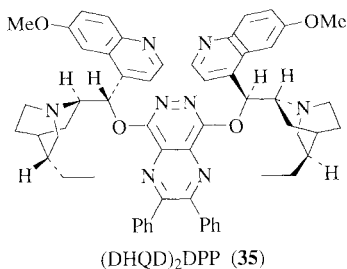
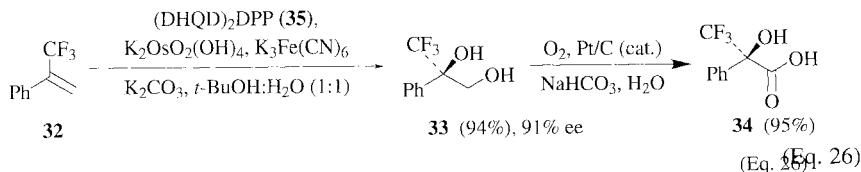
Disubstituted Alkenes

1,1-Disubstituted Alkenes. Enantiofacial discrimination in the enantioselective dihydroxylation of 1,1-disubstituted alkenes is dependent not only on the efficiency of the catalyst, but also on its ability to differentiate the two alkene substituents. When the alkene substituents possess similar steric and electronic properties, the energetic differences for oxidation at either enantiomeric face of the alkene are diminished, resulting in reduced enantioselectivity. While the asymmetric dihydroxylation of these substrates with simple chiral 1,2-diamine ligands has not been reported, the catalytic dihydroxylation of 1,1-disubstituted alkenes with cinchona alkaloids has been extensively studied. For these substrates, enantioselectivities are generally lower than those observed for terminal alkene dihydroxylation due to competition of each alkene substituent for interaction with the catalyst's binding pocket. This effect is dramatically evident when comparing the enantioselectivities for the dihydroxylation of a variety of α -substituted styrenes. The highest enantioselectivities in the dihydroxylation with (DHQD)₂PHAL (7) are realized with bulky, short, or hydrophilic α -substituents (Eqs. 24a-c), whereas substrates such as 2-

phenyl-1-octene, which possesses two groups that can interact effectively with the catalyst binding pocket, react with poor facial selectivity (Eq. 25).^{87,88}

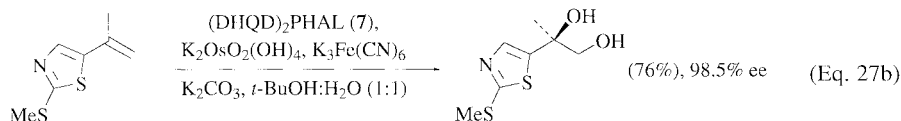
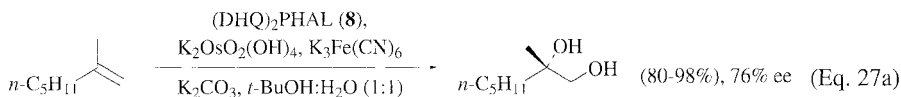


The highly enantioselective dihydroxylation of α -substituted styrenes affords a short route to a Mosher's acid precursor in which the dihydroxylation of α -trifluoromethylstyrene (**32**) catalyzed by (DHQD)₂DPP (**35**) gives the product diol **33** in 94% yield and 91% ee (Eq. 26).⁸⁹ Oxidation of the diol with oxygen in the presence of platinum affords carboxylic acid derivative **34**, which crystallizes as a conglomerate, allowing the preparation of enantiomerically pure material after a single recrystallization.

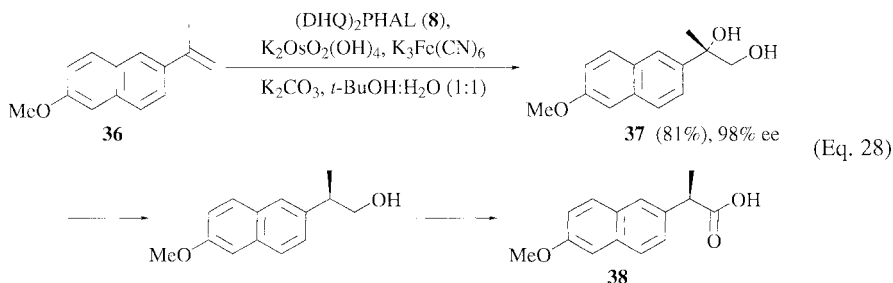


Simple 2-substituted propenes are oxidized with moderate to high enantioselectivity that is strongly dependent on the properties of the alkene substituent. In gen-

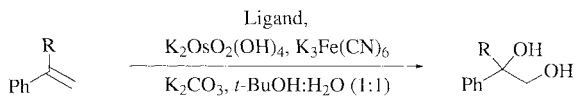
eral, substrates possessing aromatic or heteroaromatic substituents react with higher enantioselectivity than those containing aliphatic groups (Eqs. 27a and 27b).^{19,77,90} This trend is similar to that observed with enantioselective terminal alkene dihydroxylation.



The diol products derived from the asymmetric dihydroxylation of these substrates are important chiral building blocks for the synthesis of medicinal and natural products. For example, the enantioselective dihydroxylation of 2-(6-methoxynaphthyl)propene (**36**) using (DHQ)₂PHAL (**8**) produces diol **37**, which, after deoxygenation and oxidation, affords the important non-steroidal antiinflammatory agent Naproxen (**38**) (Eq. 28).^{91,92}



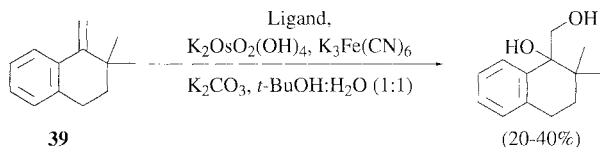
While the direction of enantioselectivity for the vast majority of cinchona alkaloid catalyzed asymmetric dihydroxylation is dictated by the configuration of the cinchona alkaloid subunit (DHQD or DHQ), the preference of the PHAL linked ligands for aromatic substituents vs. the preference of PYR linked ligands for branched aliphatic substituents results in an interesting ligand-dependent reversal in enantioselectivity for 1,1-disubstituted alkenes bearing each substituent type (Eq. 29).⁸⁸ Thus, dihydroxylation of α -substituted styrenes bearing simple hydrocarbon chains with (DHQD)₂PHAL (**7**) produces the *R* diol preferentially, whereas the use of (DHQD)₂PYR (**25**) affords the *S* diol, even though both ligands bear the same cinchona alkaloid subunit. This phenomenon is a dramatic illustration of the effect of alkene substituent competition for the catalyst's binding pocket.



R	(DHQD) ₂ PHAL (7) (yield) % ee, config.	(DHQD) ₂ PYR (25) (yield) % ee, config.
<i>n</i> -Pr	(85-95%) 60, R	(85-95%) 16, S
<i>n</i> -Bu	(85-95%) 56, R	(85-95%) 28, S
<i>n</i> -C ₅ H ₁₁	(85-95%) 48, R	(85-95%) 30, S
<i>n</i> -C ₆ H ₁₃	(85-95%) 37, R	(85-95%) 35, S
<i>i</i> -Pr	(85-95%) 82, R	(85-95%) 8, S
<i>c</i> -C ₃ H ₅	(85-95%) 70, R	(85-95%) 24, S
<i>c</i> -C ₄ H ₇	(85-95%) 58, R	(85-95%) 59, S
<i>c</i> -C ₅ H ₉	(85-95%) 55, R	(85-95%) 66, S
<i>c</i> -C ₆ H ₁₁	(85-95%) 57, R	(85-95%) 68, S
<i>t</i> -Bu	(30-40%) 8, R	(30-40%) 33, S

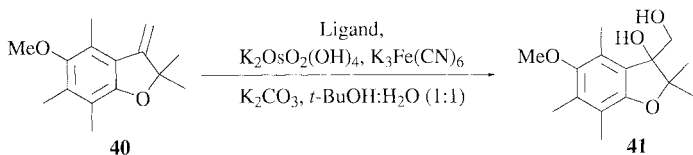
(Eq. 29)

The reversal in enantiofacial selectivity is especially pronounced for exocyclic 1,1-disubstituted alkenes, such as 2,2-dimethyl-1-methylenetetrahydronaphthalene (**39**), a rigid analog of α -*tert*-butylstyrene (Eq. 30).⁸⁸ The poor enantioselectivity observed in the dihydroxylation of the latter substrate (Eq. 29) is attributed to poor presentation of the phenyl group to the catalyst's binding pocket as a result of conformational restrictions imposed by the *tert*-butyl group. Another important example in this series is the asymmetric dihydroxylation of **40** to produce diol **41**, which was used as an intermediate in the synthesis of a pharmaceutical compound (Eq. 31).⁹³



(Eq. 30)

Ligand	% ee	Config.
(DHQD) ₂ PHAL (7)	82	R
(DHQD) ₂ PYR (25)	59	S

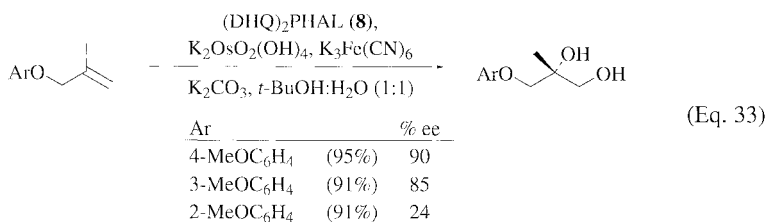
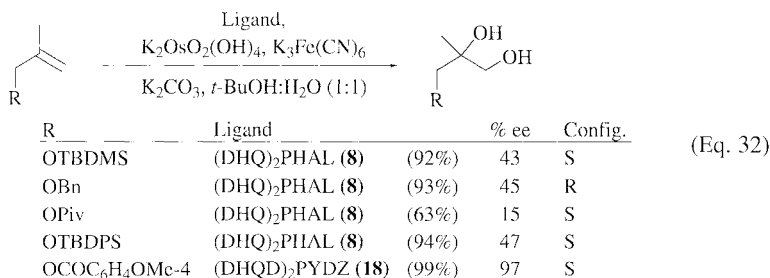


(Eq. 31)

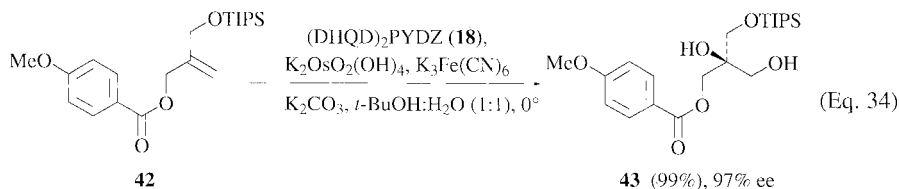
Ligand	% ee	Config.
(DHQD) ₂ PHAL (7)	36	R
(DHQD) ₂ PYR (25)	93	S

The enantioselective dihydroxylation of 2-methallyl alcohol derivatives and homologs proceeds with high levels of enantioselectivity, provided that the appro-

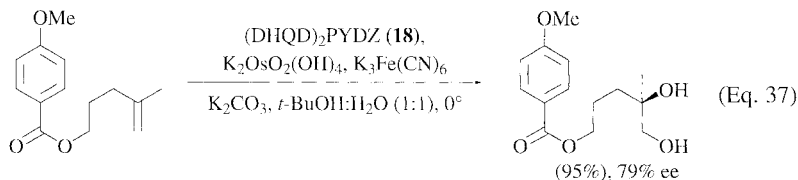
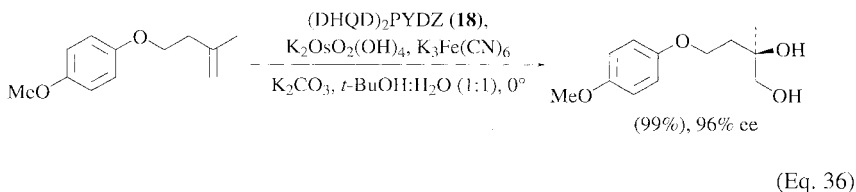
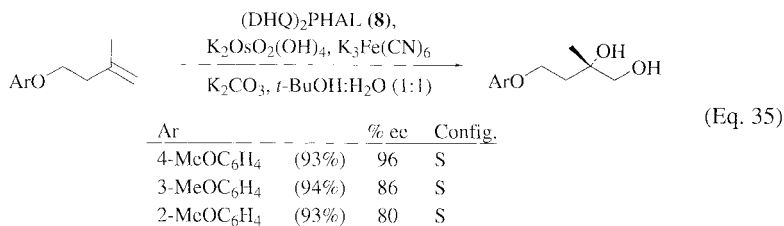
appropriate ligand and protecting group are used (Eq. 32).^{61,94} In general, enantioselectivity trends for this class of substrates follow those observed for allyl alcohol derivatives. Protection of the hydroxy group as an aromatic ester that can interact favorably with the catalyst binding pocket results in high enantioselectivity in the asymmetric dihydroxylation, whereas substrates possessing bulky silyl ether or pivaloyl protecting groups react with much lower selectivity.^{61,94} Moreover, the sense of enantioselectivity changes depending on the preference of the catalyst's binding pocket to accommodate the methyl substituent vs. the other olefin substituent. Much more subtle changes in the protecting group can profoundly influence enantioselectivity, as illustrated by a study of the asymmetric dihydroxylation of methoxy-substituted aryl methallyl ethers (Eq. 33).⁹⁵ Here enantioselectivity falls as the methoxy group is moved from the para to the meta and finally to the ortho position, with the latter substrate affording the diol product in only 24% ee.



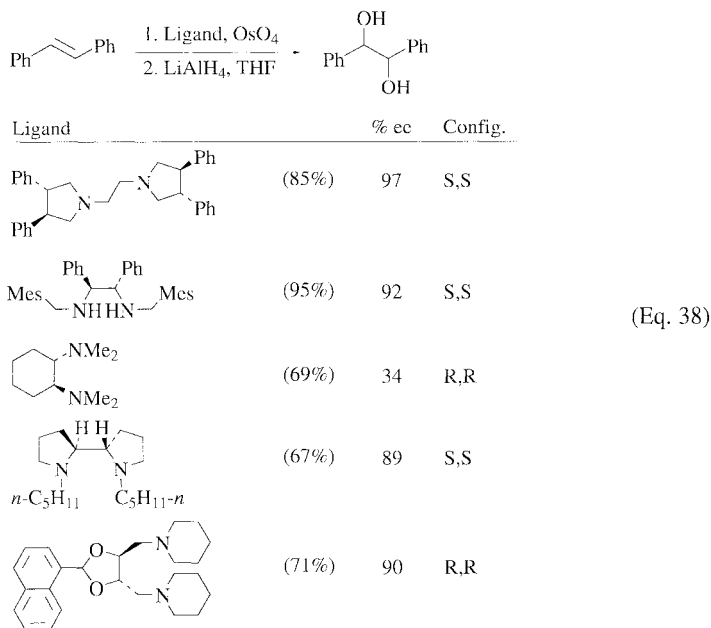
The preferential binding of aromatic substituents is exemplified by the highly enantioselective dihydroxylation of ester **42** by (DHQD)₂PYDZ (**18**) to afford product **43**, a differentially protected derivative of tris(hydroxymethyl)methanol, which is a synthetically useful chiral building block (Eq. 34).⁶¹



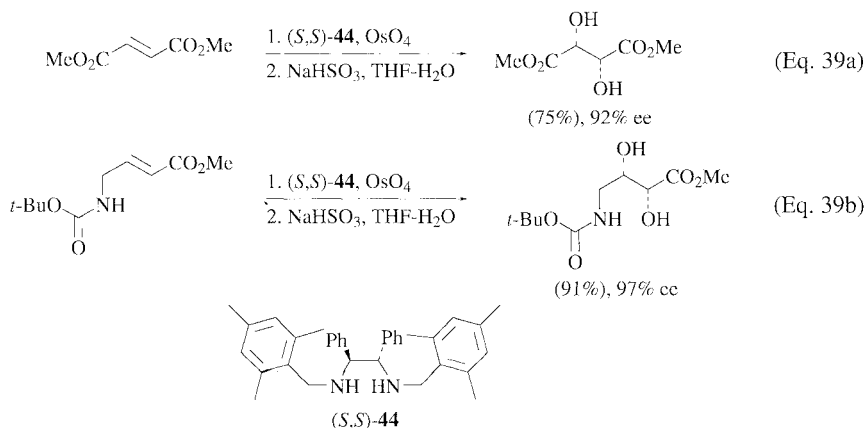
As was observed for terminal alkenes, the selection of an appropriate protecting group is critical for high enantioselectivity in the dihydroxylation of homoallylic and bis(homoallylic) alcohol derivatives of this substrate class. In contrast to what is observed for substituted methallyl aryl ethers, subtle changes in substitution of 2-methylbutenyl aryl ethers modestly affect enantioselectivity (Eq. 35),⁹⁵ and the preferred protecting group for homoallylic alcohols is the 4-methoxyphenyl ether (Eq. 36). Bis(homoallylic) alcohols should be protected as the corresponding 4-methoxybenzoate esters (Eq. 37).^{61,82,83}



E-1,2-Disubstituted Alkenes. The dihydroxylation of E-1,2-disubstituted alkenes has been extensively investigated with chiral 1,2-diamine ligands. Enantioselectivity is generally highest with this substrate class, and this can in part be attributed to the C₂ symmetry of substitution about the alkene carbon atoms of these substrates, which is complementary to a C₂-symmetrical chiral environment presented by the ligand. The most extensively studied substrate for these reactions is *E*-stilbene, which is oxidized with high enantioselectivity using ligands derived from tartaric acid, diphenyldiaminoethane, *N,N'*-dialkyl-2,2'-bipyrrrolidine, and 1,2-bis(3,4-diphenylpyrrolidino)ethane (Eq. 38).^{10-12,14,96} Catalytic turnover is not observed in any of these systems, and stoichiometric amounts of ligand and OsO₄ are required in these oxidations. In addition to that of *E*-stilbene, highly enantioselective dihydroxylation (ee > 90%) of other trans alkenes such as *E*- β -methylstyrene, dimethyl fumarate, and *E*-3-hexene occurs with each of the aforementioned ligands.



Enantioselective dihydroxylation of *trans* alkenes using *N,N'*-bis(2,4,6-trimethylbenzyl)-1,2-diphenyl-1,2-diaminoethane (**44**) occurs with generally high levels of enantioselectivity to produce synthetically useful products.¹¹ This ligand, which is also useful for asymmetric Diels-Alder, aldol, and carbonyl allylation processes, is particularly effective for the enantioselective osmylation of α,β -unsaturated esters (Eqs. 39a and 39b).¹¹ A simple extraction procedure followed by chromatography allows efficient recovery of the diamine ligand and recycling of osmium.



The catalytic asymmetric dihydroxylation of E-1,2-disubstituted alkenes with cinchona alkaloid catalysts generally proceeds with high levels of asymmetric induction, and the level of enantioselectivity is much less sensitive to the nature of the alkene substituents than is seen for oxidations of terminal or 1,1-disubstituted alkenes. While the rate of osmylation of these substrates is higher than the corresponding rate of reaction of terminal alkenes, the overall catalytic reaction can be slower compared to monosubstituted alkenes. The presence of a substituent at each olefinic carbon atom of the substrate results in a dramatic reduction in the rate of hydrolysis of the Os(VI) ester intermediate. The reaction is accelerated by addition of a stoichiometric equivalent of methanesulfonamide to the standard AD-mix where potassium ferricyanide is used as the terminal oxidant, or tetraalkylammonium acetate when NMO is used as the stoichiometric oxidant.^{19,69,72}

The breadth of scope for the highly enantioselective dihydroxylation of E-1,2-disubstituted alkenes can be understood on examination of the chiral template presented by both monomeric and dimeric cinchona alkaloid catalysts represented by Figure 2.²⁰ Positioning the two alkene substituents into the open regions of the catalyst template results in the observed face-selective dihydroxylation. The dihydroxylation of the opposite alkene face is highly disfavored due to severe steric interactions between the double bond substituents and a sterically congested region of the catalyst. In the U-shaped binding pocket model, correct positioning of the substrate results in binding of one of the substituents in the U-shaped pocket, whereas the other alkene substituent resides in the open space in front of the linker group. Dihydroxylation of the opposite alkene face is highly disfavored due to severe steric interactions between one of the alkene substituents and the linker group. Thus, hydrophobic binding interactions favoring dihydroxylation of the observed alkene face and prohibitive steric interactions disfavoring osmylation of the opposite alkene face act in concert to produce the observed high enantioselectivity. This effect is best illustrated by comparison of the enantioselectivity observed for the dihydroxylation of terminal alkenes compared with that of the corresponding C₂ symmetrically substituted trans alkenes (Eq. 40).^{20,77,86}

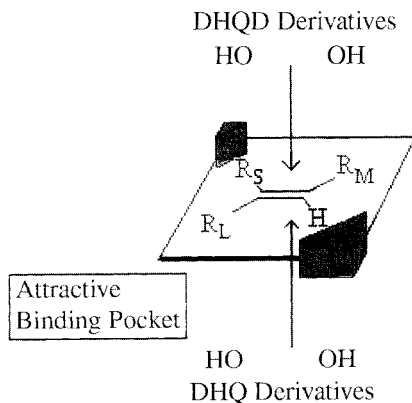
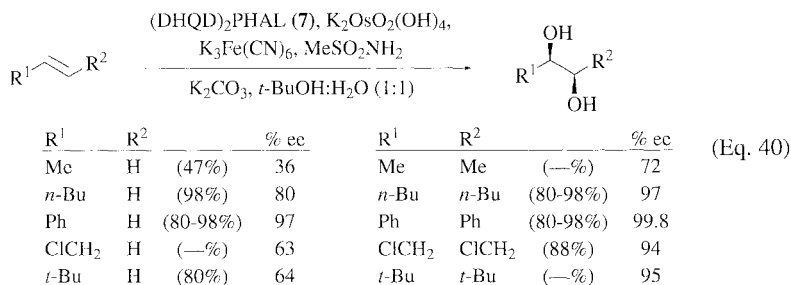
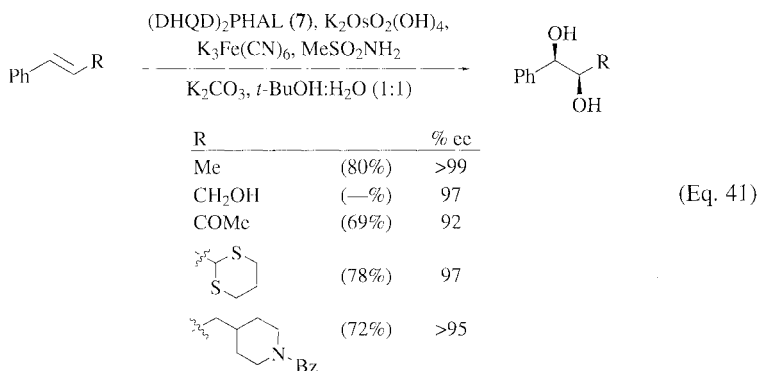


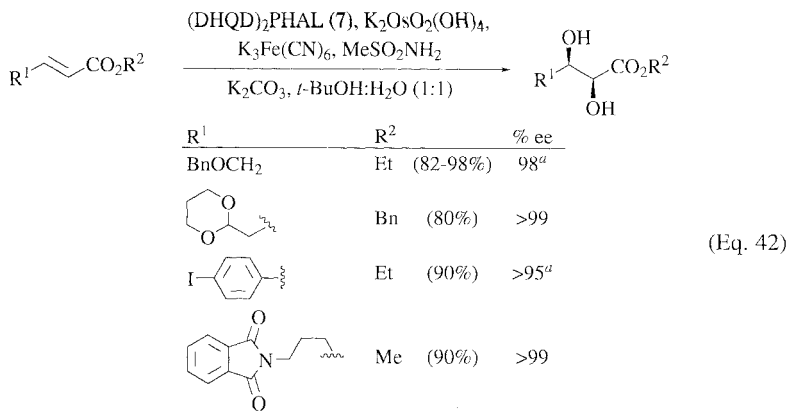
Figure 2. Representation of the Chiral Template of Both Monomeric and Dimeric Cinchona Alkaloid Catalysts.



A wide variety of substrates of this alkene class are oxidized by the dimeric PHAL-linked ligands with high levels of enantioselectivity provided that one of the alkene substituents can interact favorably with the catalyst binding pocket. Ligands such as (DHQD)₂PHAL (**7**) prefer aromatic substituents, and *trans* β -styrenes are oxidized to diols of high enantiomeric purity regardless of the steric or electronic properties of the β -substituent (Eq. 41).⁹⁷⁻¹⁰¹

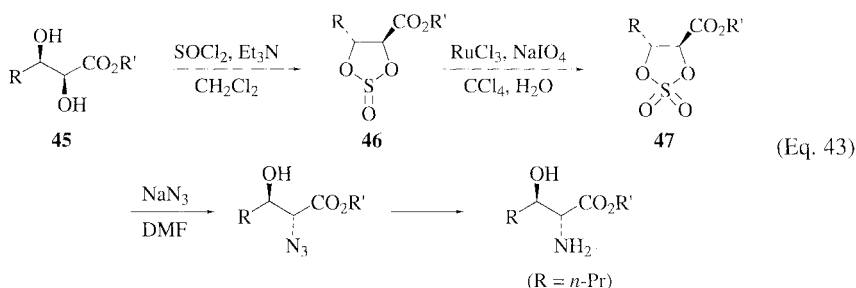


The asymmetric dihydroxylation of *trans* β -substituted acrylic esters using dimeric PHAL-based ligands is very general and proceeds with high enantioselectivity (Eq. 42).¹⁰²⁻¹⁰⁵ A diverse array of protected β -substituent functionality is tolerated, including ethers, acetals, phthalimides, and arenes. This breadth of scope, combined with tolerance of a variety of ester groups, allows convenient protecting group manipulation of the highly functionalized products. The α -hydroxy acid products are synthetically versatile intermediates, allowing for convenient preparation of enantiomerically pure α -amino acid derivatives through a four-step sequence (Eq. 43).^{105,106} The product diols **45** can be converted into cyclic sulfate intermediates **47**, which are versatile synthetic epoxide equivalents, allowing replacement of one or both of the hydroxy groups with a nucleophile. Cyclic sulfate formation is typically accomplished by treatment of the appropriate diol with thionyl chloride and triethylamine to form the cyclic sulfite **46**, followed by oxidation to the cyclic sulfate **47** using sodium periodate and catalytic ruthenium (III) chloride. Thus, asymmetric osmylation of methyl 6-phthalimido-2-hexenoate (**48**), followed by bromohydrin formation and nucleophilic displacement of the bromide by sodium azide



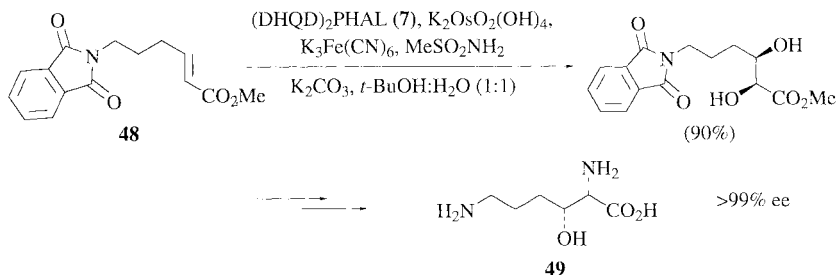
(Eq. 42)

^a The reaction was conducted using (DHQ)₂PHAL (8), giving the opposite enantiomer to that depicted.

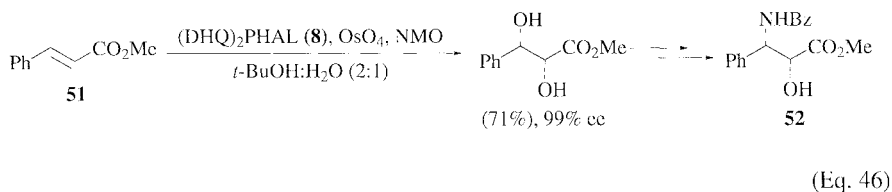
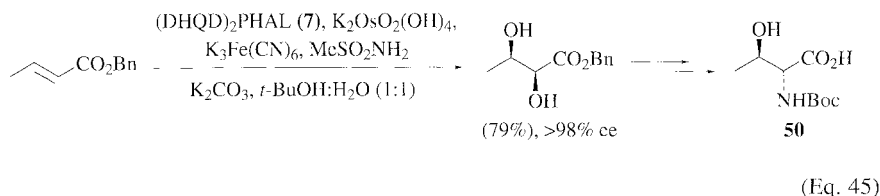


(Eq. 43)

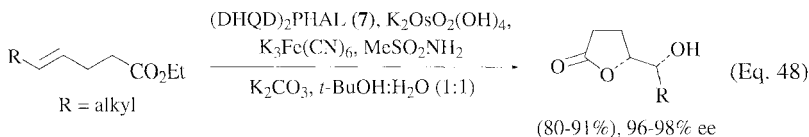
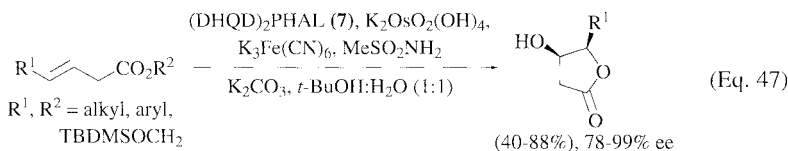
establishes both stereocenters of 3-hydroxylysine (**49**), a naturally occurring amino acid and putative intermediate in the biosynthesis of balanol (Eq. 44).¹⁰⁵ A variety of synthetically important β -hydroxy amino acids can be similarly prepared, such as the allothreonine derivative **50** (Eq. 45) and hydroxyvaline.¹⁰⁶ The enantioselective dihydroxylation of methyl *trans* β -phenylacrylate (**51**) using (DHQ)₂PHAL (7) is the key step in a short, industrially scaleable synthesis of the Taxol® side chain **52** (Eq. 46).¹⁰⁷



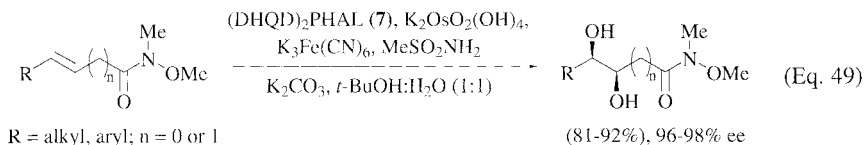
(Eq. 44)



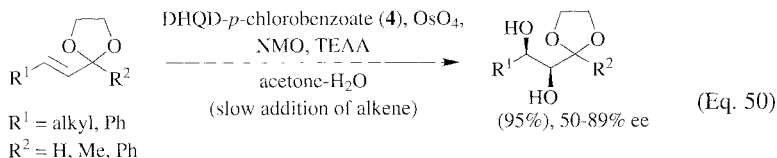
The asymmetric dihydroxylation of β,γ or γ,δ -unsaturated esters proceeds with high enantioselectivity, and subsequent cyclization of the ester group and one of the newly installed hydroxy groups provides an elegant solution to the problem of functional differentiation of the diol (Eq. 47). Treatment of the hydroxylactone intermediate with triethylamine and methanesulfonyl chloride in methylene chloride at 0° results in elimination of the remaining hydroxy group and provides convenient access to synthetically useful chiral butenolides in high yield.¹⁰⁸ Under the basic reaction conditions of the $\text{K}_3\text{Fe}(\text{CN})_6$ - K_2CO_3 secondary oxidant system, the diol esters derived from γ,δ -unsaturated esters spontaneously cyclize to produce functionalized γ -lactones, which are important intermediates for the synthesis of a number of natural products and medicinally active substances, including precursors for HIV-protease inhibitors.^{108,109} Although the presence of two hydroxy groups offers the possibility of formation of γ and δ lactones, the formation of the five-membered ring is kinetically favored and occurs selectively (Eq. 48). The cyclization of the diol ester products can be prevented by utilization of the corresponding γ,δ -unsaturated *tert*-butyl esters, which are sufficiently hindered to prevent lactone formation under the slightly basic reaction conditions.¹¹⁰



The dihydroxylation of α,β - and β,γ -unsaturated amides also proceeds with high enantioselectivity using (DHQD)₂PHAL (**7**) as the chiral ligand (Eq. 49).¹¹¹ These alkenes react more sluggishly than the corresponding esters, presumably due to slower hydrolysis of the intermediate osmate ester. This problem is easily solved by increasing the catalyst loading to 5 mol % of chiral ligand and 1 mol % of OsO₄ in addition to the use of stoichiometric methanesulfonamide, which is recommended for the reaction of all trans alkenes using the K₃Fe(CN)₆-K₂CO₃ counteroxidant system. Because *N*-methoxy-*N*-methyl amides (Weinreb amides) can be readily converted into aldehydes and ketones by reduction or nucleophilic substitution, the dihydroxylation of unsaturated Weinreb amides can be used to produce masked dihydroxy aldehydes and dihydroxy ketones.

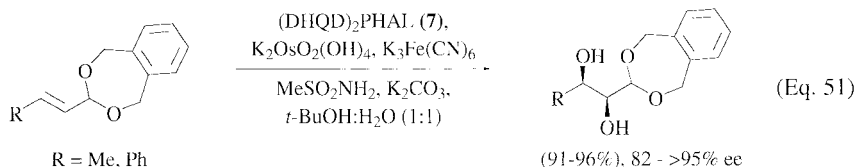


The enantioselective dihydroxylation of α,β -unsaturated ketals and acetals provides an alternative access to protected dihydroxy aldehydes and ketones. The only reported general study of the cinchona alkaloid catalyzed asymmetric dihydroxylation of these substrates utilizes the DHQD-*p*-chlorobenzoate (**4**) ligand (Eq. 50),

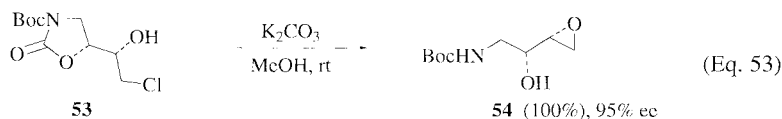
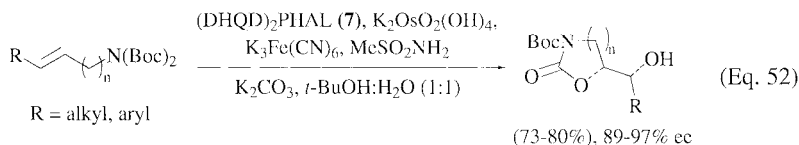


TEAA = tetraethylammonium acetate

which is known to be inferior to the dimeric ligands such as (DHQD)₂PHAL (**7**), for the enantioselective dihydroxylation of many substrates.¹¹² These reactions were also conducted using NMO as the stoichiometric oxidant, requiring the addition of tetraethylammonium acetate and slow addition of the alkene to preclude the second cycle that is known to cause a reduction in enantioselectivity and reaction rate. Thus, although the reported enantioselectivities are in the 50–89% ee range, the use of one of the more recently discovered ligands and the ferricyanide secondary oxidant system may produce higher enantioselectivity for the oxidation of these substrates. Indeed, the dihydroxylation of α,β -unsaturated acetals derived from 1,2-phenylenedimethanol using the dimeric PHAL ligands with potassium ferricyanide as the stoichiometric oxidant affords the diol products in high yield and enantioselectivity (Eq. 51).⁸⁴

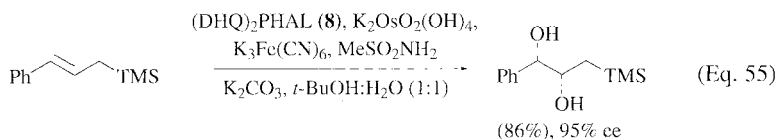
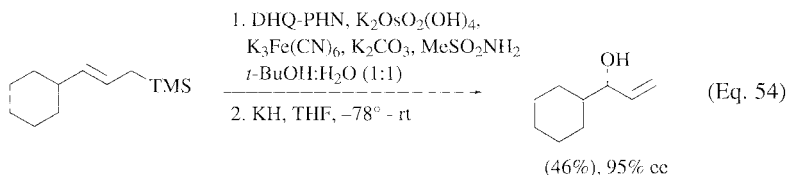


The reactions of E-1,2-disubstituted *N,N*-di(*tert*-butoxycarbonyl)allylic or homoallylic amines also proceed with high levels of enantioselectivity using (DHQD)₂PHAL (**7**) as ligand (Eq. 52).⁸⁵ The diols derived from these substrates also undergo spontaneous cyclization with one of the *tert*-butoxycarbonyl groups to provide cyclic *N*-Boc carbamates. This in situ protection of one of the hydroxy groups allows convenient differentiation of the newly installed hydroxy groups in subsequent synthetic transformations. The cyclic carbamate can be selectively hydrolyzed and decarboxylated under mildly basic conditions, such as treatment with K₂CO₃ in methanol, producing the corresponding Boc-protected amino diols. In a particularly interesting application of this methodology, the base-catalyzed hydrolysis of the diol **53** occurs with concomitant reaction of the chlorohydrin to form the highly functionalized chiral epoxide **54** in high yield (Eq. 53).⁸⁵

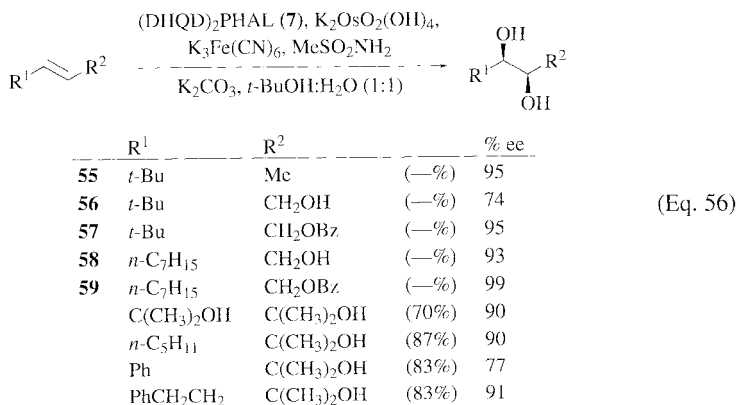


The asymmetric dihydroxylation of E-1,2-disubstituted vinyl- or allyltrimethylsilanes generally proceeds with high enantioselectivity using either PHAL- or PHN-linked ligands, although it has been reported that oxidation of allylsilanes occurs with higher enantioselectivity using the PHN class of ligands.¹¹³⁻¹¹⁵ Treatment of the diol product with potassium hydride in ether or THF forces Peterson elimination of trimethylsilanol to produce synthetically useful chiral allylic alcohols in high yield (Eq. 54).¹¹⁵ Because bulky trialkylsilanes do not interact favorably with the catalyst's binding pocket, the presence of a second alkene substituent that can serve as a modest to good binding group is required to attain synthetically useful levels of enantioselectivity when using the (DHQ)₂PHAL (**8**) ligand. Thus, whereas 3-butyl- and 3-isopropylallyltrimethylsilane react with only modest enantioselectivity using (DHQ)₂PHAL (**8**), 3-phenylallyltrimethylsilane is oxidized in 86% yield with 95% ee (Eq. 55).¹¹³ Vinylsilanes of this alkene class are also good substrates for the asymmetric dihydroxylation catalyzed by (DHQD)₂PHAL (**7**).¹¹³ Attempts to convert

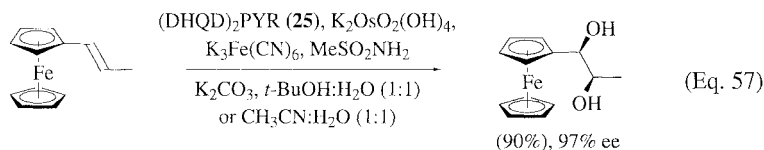
these diol products into the corresponding cyclic sulfates, thereby producing synthetically useful epoxysilane equivalents, were unsuccessful.



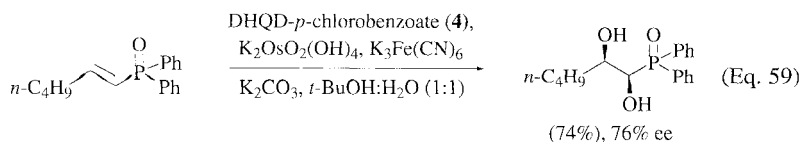
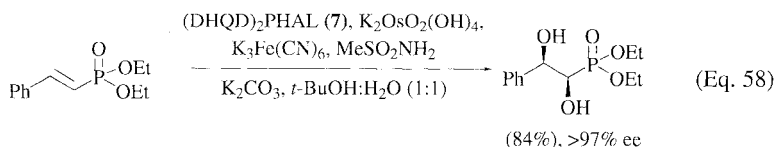
The cinchona alkaloid catalyzed asymmetric dihydroxylation of *trans* allylic alcohols affords chiral triols of moderate to high enantiomeric purity.^{98,116} The presence of the allylic hydroxy group reduces enantioselectivity compared with the reaction of the corresponding unsubstituted *trans* alkenes.⁹⁸ Thus, the enantioselective dihydroxylation of 4,4-dimethylpent-2-en-1-ol (**56**) proceeds with 74% ee using the (DHQD)₂PHAL (**7**) ligand, whereas the parent 4,4-dimethylpent-2-ene (**55**) is oxidized with 95% ee under similar conditions (Eq. 56).⁹⁸ The observation of stereo-directing effects of the hydroxy group for cyclic allylic alcohols favoring *syn* hydroxylation suggests that alkene substituents that can function as hydrogen bond donors may interact with OsO₄, and for these substrates, reduce enantioselectivity.⁹⁸ Protection of the allylic hydroxy group as its benzoate derivative easily solves this problem, and very high levels of enantioselectivity are obtained with (DHQD)₂PHAL (**7**) (e.g., compare **57** with **56** and **59** with **58**). The beneficial effect of benzoate protection may result in part from the ability of the allylic benzoate to interact favorably with the catalyst's binding pocket, as was found with terminal allylic 4-methoxybenzoates.



The highly enantioselective dihydroxylation of ferrocenyl-substituted trans alkenes illustrates the diverse functionality tolerated by the dimeric cinchona alkaloid catalysts (Eq. 57).¹¹⁷ These products have potential utility in the synthesis of chiral ligands for other asymmetric transformations. The proper choice of cinchona alkaloid ligand is critical for achieving high levels of enantioselectivity with these substrates. Unlike the enantioselective dihydroxylation of other substrates, careful optimization of ligand and osmium stoichiometry is also important for obtaining good results. Generally, the use of 10 mol% of the alkaloid ligand and 4–10 mol% of potassium osmate gives the highest enantioselectivities, and 1:1 acetonitrile-water is a better solvent system than 1:1 *t*-BuOH-water. The (DHQD)₂PYR (**25**) ligand generally provides higher enantioselectivity than the corresponding PHAL-linked ligand. This observation is consistent with the known preference of the PYR ligands for bulky alkene substituents as compared to the PHAL ligands.⁷⁷

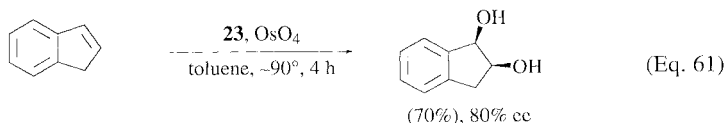
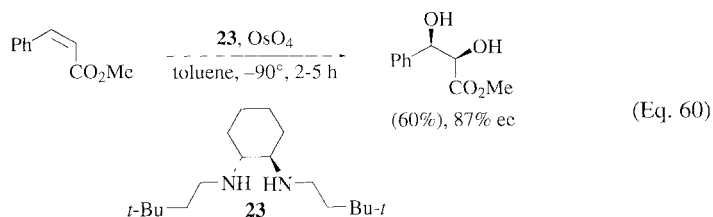


The enantioselectivity of the dihydroxylation of trans α,β -unsaturated alkyl phosphonates catalyzed by (DHQD)₂PHAL (**7**) is highly dependent on the properties of the other alkene substituent. Substrates possessing aromatic substituents are oxidized with high enantioselectivity (Eq. 58), whereas alkenes possessing small or bulky aliphatic substituents react with modest selectivity.¹¹⁸ The preference of the PHAL-linked ligands for aromatic substituents is consistent with the observed trends in enantioselectivity. The asymmetric dihydroxylation of α,β -unsaturated diphenylphosphinates proceeds with modest enantioselectivity for substrates possessing small aliphatic substituents (Eq. 59).¹¹⁹ Interestingly, the DHQD-*p*-chlorobenzoate (**4**) and DHQ-*p*-chlorobenzoate ligands were found to afford higher enantioselectivity than the dimeric cinchona alkaloids for the reactions of these substrates.¹²⁰

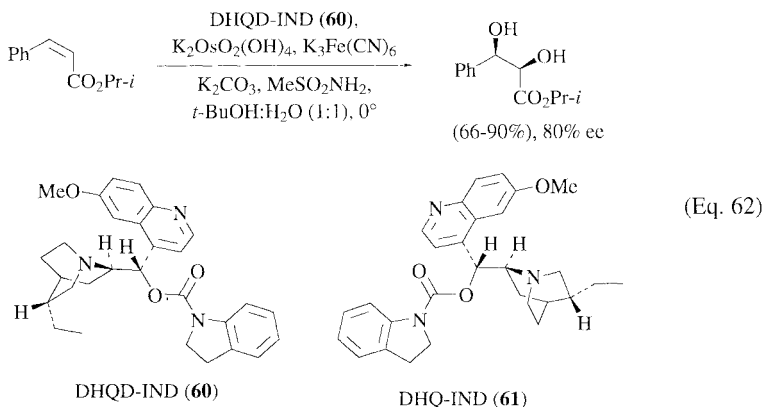


Z-1,2-Disubstituted Alkenes. Z-1,2-Disubstituted alkenes are generally the poorest substrates for enantioselective dihydroxylation. The substrate scope for which dihydroxylation occurs with preparatively useful enantioselectivity is somewhat limited, and specialized ligands have been developed to enhance reactivity and enantioselectivity. The narrow scope observed for this alkene class can be understood in terms of the inability of the ligand-OsO₄ complex to discriminate between the two alkene substituents, particularly when they have similar steric and electronic properties. This phenomenon has been referred to as the meso effect, as Z-1,2-disubstituted alkenes that possess identical substituents produce meso diols upon cis-dihydroxylation.

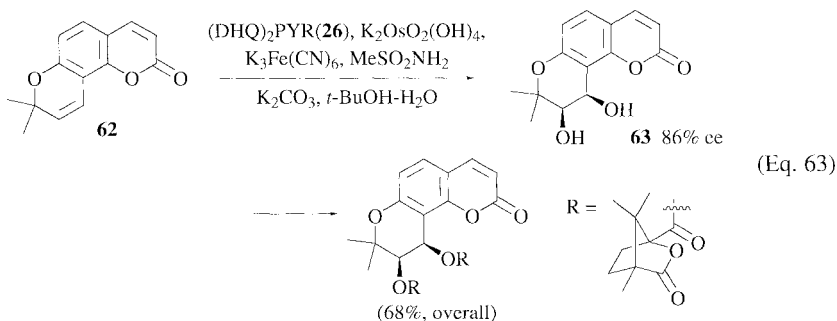
There are several examples of enantioselective dihydroxylation of Z-1,2-disubstituted alkenes using chiral 1,2-diamine ligands. The most useful of these ligands is **23**, which is derived from (*R,R*)-*trans*-1,2-diaminocyclohexane. This ligand has been used to oxidize a variety of alkenes in moderate to high enantiomeric excess, including acyclic (Eq. 60) and endocyclic (Eq. 61) cis alkenes.⁹ Unfortunately, simple aliphatic cis alkenes do not give good selectivity under these conditions. Dihydroxylations using 1,2-diamine ligands such as *N,N'*-bis(3,3-dimethylbutyl)-1,2-cyclohexanediamine (**23**) are typically performed at low temperature and require stoichiometric OsO₄ and ligand, thereby limiting their utility for large-scale reactions.



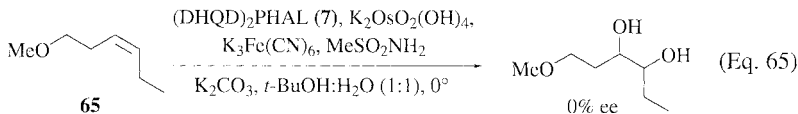
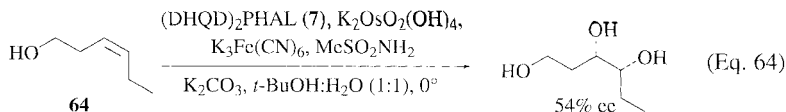
The optimum cinchona alkaloid ligands for the enantioselective dihydroxylation of Z-1,2-disubstituted alkenes are DHQD-IND (**60**) and DHQ-IND (**61**). The catalytic enantioselective dihydroxylation of Z-1,2-disubstituted alkenes typically proceeds with low to moderate enantioselection, and there are only a few substrate-catalyst combinations that produce diols of greater than 80% ee (Eq. 62).¹²¹ As observed for other cinchona alkaloid ligands, reactions using DHQ-IND (**61**) consistently result in lower enantioselectivity than the pseudoenantiomeric DHQD-IND (**60**).¹²¹



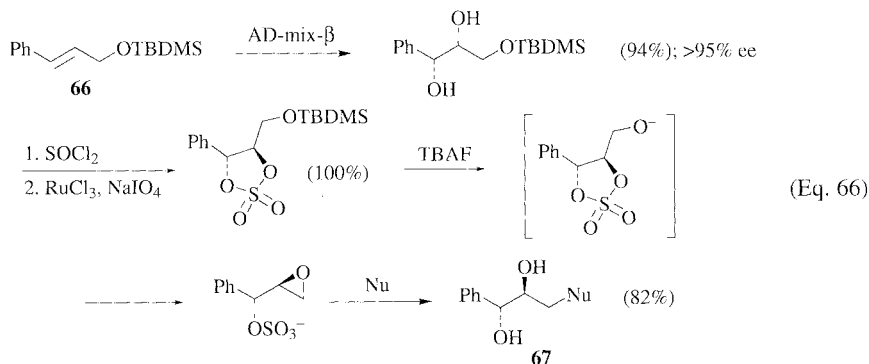
Although the asymmetric dihydroxylation of *Z*-1,2-disubstituted alkenes can generally be expected to proceed with moderate enantioselectivity, there are isolated examples where high enantioselectivity is observed. Thus, the catalytic asymmetric dihydroxylation of alkene **62** using the (DHQ)₂PYR (**26**) ligand under standard conditions produces diol **63** in 86% ee (Eq. 63).¹²² This intermediate was used to prepare 3',4'-di-*O*-(–)-camphanoyl-(+)-*cis*-khellactone, a potent anti-HIV agent.¹²²



The dihydroxylation of *Z*-allylic and homoallylic alcohols has been reported to proceed with moderate enantioselectivity using the PHAL class of ligands. The higher enantioselectivity observed with these substrates than that generally seen with *cis* alkenes presumably results from hydrogen-bonding interaction between the catalyst and the hydroxy group of the substrate. This hypothesis is supported by the fact that *cis*-3-hexen-1-ol (**64**) reacts to give the triol with 54% ee in spite of the fact that the two alkene substituents are of very similar size (Eq. 64).¹²³ Conversely, the corresponding methyl ether **65** reacts under the same conditions to give racemic triol (Eq. 65).¹²³ Certain endocyclic dienes are also effective substrates for the catalytic enantioselective dihydroxylation. These examples are treated in the section describing polyalkene substrates, as both regioselectivity and facial selectivity are important parameters for these reactions.

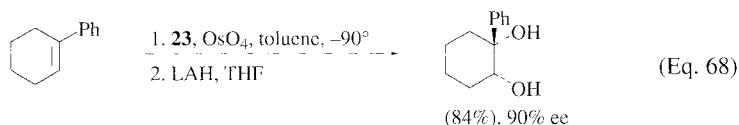
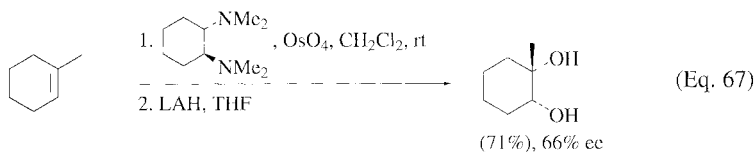


In order to overcome the difficulties associated with enantioselective dihydroxylation of *Z*-1,2-disubstituted alkenes, a strategy has been developed that utilizes the highly enantioselective dihydroxylation of *E*-1,2-disubstituted alkenes followed by stereoinversion of one of the resulting hydroxy groups. The three-step process involves (1) asymmetric dihydroxylation of an *E*-1,2-disubstituted alkene, (2) formation of a cyclic sulfate² and, (3) inversion of one of the alcohols via a Payne-type rearrangement followed by nucleophilic opening of the resulting epoxide (Eq. 66). The sequence is illustrated by the conversion of alkene **66** into product **67**.^{124,125} The entire process, post isolation of the diol, can be completed in a single reaction vessel and generally results in the formation of the formal products of dihydroxylation of a *cis* alkene in high enantioselectivity and good overall chemical yield. Nucleophiles that have been used to open the epoxide formed from the Payne-type rearrangement include sulfide, azide, acetate, cyanide, iodide, and organometallic reagents.^{124,125}

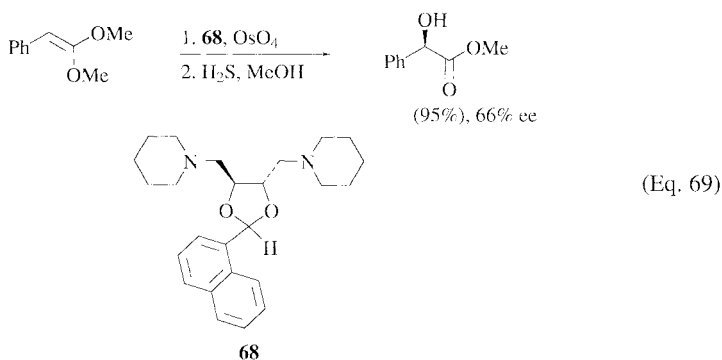


Trisubstituted Alkenes

The enantioselective osmylation of trisubstituted alkenes has been examined using a variety of 1,2-diamine ligands. Both 1-methylcyclohexene and 1-phenylcyclohexene are commonly used substrates for the study of this reaction (Eqs. 67 and 68).^{9,10,12} The *N,N'*-di(*tert*-butylethyl)-1,2-cyclohexanediamine ligand (**23**) is the most effective chiral controller for this reaction, affording 90% ee in the osmylation of phenylcyclohexene (Eq. 68).⁹ The dihydroxylation of other trisubstituted alkenes using this ligand has not been reported.



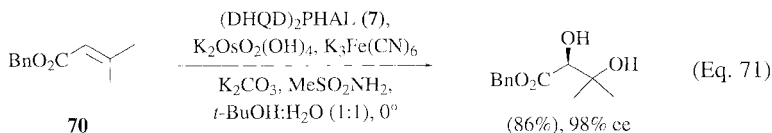
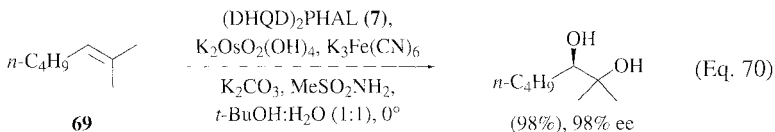
Chiral diamine ligands derived from tartaric acid are moderately effective for the asymmetric dihydroxylation of silyl ketene acetals, affording synthetically useful α -hydroxy esters (Eq. 69).⁹⁶ These reactions are conducted in methylene chloride at -78° to -100° , and the intermediate osmate ester is converted into the α -hydroxy ester using H_2S in methanol due to the sensitivity of the ester groups to LiAlH_4 . The enantioselectivity of the reaction appears to be independent of the properties of the ketene acetal group, but is strongly influenced by the nature of the remaining alkene substituent.



The catalytic enantioselective dihydroxylation of trisubstituted alkenes using cinchona alkaloid ligands is very general; endocyclic, exocyclic, and acyclic alkenes all react with high enantioselectivity depending on the nature of the alkene substituents and the alkene configuration. Often the best results are obtained with substrates wherein the group being presented to the catalyst's binding pocket is *cis* to the vinylic proton of the substrate, although there are several exceptions to this trend. In general, trisubstituted alkenes are electronically activated relative to less substituted alkenes toward the osmylation by cinchona alkaloid- OsO_4 complexes; however, the hydrolysis of the trisubstituted Os(VI) ester is often slow as a result of steric hindrance. A stoichiometric equivalent of methanesulfonamide is typically added to ferricyanide-supported oxidations of trisubstituted alkenes in order to accelerate the hydrolysis of the intermediate Os(VI) ester. The use of NMO as the stoichiometric

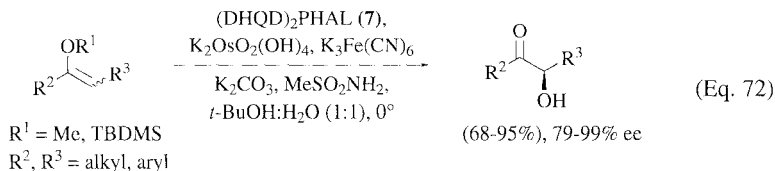
oxidant typically requires the addition of tetraethylammonium acetate and slow addition of the alkene to preclude the second cycle that degrades both the rate and enantioselectivity of the reaction. Since the dihydroxylation of trisubstituted alkenes produces chiral diols with dense and often diverse functionality, the reaction of these substrates has often been used to establish the first chiral centers in the synthesis of complex natural products. This review of the catalytic enantioselective dihydroxylation of trisubstituted alkenes is divided into three sections: acyclic trisubstituted alkenes, exocyclic trisubstituted alkenes, and endocyclic trisubstituted alkenes.

Acyclic Trisubstituted Alkenes. The catalytic enantioselective dihydroxylation of acyclic trisubstituted alkenes has been extensively studied within the context of oxidation of prenyl groups present in polyalkene substrates, such as terpenes, and additional material can be found in the section describing the reaction of polyunsaturated substrates. The reactions of simple prenyl groups proceed with high enantioselectivity using the PHAL and PYR class ligands and are representative of the high selectivities typically observed for the reactions of higher polyunsaturated substrates. Thus, the reaction of 2-methyl-2-heptene (**69**) using (DHQD)₂PHAL (**7**) proceeds with 98% ee to give the 1,2-diol in 98% yield (Eq. 70).¹⁹ A variety of aliphatic and aromatic substituents are tolerated, and the oxidation of these substrates provides synthetically useful products with high levels of enantioselectivity. For example, the diol derived from the oxidation of benzyl 3,3-dimethylacrylate (**70**) using (DHQD)₂PHAL (**7**) is a useful intermediate for the synthesis of enantiomerically pure β -hydroxyvaline (Eq. 71).¹⁰⁶

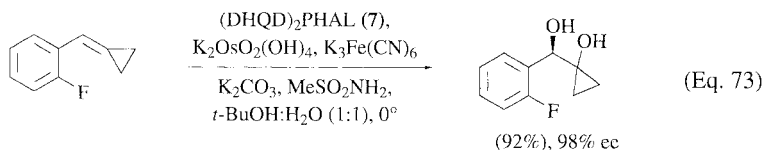


Trisubstituted enol ethers and silyl enol ethers are generally good substrates for catalytic asymmetric dihydroxylation using (DHQD)₂PHAL (**7**) (Eq. 72). The diol products spontaneously hydrolyze, affording α -hydroxy ketones of high enantiomeric purity.¹²⁶ There is a slight dependence of enantioselectivity on alkene geometry, and the *Z*-isomer is generally preferred for high selectivity. Highly *Z*-rich enol ethers derived from aliphatic ketones can be prepared by treatment of the parent ketone with trimethyl orthoformate and catalytic *p*-toluenesulfonic acid.¹²⁷ The treatment of aryl ketones with trimethyl orthoformate affords mixtures of enol ethers containing substantial amounts of the *E*-isomers. In these cases, the corresponding silyl enol ethers may be prepared as mainly the *Z*-isomers by treatment of

the corresponding ketone with LDA in THF-HMPA and trapping the resultant enolate with *tert*-butyldimethylsilyl chloride.¹²⁸ These silyl enol ethers afford the same α -hydroxy ketone products after asymmetric dihydroxylation as the corresponding methyl enol ethers, but with greater enantiomeric purity.

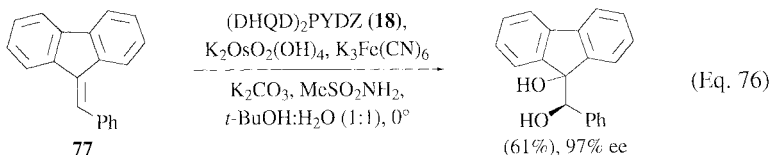
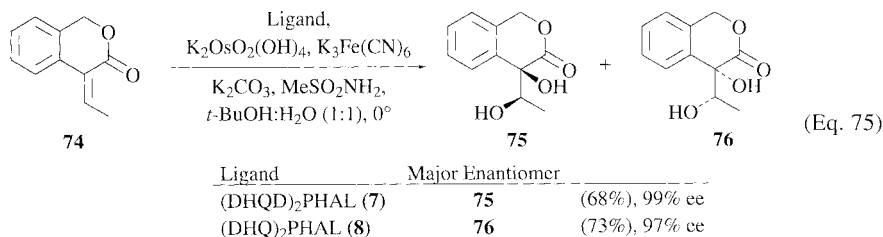
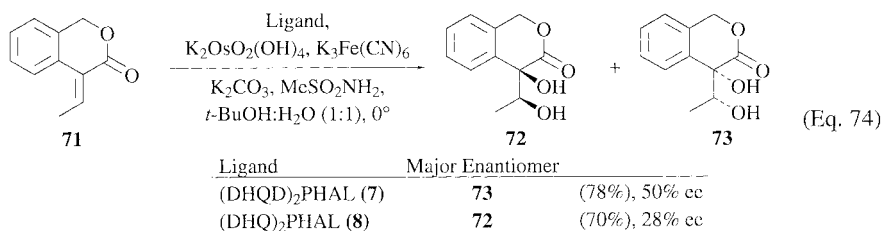


Exocyclic Trisubstituted Alkenes. The enantioselective dihydroxylation of substituted methylenecyclopropanes has been extensively studied, and the diol products can be easily converted into enantiomerically enriched substituted cyclobutanones by pinacol rearrangement catalyzed by $\text{BF}_3 \cdot \text{OEt}_2$ in THF at ambient temperature.¹²⁹ It is critical that the pinacol rearrangement be conducted under carefully selected conditions in order to avoid racemization. The conversion of such diols to enantiomerically enriched cyclobutanones using thionyl chloride and triethylamine in methylene chloride is believed to occur with substantial racemization.^{130,131} For these substrates, enantioselectivity is highly dependent on the characteristics of the cyclopropylidene substituent, with aromatic substituents providing the highest selectivity (Eq. 73).¹³¹ The reaction of aliphatic methylenecyclopropanes typically affords diol products with moderate enantioselectivity (50–70% ee). The reduction in enantioselectivity observed on switching from the $(\text{DHQD})_2\text{PHAL}$ (**7**) ligand to the pseudoenantiomeric $(\text{DHQ})_2\text{PHAL}$ (**8**) ligand is more pronounced with these substrates (10–20%) than is typically observed for other trisubstituted alkenes (5–10%).



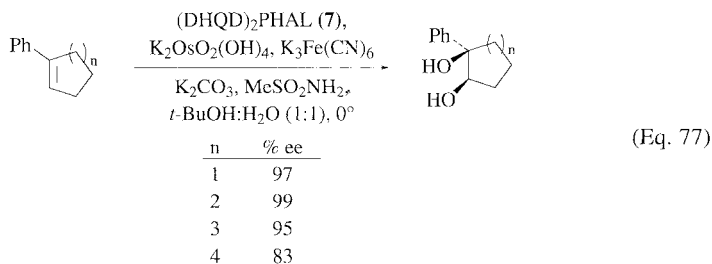
The reactions of other exocyclic trisubstituted alkenes have not been as thoroughly studied. There are several examples where high enantioselectivities have been observed using the $(\text{DHQD})_2\text{PHAL}$ (**7**) or $(\text{DHQD})_2\text{PYDZ}$ (**18**) ligands, and facial selectivity can be strongly dependent on alkene geometry. One of the most striking demonstrations of this effect is the difference in enantioselectivity observed for the dihydroxylation of the *E* and *Z* exocyclic alkenes **71** and **74**, which were model substrates used in synthetic studies of the DE ring fragment of the antineoplastic agent camptothecinTM (Eq. 74).¹³² Although the results observed for the reaction of the *E* isomer **71** were disappointing, the corresponding *Z* isomer **74** affords the diol product in 68% yield and 99% ee using $(\text{DHQD})_2\text{PHAL}$ (**7**)

(Eq. 75).¹³² Moreover, the reduced enantioselectivity **noted in the reaction of 74** with (DHQ)₂PHAL (**7**) is less significant than that noted for the reaction of substrate **71**. These results can be rationalized in terms of the hydrophobicity of the group that is *cis* relative to the vinylic proton of the substrate and is presented to the catalyst's binding pocket. In the case of the E substrate **71**, that group is the carbonyl moiety of the lactone ring. In the case of substrate **74**, the phenyl ring of the substrate is *cis* to the vinyl proton and is presented to the catalyst's binding pocket. The preference of the PHAL ligands to bind aromatic substituents makes this an especially favorable interaction, resulting in the observed higher levels of enantioselectivity. A similar orientation of an aromatic group relative to the vinylic proton of **77** results in high enantioselectivity in the asymmetric dihydroxylation using the related catalyst (DHQD)₂PYDZ (**18**) (Eq. 76).⁶⁶

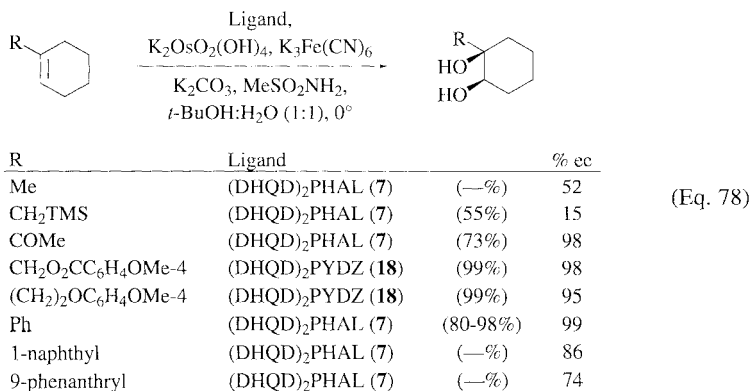


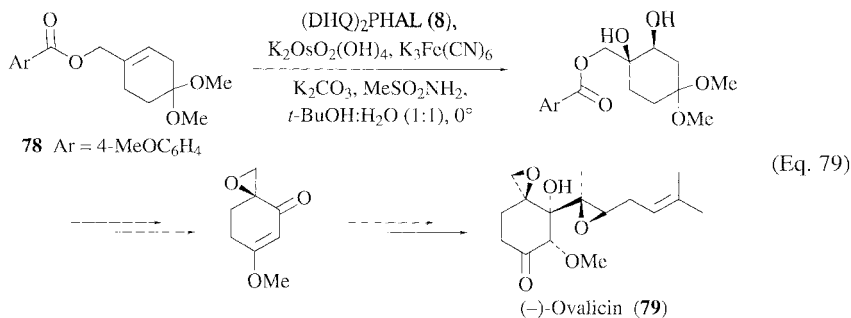
Endocyclic Trisubstituted Alkenes. The catalytic enantioselective dihydroxylation of endocyclic trisubstituted alkenes has been thoroughly studied, and the diol products derived from these reactions have been widely used in the total synthesis of complex natural products. The reaction of simple, hydrocarbon-substituted substrates of this class generally proceeds with moderate to high enantioselectivity and is dependent on both the nature of the exocyclic substituent as well as the ring size (Eq. 77).^{19,20} The effect of ring size on enantioselectivity is illustrated by comparing the results obtained from simple phenylcycloalkenes using (DHQD)₂PHAL (**7**).

Enantioselectivity is optimum for the six-membered ring, with a slight reduction noted as ring size increases, especially for the reaction of 1-phenylcyclooctene.



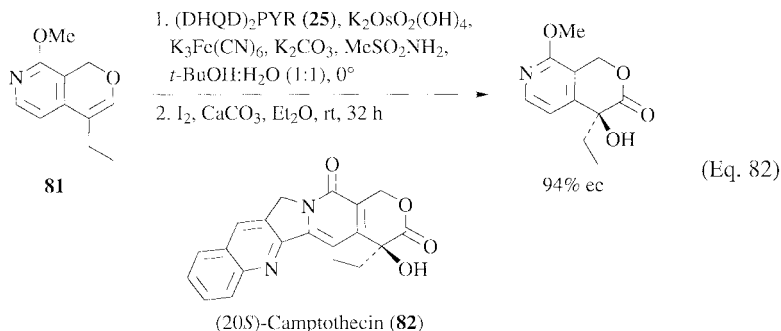
While most substrates belonging to this alkene class yield good results in the asymmetric dihydroxylation catalyzed by PHAL or PYR ligands, enantioselectivity can be affected by the nature of the exocyclic substituent (Eq. 78).^{19,20,61,99,115} Thus, for a series of 1-substituted cyclohexenes, enantioselectivity is highly dependent on the ability of the pendant substituent to interact effectively with the catalyst's binding pocket. For the PHAL ligand class, substituent preferences mirror those observed for other alkene classes, and non-bulky hydrophobic or aromatic groups are preferred to more hydrophilic or sterically demanding groups. Thus, phenylcyclohexene reacts with high enantioselectivity using (DHQD)₂PHAL (**7**) as catalyst, but the corresponding reaction of 1-naphthyl- and 9-phenanthryl-substituted cyclohexenes proceeds with lower enantioselectivity. This reduction in selectivity is presumably due to the steric demand of the twisted and extended aromatic substituent.²⁰ Similarly, whereas methylcyclohexene reacts with only 52% ee, protected allylic and homoallylic alcohol derivatives are oxidized with very high enantioselectivity, allowing convenient access to cyclic chiral glycerol derivatives. This effect was utilized for the enantioselective synthesis of the angiogenesis inhibitor ovalicin (**79**), where the initial chirality was established using an asymmetric dihydroxylation of the allylic 4-methoxybenzoate **78** (Eq. 79).¹³³



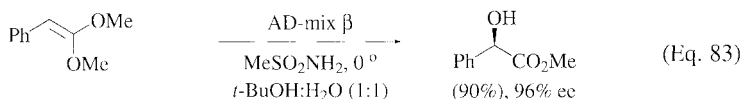


Cyclic enol ethers are oxidized to lactol derivatives with moderate to high enantioselectivity depending on alkene substitution, ring size, and choice of ligand (Eq. 80).¹³² Moderate enantioselectivity is typically obtained with the exception of substrate **80**, which is converted into the corresponding lactol in 91% ee using (DHQD)₂PYP (**25**) (Eq. 81). The enantioselectivity observed in the reaction of this substrate strongly depends on the type of cinchona alkaloid ligand used, and the corresponding reaction catalyzed by (DHQD)₂PHAL (**7**) produces the lactol product with only 74% ee. The lactol products can be easily oxidized to the corresponding lactones using iodine in ether in the presence of calcium carbonate.

The chiral α -hydroxy lactones that are produced are useful intermediates for natural product synthesis. The catalytic enantioselective dihydroxylation of substrate **81** was studied as part of an investigation toward an industrially scaleable route to the DE ring of camptothecin (**82**) and its analogs.^{134,135} Whereas the reaction of **81** using (DHQD)₂PHAL (**7**) affords the lactone product with only 26% ee after oxidation with I₂ and CaCO₃, the corresponding reaction using (DHQD)₂PYP (**25**) affords the same product with 94% ee (Eq. 82).^{134,135} Comparing these results with those obtained for the non-heterocyclic analog underscores the importance of a systematic investigation of ligand effects on enantioselectivity where the first choice affords poor results and further illustrates the complementary nature of the PHAL and PYP ligand classes with respect to substrate preferences.



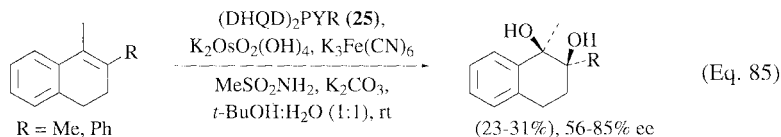
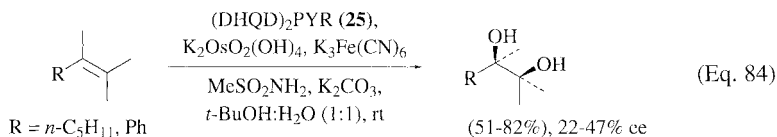
Trisubstituted ketene *O,O*-acetals have been shown to be excellent substrates for the catalytic asymmetric dihydroxylation utilizing the (DHQD)₂PHAL (**7**) and (DHQ)₂PHAL (**8**) ligands (Eq. 83). The ketene *O,O*-acetals are prepared from the corresponding aldehydes by the Horner-Wittig reaction with dialkoxymethyldiphenylphosphine oxides. After the dihydroxylation sequence, the intermediate diol hydrolyzes to the corresponding α -hydroxy ester.¹³⁶ This sequence has been successfully used to produce α -hydroxy esters starting with *O,O*-ketene acetals derived from aromatic, α,β -unsaturated, and aliphatic aldehydes, and is an attractive alternative to the conventional alkylation of aldehydes with nucleophilic carbanions, which can be challenging due to difficulties controlling the configuration of the newly created stereocenter.



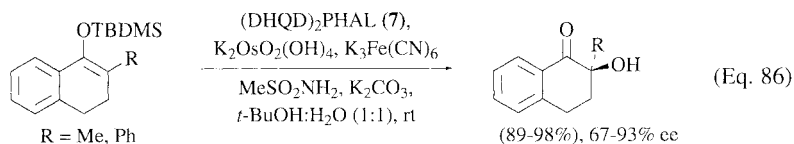
Tetrasubstituted Alkenes

Very few asymmetric dihydroxylations of tetrasubstituted alkenes have been reported, and all utilize cinchona alkaloid ligands under catalytic conditions. This limited scope is due to the sluggish rate of hydrolysis of the osmate ester formed during the catalytic cycle as well as to the crowded asymmetric dihydroxylation transition state would not effectively accommodate tetrasubstituted alkenes. In the limited number of examples that have been reported, the use of at least one equivalent of methanesulfonamide and 1 mol% osmium catalyst has helped to overcome the turnover problem.¹³⁷ The reactions of tetrasubstituted enol ethers proceed at 0° with one equivalent of methanesulfonamide,¹³² however, the asymmetric dihydroxylation of all-carbon tetrasubstituted alkenes requires three equivalents of methanesulfonamide, and reactions of these substrates are typically performed at room temperature. The reported reactions of all-carbon tetrasubstituted alkenes proceed with moderate enantioselectivity using either the PHAL or PYR class of ligands, and endocyclic alkenes generally give the best results (Eqs. 84 and 85).¹³⁷ However, there are examples where the chemical yields are low due to incomplete reaction. Due to

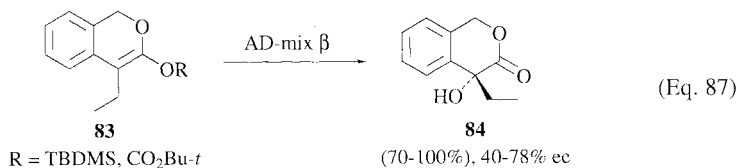
the lack of known compounds for comparison, the absolute **configuration** of the diol products was tentatively assigned using the face-selection mnemonic.



Tetrasubstituted enol ethers react to give α -hydroxy ketones in good yield and good to excellent enantioselectivity using either the PHAL or PYR chiral ligands (Eq. 86).¹³⁷



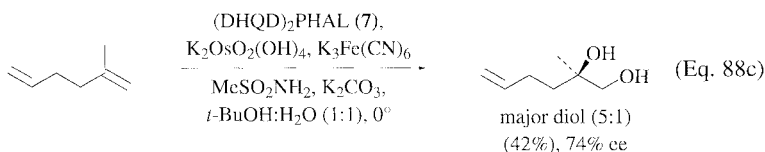
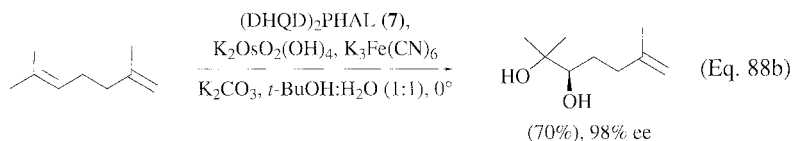
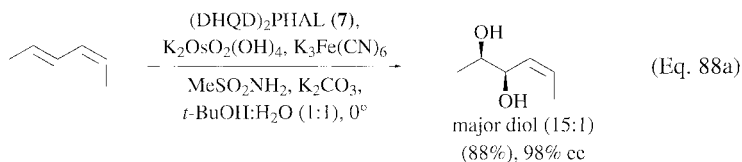
A limited number of examples of the asymmetric dihydroxylation of tetrasubstituted ketene acetals and enol esters such as **83** have been reported. These reactions also require higher catalyst loading and proceed with moderate enantioselectivity and chemical yield to form the α -hydroxy esters **84** (Eq. 87).¹³²



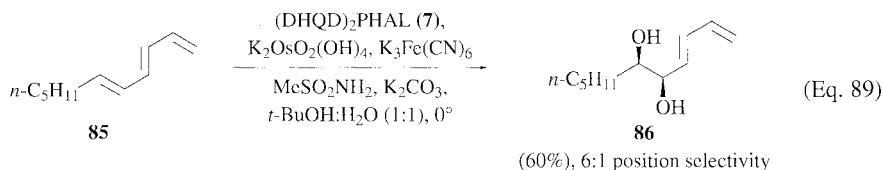
Polyalkene Substrates

Catalytic enantioselective dihydroxylation has been successfully used to control both the facial selectivity and regioselectivity of the oxidation of polyalkene substrates. The position selectivity of these oxidations is controlled by both the steric and the electronic properties of the individual double bond units. This section covers position and face selectivity observed in the catalytic asymmetric dihydroxylation of conjugated polyalkenes, non-conjugated polyalkenes, and endocyclic polyalkenes. Recent reviews provide additional detail regarding the regioselective asymmetric oxidation of these substrates.¹³⁸

There are numerous examples of the regioselective asymmetric dihydroxylation of simple aliphatic polyenes. These reactions typically proceed with high enantioselectivity at the more electron-rich alkene using the (DHQD)₂PHAL (**7**) ligand. Both conjugated and non-conjugated alkenes are good substrates for the reaction, and the order of reactivity can be predicted based on kinetic trends noted for the osmylation of simple alkenes by cinchona alkaloid-OsO₄ complexes.⁵⁰ Thus, E-alkenes are dihydroxylated in preference to Z-alkenes, and 1,1-disubstituted double bonds are oxidized in preference to terminal alkenes (Eqs. 88a-88c).¹³⁹

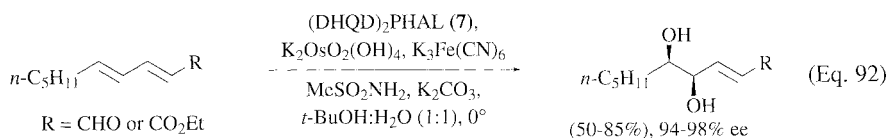
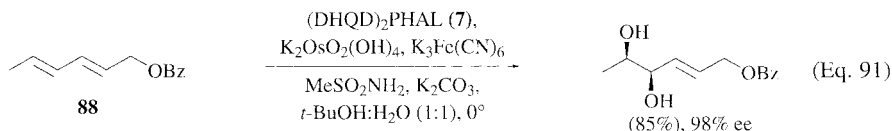
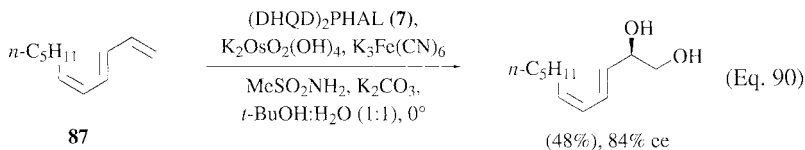


Conjugated substrates are preferentially oxidized such that a minimal disruption of conjugation occurs. For example, the reaction of triene **85** gives primarily diol **86** along with a small amount of the diol resulting from oxidation at the terminal alkene (Eq. 89).¹³⁸ This regioisomer is expected on the basis of a reaction at the most electron-rich trans alkene with minimal disruption of conjugation. In contrast, when triene **87**

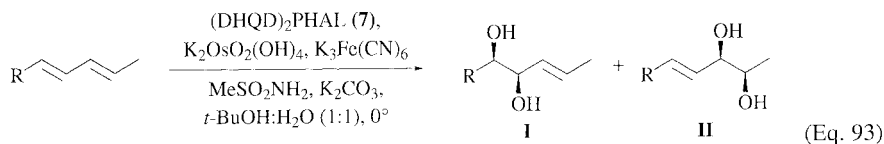


is subjected to the same conditions reaction occurs exclusively at the terminal alkene (Eq. 90).¹³⁸ This regioselectivity is most likely due to a preference not to disrupt conjugation via reaction at the internal trans alkene as well as a strong kinetic preference of the cinchona alkaloid-OsO₄ catalyst for oxidation of terminal alkenes compared to cis alkenes. Strong electron-withdrawing groups can also influence the regioselectivity of these reactions. In substrate **88** the benzoyl group directs the dihydroxylation to the more distal alkene with 14:1 regioselectivity, affording the diol product

in high enantiomeric excess (Eq. 91).¹³⁸ Similarly, conjugated esters and aldehydes react preferentially at the most electron-rich alkene forming the corresponding diol in high chemical yield with excellent enantioselectivity (Eq. 92).^{139,140} This regiochemical preference is also consistent with minimal disruption of conjugation.

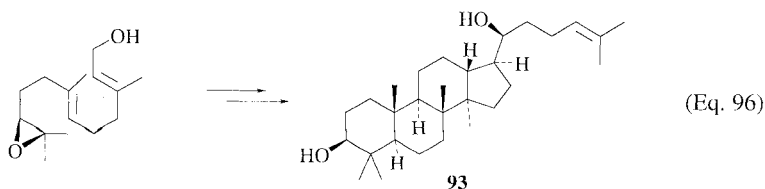
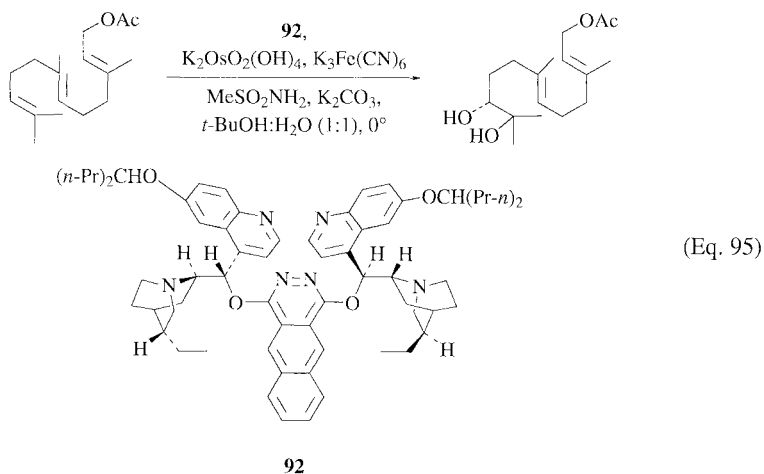
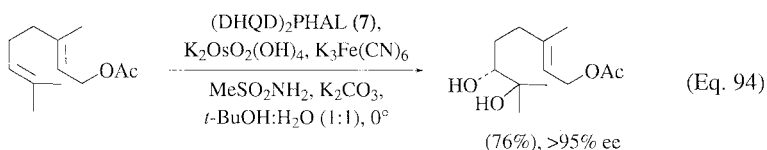


The catalytic asymmetric dihydroxylation reactions of dienes containing an aryl substituent generally proceed with high enantioselectivity due to favorable interactions between the catalyst's binding pocket and the aromatic ring of the substrate. The positional selectivity of these reactions is partially governed by the nature of the substituents on the aromatic ring (e.g. substrate **90**) (Eq. 93). Generally, reactions occur at the double bond that is distal to the aromatic ring in order to preserve conjugation, and regioselectivity is further improved when bulky groups are present on the aromatic ring. Interestingly, replacement of phenyl (**89**) with β -naphthyl (**91**) causes a reversal in regioselectivity that favors oxidation of the internal double bond (Eq. 93). This reversal of position-selectivity can be understood in terms of a combination of highly favorable interactions between the catalyst and the naphthyl ring of **91** as well as differences in the conjugation energies of the phenyl- (**89**) versus the naphthyl- (**91**) substituted dienes.¹³⁸

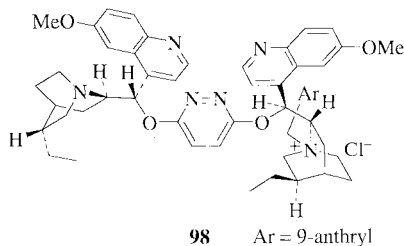
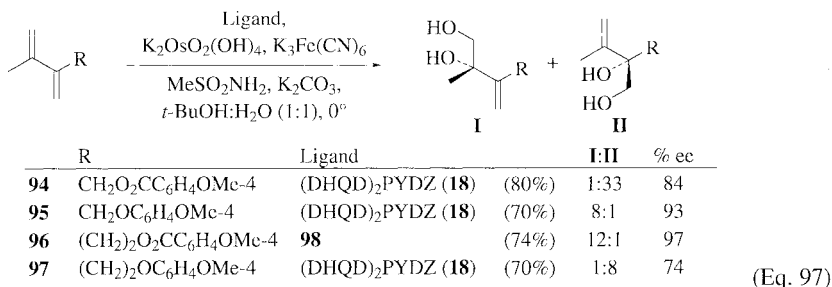


R		I:II	% ee (major isomer)
Ph	89	(83%) 1:4	92
3,5-(<i>t</i> -Bu) ₂ C ₆ H ₃	90	(76%) 1:15	92
2-naphthyl	91	(71%) 4:1	98

There are numerous examples of the position-selective dihydroxylation of geranyl, farnesyl, and other oligoprenyl substrates. Use of the (DHQD)₂PHAL (**7**) ligand gives good positional selectivity in the dihydroxylation of monoterpenes, such as geraniol, geranyl acetate, and neryl acetate due to the electronic differentiation of the two substrate double bonds that favors dihydroxylation of the terminal prenyl unit (Eq. 94).¹⁴¹ With higher terpenes, such as 2,6-*E,E*-farnesyl acetate, the electronic similarity of the terminal vs. internal prenyl units requires the use of modified bis(cinchona) alkaloid ligands in order to obtain high positional selectivity.⁶² Thus, whereas enantioselective dihydroxylation of farnesyl acetate using (DHQD)₂PYDZ (**18**) affords a 2:1 mixture of diols derived from oxidation of the terminal and internal prenyl units, the use of ligand **92** affords the product of terminal oxidation with 80% yield, 120:1 positional selectivity and 96% ee (Eq. 95).⁶² This highly selective terminal oxidation of oligoterpenes has been used in the synthesis of complex terpenoid natural products, such as dammaranediol **II** (**93**) (Eq. 96).¹⁴²

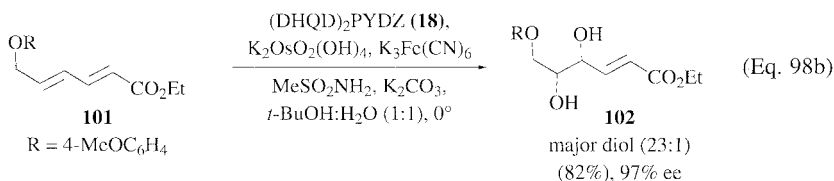
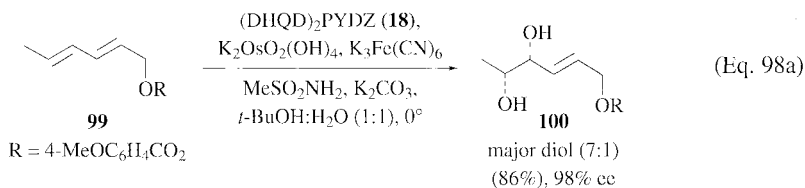


The discovery that *p*-methoxybenzoate esters of allylic alcohols are excellent substrates for the catalytic asymmetric dihydroxylation reaction led to the investigation of regioselective dihydroxylation of suitably protected bis unsaturated alcohols.⁶⁴ The observation that allylic and bis(homoallylic) 4-methoxybenzoates are dihydroxylated with high enantioselectivity, as opposed to the poor selectivity noted for homoallylic benzoates, prompted an investigation of the utility of this protecting group to control position-selectivity in the oxidation of conjugated dienyl alcohols. For example, the reaction of diene **94** catalyzed by the (DHQD)₂PYDZ (**18**) ligand favors oxidation at the double bond proximal to the 4-methoxybenzoyl group (Eq. 97).⁶⁴ This observation can be explained in terms of unfavorable interactions between the catalyst's pyridazine ring nitrogen atoms and the ester carbonyl group of the substrate that prevent reaction at the distal alkene. Oxidation of the other double bond of the substrate is favored by attractive interactions between the allylic 4-methoxybenzoyl group of the substrate and the catalyst's U-shaped pocket. Using the corresponding *p*-methoxyphenyl ether **95** as the substrate reverses this regioselectivity. Similarly, the reaction of substrate **96** favors the product of oxidation at the bis(homoallylic) position,⁸² whereas position-selectivity is reversed in the reaction of the corresponding *p*-methoxyphenyl ether **97**.

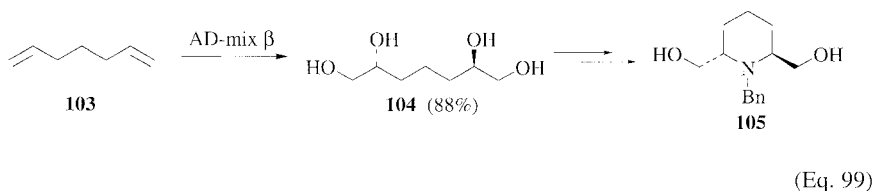


The utility of *p*-methoxybenzoate esters and *p*-methoxyphenyl ethers in directing position-selective dihydroxylation of dienes is demonstrated by the synthesis of hexose and 6-deoxyhexose derivatives.¹⁴³ Thus, the asymmetric dihydroxylations of dienes **99** and **101** using the (DHQD)₂PYDZ (**18**) ligand proceed in high yield and with high regio- and enantioselectivity affording the diols **100** and **102**, which can

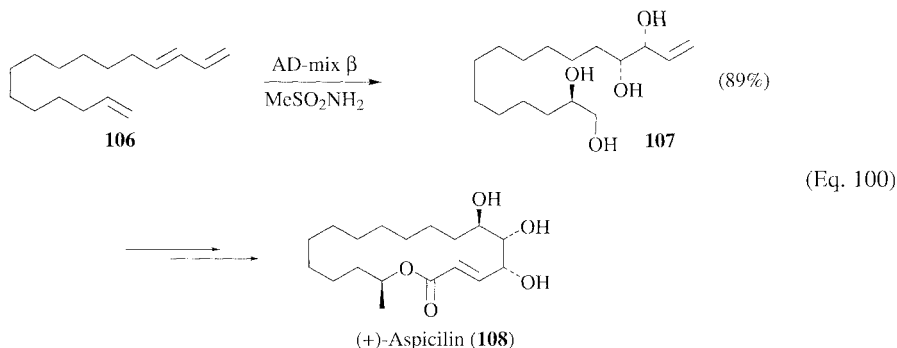
be subsequently protected and converted into the corresponding hexoses via a reagent-controlled, selective dihydroxylation (Eqs. 98a and 98b).



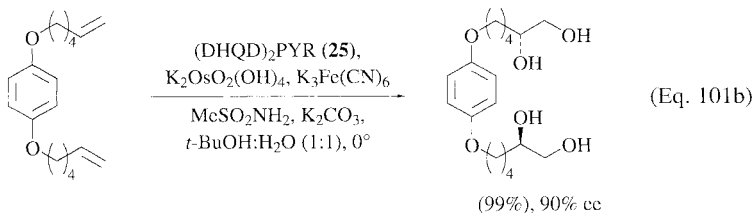
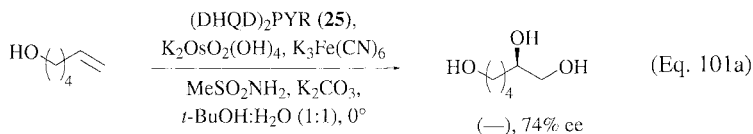
The asymmetric dihydroxylation of polyunsaturated substrates has been successfully used to access synthetically useful enantiomerically enriched polyalcohols. In these cases, overall enantiomeric purity is enhanced due to minimal influence of the diol that is installed first on the facial selectivity of the second dihydroxylation. If either one of the first or the second dihydroxylation reactions proceeds from the wrong face of the double bond, the resulting product is the meso diastereomer, which can be separated chromatographically. Thus, the asymmetric dihydroxylation of diene **103** using AD-mix β produces tetraol **104** in 88% yield. This material can be subsequently converted into piperidine **105**, which is obtained in 93% ee. Related piperidine derivatives are potentially useful C2-symmetric chiral directors (Eq. 99).¹⁴⁴



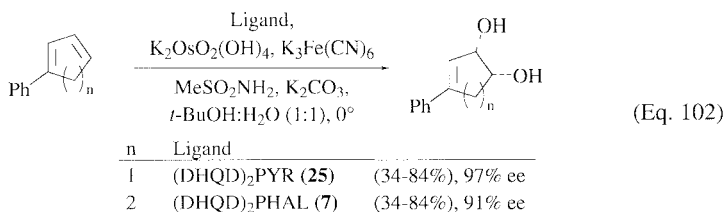
In another example triene **106** is efficiently converted into tetraol **107** in 89% yield using AD-mix β ; the bis-acetonide of **107** was subsequently found to be 83% enantiopure. Dihydroxylation of the remaining terminal alkene of **107** gave an intermediate useful in the synthesis of the lichen macrolide (+)-aspicilin (**108**) (Eq. 100).¹⁴⁵



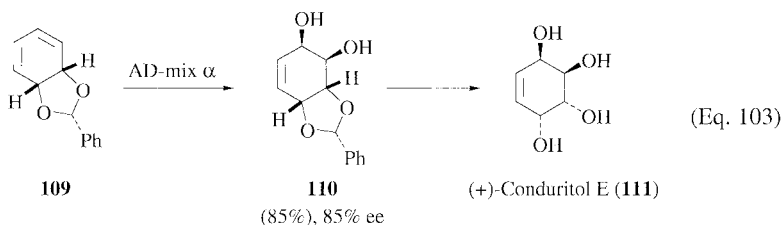
The double asymmetric dihydroxylation of two terminal alkenes tethered by a linker group, followed by removal of that linker group, is a strategy to efficiently access enantiomerically pure triols. Typically, the process gives triols of higher enantiomeric excess than the corresponding dihydroxylation of the monomer subunit alone (Eqs. 101a and 101b).¹⁴⁶ This enhancement of enantiomeric purity results from the fact that chromatography or crystallization can remove the diastereomeric product obtained from improper facial approach in the second dihydroxylation. The use of potassium ferricyanide as the stoichiometric oxidant generally gives superior results to iodine, and no single ligand is preferred in all cases.¹⁴⁶



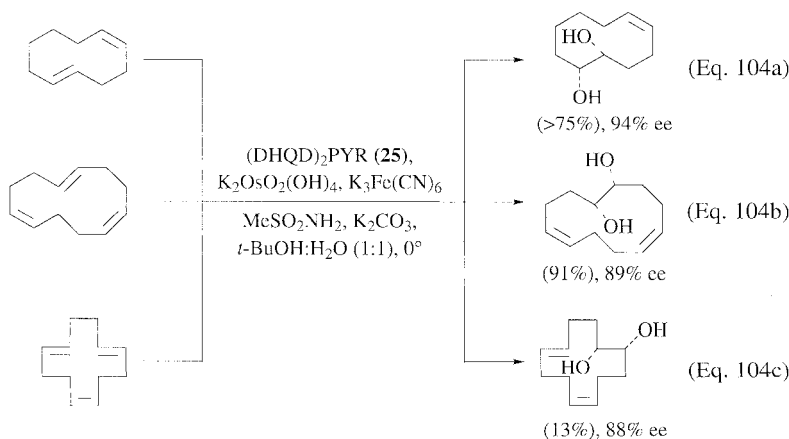
Small polyalkene ring systems generally give poor enantioselectivity in the asymmetric dihydroxylation reaction due primarily to the fact that *Z*-alkenes are among the poorest classes of alkenes for this reaction. In a few cases good to excellent enantioselectivity has been observed using the (DHQD)₂PHAL (**7**) and (DHQD)₂PYR (**25**) ligands.¹⁴⁷ The selectivity is enhanced when one of the alkenes is sterically hindered. Two of the best substrates are 1-phenylcyclopentadiene and 1-phenylcyclohexadiene, which react in the presence (DHQD)₂PHAL (**7**) at the more electron-rich double bond to give the corresponding diols in 97 and 91% ee, respectively (Eq. 102).



This dihydroxylation strategy has been used to complete an enantioselective synthesis of conduritol E.¹⁴⁸ Thus, enantioselective dihydroxylation of prochiral precursor **109** affords **110** with 85% yield and 85% ee. Removal of the benzylidene protecting group by hydrolysis affords conduritol E (**111**), an important intermediate for the preparation of cyclitols (Eq. 103).^{147,148}



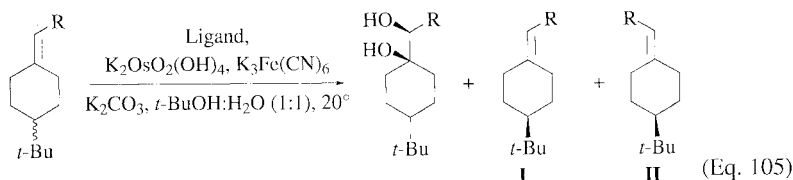
Medium and large polyalkene rings can be good substrates for the asymmetric dihydroxylation reaction, provided that at least one of the double bonds is trans. The dihydroxylation of large rings with multiple E-double bonds proceeds with high enantioselectivity; however, because the reaction must be stopped at low conversion in order to suppress bis-dihydroxylation, the reactions of some of these substrates are not synthetically useful. Typically the pyrimidine ligands are superior to the phthalazine ligands (Eqs 104a-104c).¹³⁸



Kinetic Resolutions

Because the catalytic asymmetric dihydroxylation of alkenes is a highly efficient and selective process for a wide variety of substrates, it seems logical to apply the reaction to the kinetic resolution of racemic alkenes. This approach can be used for the preparation of enantiopure diols and for the recovery of enantiopure alkenes when installation of the chiral center is difficult by other means or when separation of the alkene enantiomers is difficult. Kinetic resolutions are inherently inefficient processes, as the undesired enantiomer cannot be directly converted into the desired stereoisomer and is usually discarded. Despite its generality for enantioselective dihydroxylation of achiral alkenes, few examples exist of successful kinetic resolutions using cinchona alkaloid-based catalytic systems. Only some of the examples reported are synthetically useful, as the existing cinchona alkaloid catalysts poorly discriminate between the alkene enantiomers. The k_{rel} parameter (the ratio of the rate constant for the fast vs. slow reacting enantiomer) is a good indicator of the synthetic utility of a kinetic resolution. For example, in order to obtain greater than 40% recovery (80% of the theoretical) of alkene that is of high enantiomeric excess, the k_{rel} for the reaction must be greater than 25.¹⁴⁹ The generally low observed k_{rel} for catalytic asymmetric dihydroxylations requires reactions to be run to much greater than 50% conversion to obtain recovered substrate with high enantiomeric purity.

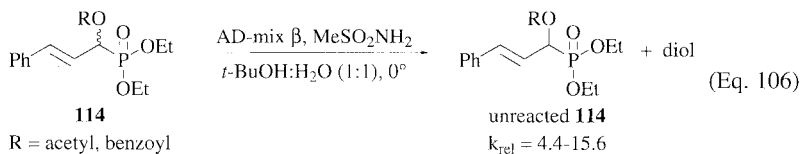
The kinetic resolution of the axially dissymmetric racemic methylenecyclohexane derivatives **112** and **113** was performed using (DHQD)₂PHAL (**7**) and (DHQ)₂PHAL (**8**) (Eq. 105).¹⁴⁹ The k_{rel} value ($k_{\text{fast}}/k_{\text{slow}}$) for these reactions ranges from 5.0 to 32.0, depending on the catalyst used and the exocyclic alkene substituent. Dihydroxylation using cinchona alkaloid catalysts produces the diol diastereomer resulting from axial attack on the alkene. In contrast, when no chiral ligand is used, the product of equatorial attack is the major dihydroxylation product observed in this reaction.¹⁴⁹



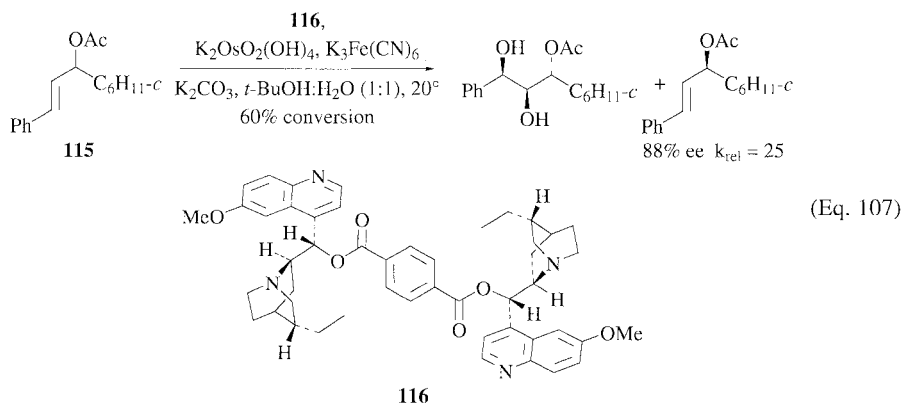
R	Ligand	k_{rel}	Recovered Olefin
112 Ph	(DHQD) ₂ PHAL (7)	9.7	I
112 Ph	(DHQ) ₂ PHAL (8)	5.0	II
113 CO ₂ Et	(DHQD) ₂ PHAL (7)	32.0	I
113 CO ₂ Et	(DHQ) ₂ PHAL (8)	26.5	II

The asymmetric dihydroxylation of a series of racemic alkenylphosphonates **114** has also been examined using the AD-mix reagents. The k_{rel} values are generally

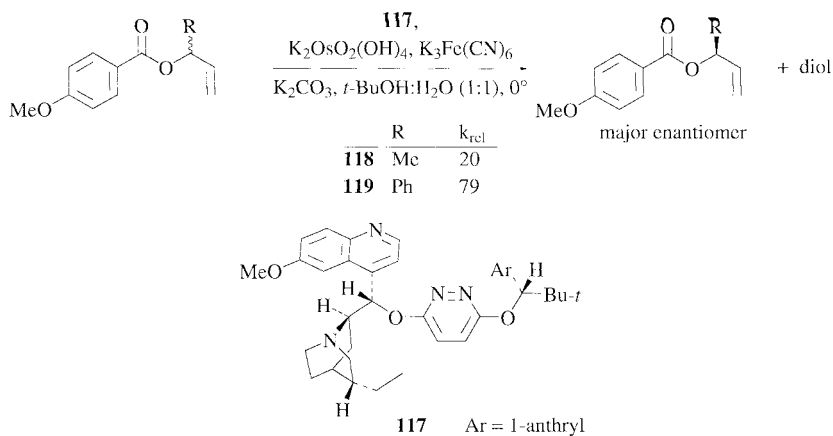
moderate (4–15) allowing the alkenes to be recovered in high enantiomeric excess only if the reactions are run to high conversion (Eq. 106). Therefore, the yields of recovered alkene with high enantiomeric excess are typically less than 40%.¹⁵⁰



A number of kinetic resolutions of allylic acetates have been performed. The reactions typically proceed with moderate k_{rel} values between 3 and 10; therefore these reactions have limited synthetic utility. For example, in the kinetic resolution of acetic acid 1-cyclohexyl-3-phenylallyl ester (**115**) using ligand **116**, the starting material is recovered in only 88% ee at 60% conversion, and the reaction needs to proceed to 70% conversion in order to recover the alkene at >98% ee (Eq. 107).^{151,152} In this example the k_{rel} value is ~25, which was the best observed and significantly higher than that of a typical allylic acetate substrate.^{151,152}



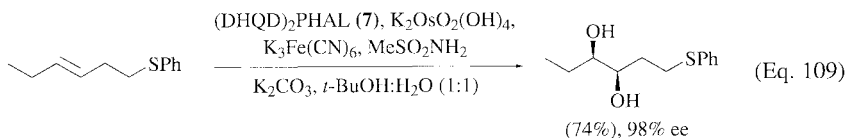
Significant improvements in efficiency are observed in the reactions of allylic 4-methoxybenzoates, particularly when ligand **117** is used (Eq. 108).⁶³ Use of this catalyst with the methyl-substituted 4-methoxybenzoate **118** gives a k_{rel} value of 20. Upon replacing the methyl substituent with the more bulky phenyl group (substrate **119**), the k_{rel} value for this reaction improves to 79. The proper choice of catalyst is critical for efficient kinetic resolutions of these substrates. Note that when the conventional C2 symmetric (DHQD)₂PYDZ (**18**) ligand is used, the k_{rel} value drops below five for each of these substrates. Thus, with proper choice of ligands and substrates, synthetically useful kinetic resolutions are quite feasible.⁶³



(Eq. 108)

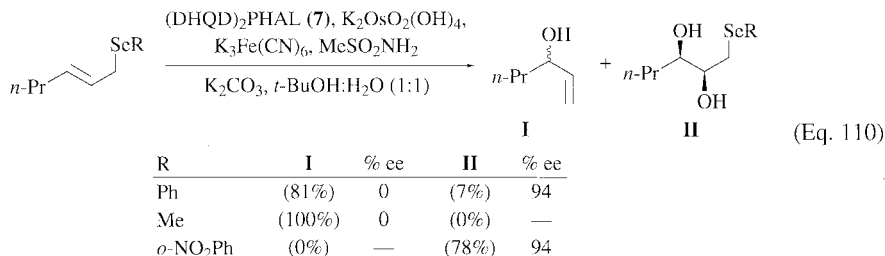
Functional Group Compatibility

The dihydroxylation of alkenes by OsO_4 is one of the most general transformations in organic chemistry and is tolerant of a wide variety of functionality on the alkene substrate. The standard conditions for catalytic asymmetric dihydroxylation using cinchona alkaloid ligands are compatible with a wide variety of substrate functional groups, including: aliphatic and aromatic substituents, alkynes, alcohols, ethers, esters, amides, carbamates, nitriles, and sulfonamides. In addition to the high levels of enantioselectivity that are observed for a broad range of substrates, the cinchona alkaloid catalyzed asymmetric dihydroxylation offers improved chemoselectivity for the dihydroxylation of alkenes over other functional groups that are normally oxidized by OsO_4 alone. One of the most striking examples of this chemoselectivity is the asymmetric dihydroxylation of alkenes containing sulfur substituents. Osmium tetroxide is known to oxidize aromatic and aliphatic sulfides to sulfones preferentially to the dihydroxylation of alkenes present on the same substrate. In contrast, sulfides are oxidized slowly under the standard cinchona alkaloid catalyzed asymmetric dihydroxylation conditions, whereas the rate of alkene dihydroxylation is accelerated. Thus, chemoselective dihydroxylation of carbon-carbon double bonds is possible with substrates containing sulfur functionality.¹⁰⁰ High yields and enantioselectivity are obtained for substrates containing aromatic and aliphatic sulfides, dithianes, or disulfides (Eq. 109).¹⁰⁰

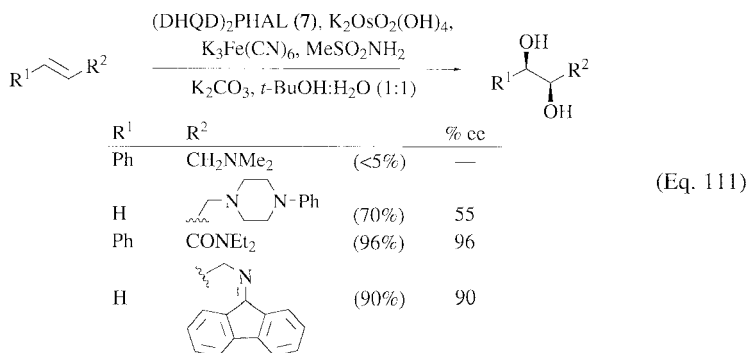


In contrast to the chemoselective dihydroxylation of allylic sulfides and dithianes, the catalytic enantioselective dihydroxylation of allylic selenides affords products derived from the reaction of both the substrate double bond and the selenide func-

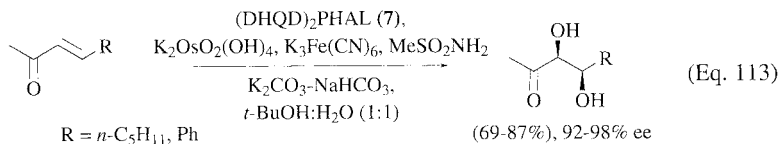
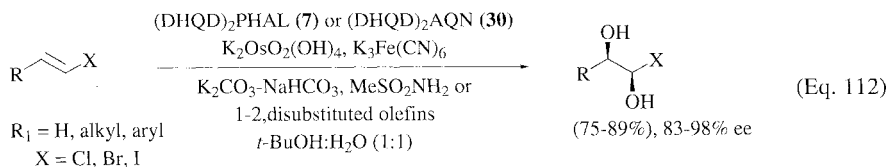
tional group.¹⁵³ Oxidation at selenium is followed by elimination of the selenoxide, affording chiral allylic alcohols with low enantioselectivity. Since the diol product resulting from chemoselective alkene oxidation is formed with high enantioselectivity, it is unclear whether the low enantiomeric purity of the allylic alcohol products results from racemization of the newly formed chiral center or from poor facial discrimination in the dihydroxylation of the allylic selenoxides. The rate of oxidation at selenium can be controlled by the electronic properties of the selenide, and allylic 2-nitrophenylselenides are selectively oxidized at the carbon-carbon double bond (Eq. 110).¹⁵³



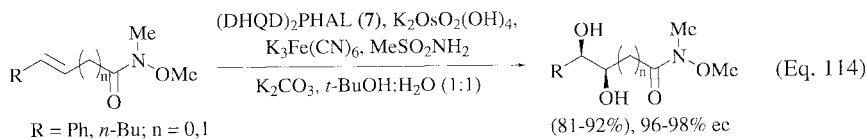
Whereas the enantioselective dihydroxylation of many nitrogen-containing substrates has been reported using cinchona alkaloid catalysts, the reaction of allylic and homoallylic amines does not proceed with useful yields or enantioselectivity. For example, the enantioselective dihydroxylation of *N,N*-dimethylcinnamylamine using modified AD-mix β , wherein the loading of ligand and potassium osmate is increased to 5 mol% and 1 mol%, respectively, affords only trace amounts of the diol product after 36 hours at room temperature.¹¹¹ Similarly, 4-phenyl-1-allylpiperazine gives the corresponding diol product in 70% conversion and only 55% ee after 7 days at room temperature.¹¹¹ In sharp contrast to the above results, several successful catalytic asymmetric dihydroxylation using cinchona alkaloid ligands have been reported for substrates where the allylic or homoallylic nitrogen functionality is protected as an imine, carbamate, or amide (Eq. 111).^{61,111} Thus, it appears that turnover in the cinchona alkaloid catalyzed enantioselective dihydroxylation is dependent on the basicity of the nitrogen functionality that is proximal to the reactive double bond.



Certain substrates possessing base-sensitive functionality decompose under the moderately basic conditions of the catalytic enantioselective dihydroxylation using potassium ferricyanide as the secondary oxidant. The basicity of the reaction can be reduced somewhat by using a mixed sodium bicarbonate-potassium carbonate buffer system. With these modified conditions, the asymmetric dihydroxylation of allylic halides proceeds with good yields and enantioselectivities, especially when the AQN ligands are used (Eq. 112).^{86,154} Unfortunately, total replacement of potassium carbonate with sodium bicarbonate results in a loss of catalytic turnover for the cinchona alkaloid catalyzed dihydroxylation. The reaction of unsaturated ketones proceeds well using this mixed buffer system, which, in most cases, circumvents the problems of epimerization at the α -carbon or retro-aldol fragmentation of the product, a side reaction that may occur under more basic conditions (Eq. 113).¹⁵⁵



Whereas the enantioselective dihydroxylation of α,β -unsaturated ketones, amides, and esters affords products of high enantiomeric purity in good yield, the corresponding reactions of α,β -unsaturated aldehydes are generally not successful. However, α,β -unsaturated *N*-methyl-*N*-methoxy amides (Weinreb amides) are good substrates for the cinchona alkaloid catalyzed asymmetric dihydroxylation and can serve as useful synthons for enantiomerically enriched 2,3-dihydroxyaldehydes (Eq. 114).¹¹¹



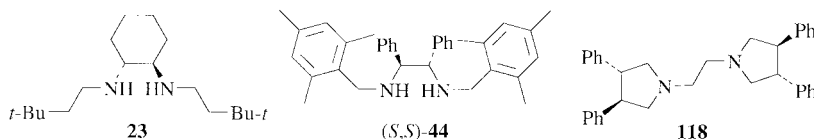
EXPERIMENTAL CONDITIONS

Note: Osmium and its salts are highly toxic and must be handled using appropriate personal protective equipment. OsO₄ is very toxic by inhalation, in contact with skin, and if swallowed. Osmium tetroxide is a highly volatile (bp 130°) low melting solid (mp 40°) that should only be handled in a fume cupboard by qualified individ-

uals using chemical-resistant gloves. Osmium salts should be properly disposed of in specially designated containers. Further information can be obtained from the Material Safety Data Sheet (MSDS) available from the supplier.

Stoichiometric Enantioselective Dihydroxylation Using Chiral Diamine Ligands

Selection of Ligand. Significant research has been devoted to the study of enantioselective dihydroxylation using stoichiometric amounts of chiral 1,2-diamine ligands and OsO_4 . Although catalytic turnover is precluded by the high affinity of the diamine ligand for osmium, very effective chiral ligands have been developed for the enantioselective dihydroxylation of a variety of alkene substrates. The 1,2-diamine ligands that have been surveyed thus far belong to three ligand classes: (1) acyclic 1,2-diamines, as represented by ligand **44** derived from chiral 1,2-diphenyl-1,2-diaminoethane; (2) heterocyclic diamines, exemplified by the bis(pyrrolidino)ethane ligand **118**; and (3) cyclic diamines, such as ligand **23**, derived from chiral 1,2-diaminocyclohexane.



These three ligands represent the best members of each ligand class based on substrate scope and average enantioselectivity in the asymmetric dihydroxylation. While subtle differences in enantioselectivity exist for each of the ligands in the reaction of common substrates, such as styrene or dimethyl fumarate, ligand **23** has the widest reported scope, with enantioselectivities for many substrates rivaling the cinchona alkaloid catalyzed asymmetric dihydroxylations. The enantioselectivities observed for the asymmetric dihydroxylation of *cis* alkenes are among the highest reported, making **23** the ligand of choice for the oxidation of these substrates.

Solvent, Temperature, and Concentration. The choice of solvent for these reactions has a significant effect on enantioselectivity and is best guided by empirical observations for the ligand under consideration. The reaction is typically conducted in an aprotic organic solvent, such as THF, toluene, or methylene chloride, under anhydrous conditions. Complexation of the 1,2-diamine ligand with OsO_4 produces a bright red or orange complex that is soluble and highly reactive at temperatures as low as -110° . These reactions are generally conducted at these very low temperatures to ensure low background reaction rates and optimum enantioselectivity. The effect of concentration on rate and enantioselectivity has not been explicitly studied for these reactions. Laboratory-scale reactions are generally conducted at relatively low concentrations (0.04 to 0.2 M).

Recovery of Ligand and Osmium. Because these reactions require the use of a stoichiometric amount of OsO_4 and the chiral ligand, procedures for the recovery

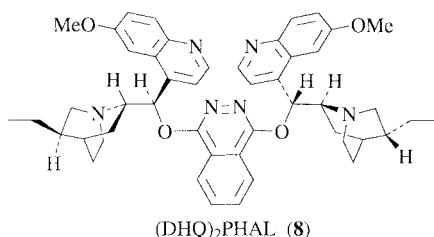
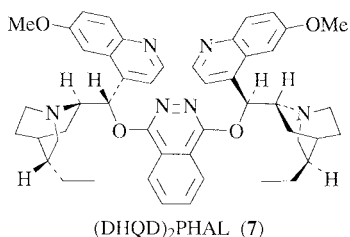
of each of these components are critical for economic reasons. The tightly associated ligand-bound osmate ester complex is typically broken up by a reductive quench with either lithium aluminum hydride or aqueous sodium bisulfite. The chiral ligand can typically be recovered through either extraction of the mixture with aqueous acid, basification of the aqueous layer, and extraction of the ligand into an organic solvent, or by chromatographic separation of the crude reaction mixture.¹¹ The recovery of OsO_4 is somewhat more complicated. Isolation of spent osmium is accomplished by adsorption of the crude reaction mixture onto silica gel, followed by separation of the dark-colored silica after elution of the diol product and the diamine ligand. Oxidation of the osmium-impregnated silica with a mixture of 30% hydrogen peroxide and methylene chloride, separation of the organic phase, and drying with MgSO_4 produces a concentrated solution of OsO_4 in methylene chloride that contains >80% of the originally used osmium.¹¹

Catalytic Enantioselective Dihydroxylation Using Cinchona Alkaloid Ligands

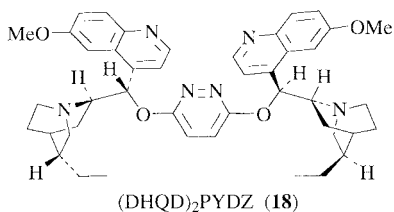
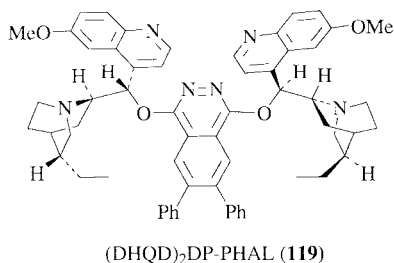
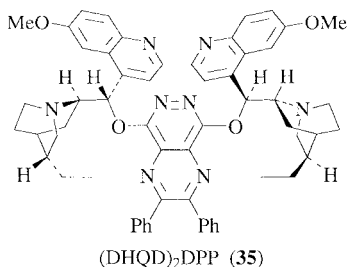
Selection of Ligand. Extensive studies on the effects of ligand structure on enantioselectivity have resulted in the discovery of specialized ligands for the highly enantioselective oxidation of specific substrate classes. The choice of cinchona alkaloid ligand is critical for highly enantioselective dihydroxylation and to a certain extent can be empirical when the first selection does not yield satisfactory results. Indeed, many extensions to the scope of the asymmetric dihydroxylation have been discovered by surveying the panel of commercially available ligands in the oxidation of a new substrate. Many cinchona alkaloid derivatives have been reported for the asymmetric dihydroxylation of various substrates, and only those that are commercially available or offer optimum selectivity for special substrate classes will be reported here. The proper choice of cinchona alkaloid ligand can be guided by a few simple observations of ligand-substrate preferences. Many of these observations were detailed earlier in the description of the dihydroxylation of various substrate classes and will only be briefly summarized here. The determination of which cinchona alkaloid derivative to be used (DHQ or DHQD) is dictated by the desired direction of enantiofacial selectivity. The sense of enantioselectivity is readily predicted using the mechanistic models detailed earlier or can be simply estimated using the mnemonic device depicted in Figure 2.

Recovery of the ligands upon workup is typically achieved by extraction of the organic phase with aqueous acid, followed by basification of the aqueous phase and extraction into organic solvent. In cases where the diol product is very hydrophilic or easily extracted into aqueous acid, the cinchona alkaloid ligand may be recovered upon chromatography of the product and typically elutes from silica gel with 5–10% methanol in methylene chloride with 1% aqueous ammonium hydroxide added as a modifier.

The bis(cinchona) alkaloids are optimum ligands for the dihydroxylation of the vast majority of substrates and have replaced the first-generation mono-cinchona alkaloids for most applications. In general, the PHAL-linked ligands $(\text{DHQD})_2\text{PHAL}$ (**7**) or $(\text{DHQ})_2\text{PHAL}$ (**8**) are often good first choices to explore the enantioselective dihydroxylation of a new substrate.¹⁹

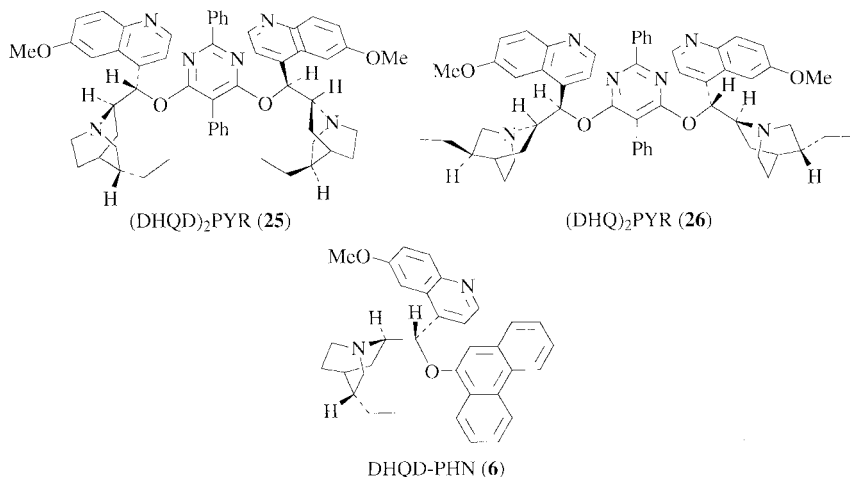


These ligands afford high enantioselectivities in the asymmetric dihydroxylation of terminal, 1,1-disubstituted, E-1,2-disubstituted, trisubstituted, and tetrasubstituted alkenes, and as such, offer the broadest substrate scope of the cinchona alkaloid derivatives studied to date. The highest enantioselectivities are obtained for alkenes that possess an aromatic or non-bulky aliphatic substituent that can favorably interact with the catalyst's binding pocket. Terminal alkenes possessing bulky substituents and Z-1,2-disubstituted alkenes react with modest to poor enantioselectivity. Several variants of the PHAL-linked ligands, such as (DHQD)₂PYDZ (**18**), (DHQD)₂DPP (**35**), and (DHQD)₂DP-PHAL (**119**) have been evaluated in the enantioselective dihydroxylation of simple hydrocarbon substrates.^{156,157} Although the (DHQD)₂DPP (**35**) and (DHQD)₂DP-PHAL (**119**) ligands afford somewhat higher enantioselectivities for the oxidation of certain cis-alkenes, they generally offer comparable performance to the commercially available PHAL ligands.

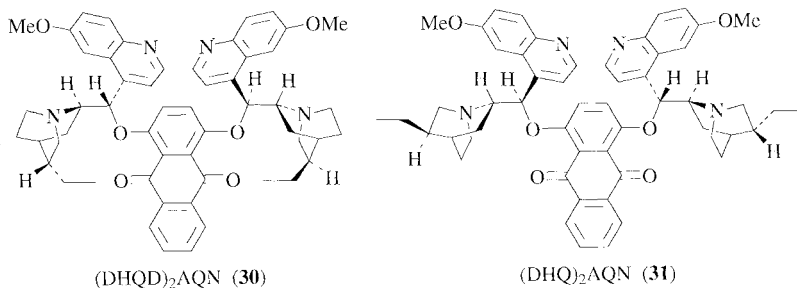


The pyrimidine-linked ligands (DHQD)₂PYR (**25**) and (DHQ)₂PYR (**26**) address some of the limitations of the PHAL-linked ligands for the dihydroxylation of terminal alkenes possessing bulky aliphatic substituents.⁷⁷ However, the PYR ligands afford significantly lower enantioselectivity than the PHAL ligands in the dihydroxylation of substrates possessing aromatic substituents. The PYR ligands are truly complementary to the PHAL ligands in that alkenes that work well for one ligand class are generally worse substrates for the other.

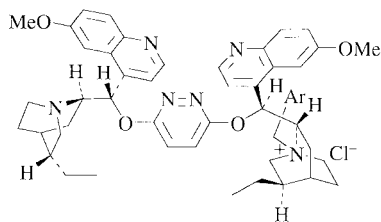
The PYR-linked alkaloids are the ligands of choice for the dihydroxylation of terminal alkenes possessing branched aliphatic substituents, such as *tert*-butylethylene and vinylcyclohexane, where enantioselectivities are significantly higher with this class of alkaloids as compared to the PHAL-linked ligands. In some cases the mono cincona alkaloid ligands, such as DHQD-PHN (**6**), offer comparable performance for the enantioselective dihydroxylation of terminal alkenes possessing a bulky aliphatic substituent. Each of these ligands is commercially available.



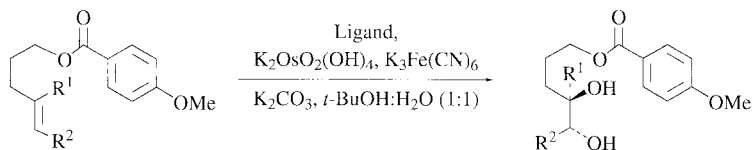
The anthraquinone-linked ligands (DHQD)₂AQN (**30**) and (DHQ)₂AQN (**31**) offer superior performance in the enantioselective dihydroxylation of allylically functionalized terminal alkenes.⁸⁶ Allylic halides and sulfonates are oxidized with 83–90% ee, affording functionalized chiral glycerol derivatives. This important substrate class affords a variety of small chiral non-racemic building blocks for asymmetric synthesis. The AQN-linked ligands provide the highest enantioselectivities for the catalytic asymmetric dihydroxylation of indene and allylbenzene, two difficult substrates for the PHAL-linked ligands, and afford enantioselectivities comparable to the PYR-linked ligands for the oxidation of *n*-alkyl-substituted terminal alkenes. Like the PYR-linked ligands, the AQN ligands exhibit worse performance than the PHAL-linked ligands in the enantioselective oxidation of substituted styrenes and other alkenes possessing aromatic substituents.



While the commercially available (DHQD)₂PHAL (**7**) and (DHQ)₂PHAL (**8**) ligands and the related PYDZ-linked ligands provide excellent enantioselectivity in the dihydroxylation of allylic 4-methoxybenzoates and homoallylic 4-methoxyphenyl ethers, the reactions of bis(homoallylic) 4-methoxybenzoates proceed with substantially lower facial selection using either of these cinchona alkaloid ligands. The reactions of these substrates can be significantly improved by using ligand **98**, which is a mono-9-anthracenylmethyl quaternary ammonium salt of the (DHQD)₂PYDZ (**18**) ligand (Eq. 115).⁸² Although this ligand is not commercially available, it is readily prepared by reaction of (DHQD)₂PYDZ (**18**) with 9-chloromethylantracene in acetonitrile at 40°, followed by chromatographic purification. The improved facial selectivity in the dihydroxylation of these substrates using the 9-anthracenylmethyl quaternary ammonium salt derivative **98** is presumably derived from this ligand's deeper binding pocket, which can interact with functional groups of the substrate that are remotely positioned relative to the double bond that is being oxidized.

**98**

Ar = 9-anthryl

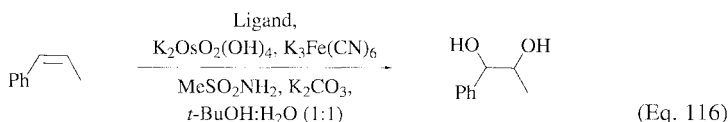
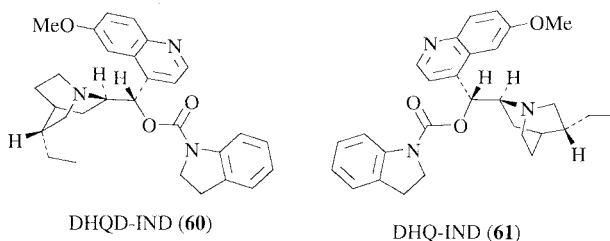


R ¹	R ²	Ligand	
		(DHQD) ₂ PYDZ (18)	98
H	H	(99%), 82% ee	(91%), 86% ee
Me	H	(95%), 79% ee	(99%), 90% ee
<i>n</i> -Bu	H	(99%), 33% ee	(99%), 62% ee
<i>t</i> -Bu	H	(88%), 92% ee	(91%), 92% ee
H	Me	(97%), 89% ee	(98%), 90% ee

(Eq. 115)

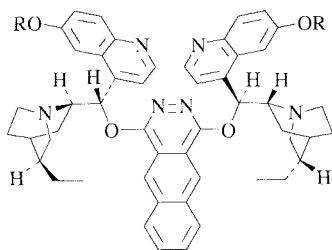
The low enantioselectivity observed for the reaction of *Z*-alkenes remains a major hurdle for the cinchona alkaloid catalyzed asymmetric dihydroxylation. Enantioselectivities above 80% ee are rare, and the mono cinchona alkaloid ligands DHQD-IND (**60**) or DHQ-IND (**61**) generally afford the highest enantioselectivities in the dihydroxylation of these substrates.¹²¹ In general, *Z*- β -substituted styrenes react with higher facial selectivity as compared to non-aromatic substrates using this ligand. Interestingly, dihydronaphthalene reacts with substantially lower enantiofacial selectivity as compared to *Z*- β -methylstyrene, suggesting that conformational flexibility in the substrate, which allows the aromatic ring to twist out of the plane of the reactive double bond, may be important for achieving high enantioselectivity. The

reduction in facial selectivity that is normally observed with the DHQ-derived ligands as compared to the corresponding DHQD-derived ligands is most striking for the IND ligand class. Thus, while the enantioselective dihydroxylation of *Z*- β -methylstyrene using DHQD-IND (**60**) affords the 1*R*,2*S* enantiomer with 72% ee, the corresponding reaction with DHQ-IND (**61**) gives the 1*S*,2*R* enantiomer with only 59% ee (Eq. 116).¹²¹

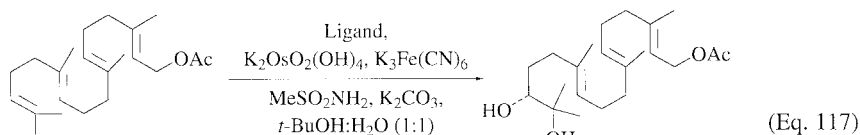


Ligand		Config.
DHQD-IND (60)	(66-90%), 72% ee	1 <i>R</i> ,2 <i>S</i>
DHQ-IND (61)	(66-90%), 59% ee	1 <i>S</i> ,2 <i>R</i>

Position-selective dihydroxylation of substrates possessing multiple unconjugated double bonds with similar substitution patterns is often problematic for the PHAL-linked cinchona alkaloid ligands. The modified cinchona alkaloid ligands **92** and **120** offer superior position-selective asymmetric dihydroxylation of terpene substrates such as farnesol and geranylgeraniol (Eq. 117).⁶² Position selectivities on



	R
92	CH(Pr- <i>n</i>) ₂
120	CH(Bu- <i>n</i>) ₂



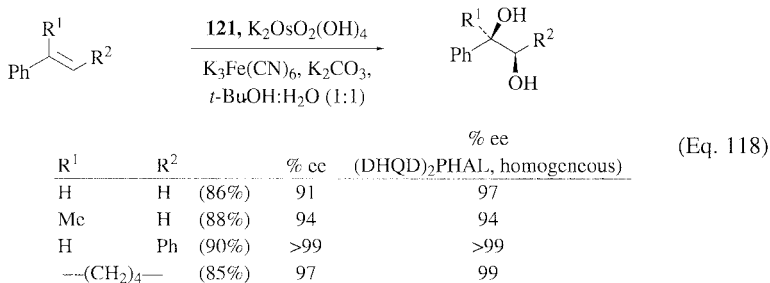
Ligand		Position Selectivity	% ee
(DHQD) ₂ PYDZ (18)	(10%)	1:1.1	—
92	(54%)	50:1	95

the order of 50:1 to 100:1 in favor of the oxidation of the terminal prenyl unit are observed using these ligands. The corresponding oxidations using (DHQD)₂PHAL (**7**) are not position-selective and afford mixtures of diols and polyols in the reaction of these substrates. Although these ligands are not commercially available, they are easily prepared and offer convenient access to functionalized terpenes that are intermediates for cation- π -cyclization reactions that afford polycyclic steroid precursors.

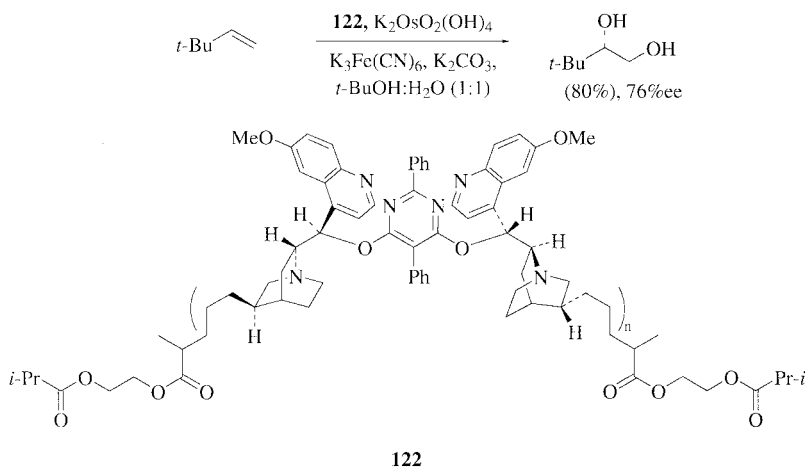
Solid-Supported Cinchona Alkaloid Catalysts

While the cinchona alkaloid-catalyzed asymmetric dihydroxylation is both very efficient and highly enantioselective for a wide variety of substrates, the recovery of the expensive chiral ligand from large-scale reactions can be difficult. Due to the high cost of both the cinchona alkaloid ligands and OsO₄, the development of facile methods for efficient catalyst recovery has been the focus of much research. The use of polymer-bound cinchona alkaloids as efficient and selective ligands for the enantioselective dihydroxylation represents a major advance. Polymer-bound catalysts for the asymmetric dihydroxylation can be divided into three classes: (1) insoluble polymer-bound ligands; (2) soluble polymer-bound ligands; and (3) silica-anchored ligands. Each of these classes has unique characteristics affecting reaction rate, enantioselectivity, and ease of recovery of the chiral ligand and/or osmium catalyst. The subject of solid-supported cinchona alkaloids and their use in catalytic asymmetric dihydroxylation reactions has been reviewed elsewhere, and only state of the art methods representing each of the classes of solid-supported ligands are presented herein.¹⁵⁸

The use of insoluble polymer-supported ligands for the catalytic enantioselective dihydroxylation reactions offers the advantage of facile ligand recovery and the potential for osmium recovery based on complexation with the polymer-supported ligand. The effectiveness of polymer-supported cinchona alkaloid ligands is dependent on the point of attachment of the cinchona alkaloid to the polymer support, the characteristics of the polymer support, and the extent of ligand incorporation. In general, the most effective polymer-bound cinchona alkaloid ligands are those in which the polymer support is attached to the pendant vinyl group of the parent cinchona alkaloid. This attachment leaves open the possibility of incorporating alkaloid ligands with different O(9) ether groups, allowing optimization of enantioselectivity and substrate specificity by modification of this critical site. The characteristics



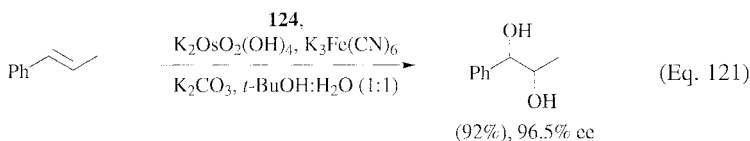
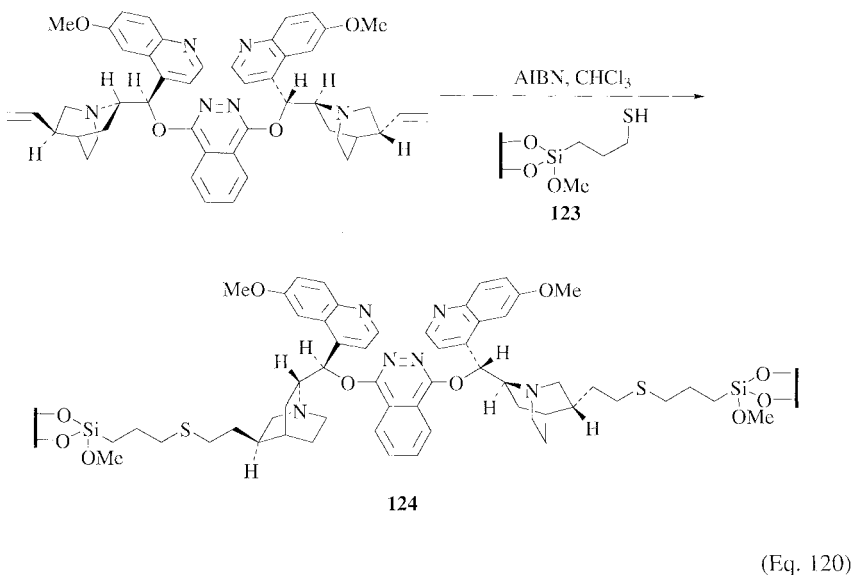
The immobilized PYR ligand **122** is also an efficient catalyst for the enantioselective dihydroxylation reaction of branched terminal alkenes (Eq. 119).¹⁶⁴ Unlike the other polymer-supported ligands described above, a slight deterioration of enantioselectivity is observed relative to the corresponding homogeneous reactions.



(Eq. 119)

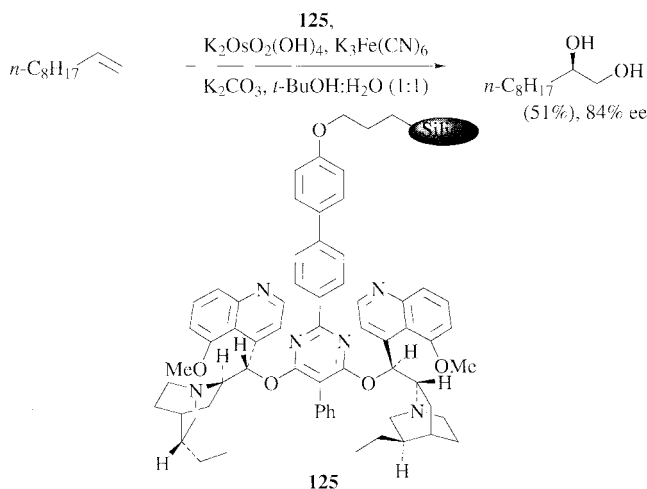
Silica gel supported bis(cinchona) alkaloid ligands are also effective for the catalytic enantioselective dihydroxylation reaction. Because the silica-supported ligands reside on the surface of the silica, substrates can access the catalytic sites easily, and reaction rates are comparable to those observed in the corresponding homogeneous reactions. These solid-supported ligands are easily prepared by the reaction of functionalized silica with the chiral monomer. Careful selection of comonomers and control of crosslinking is obviated by the use of silica as the solid support. Thus, treatment of silica gel with (3-mercaptopropyl)trimethoxysilane in 1:1 pyridine-toluene affords the functionalized silica support **123**, which, when treated with the chiral monomer 1,4-bis(9-*O*-quinyl)phthalazine and AIBN, affords

the immobilized ligand **124** with approximately 16 wt% incorporation of the alkaloid (Eq. 120).¹⁶⁵ This solid-supported alkaloid is an excellent ligand for the catalytic enantioselective dihydroxylation of aromatic alkenes under the standard conditions, as, for example, in Eq. 121.¹⁶⁵ The ligand can be recovered partially complexed with osmium by simple filtration and reused with a modest reduction in reaction rate, but no change in enantioselectivity.



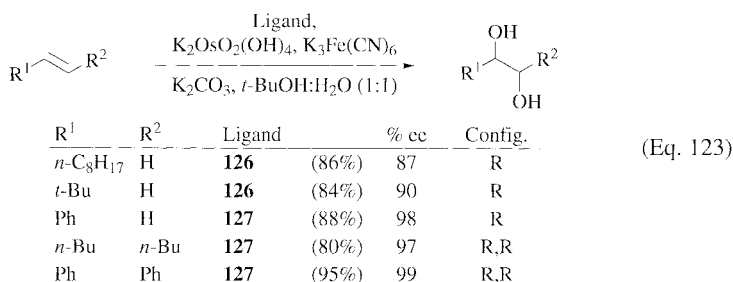
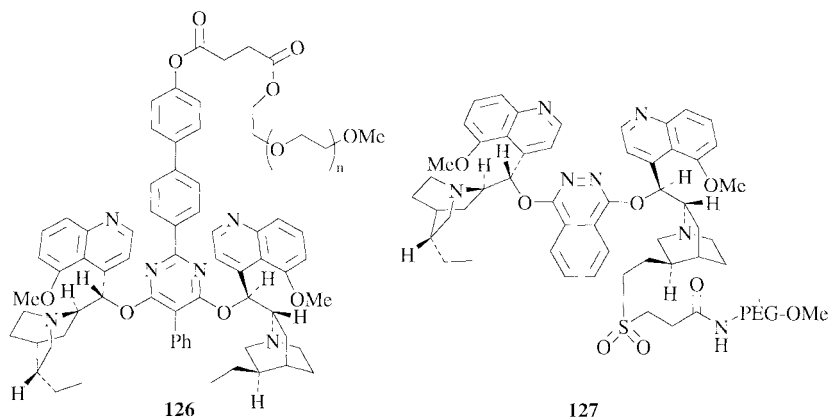
Attachment of the bis(cinchona) alkaloid ligand to the silica support by the heteroaromatic linker group has also been accomplished, and effective solid-supported catalysts based on the PHAL and PYR scaffolds have been successfully used for the catalytic enantioselective dihydroxylation of aryl- and alkylsubstituted alkenes.¹⁶⁶ Several functionalized silica supports can be used to immobilize the ligands, allowing either ester or ether functionality at the point of attachment, although attachment via an ether group is preferred owing to its improved stability under the basic reaction conditions used in the dihydroxylation. Recovery of the immobilized ligand results in a loss of the osmium catalyst due to the weak association constant

($K_{eq} = 15\text{--}30$) of the ligand- OsO_4 complex. Like the polymer-bound PYR-ligand **122**, the silica-supported PYR ligand **125** is an effective catalyst for the enantioselective dihydroxylation of aliphatic alkenes (Eq. 122),¹⁶⁶ but enantioselectivity is sometimes substantially lower than in the corresponding homogeneous reactions.



(Eq. 122)

Several soluble polymer-supported cinchona alkaloid ligands have been developed for the catalytic enantioselective dihydroxylation of alkenes that circumvent the prolonged reaction times and lower enantioselectivities associated with some of the insoluble polymer-supported ligands. Soluble polymer-supported cinchona alkaloid ligands are all based on a poly(ethylene glycol) monomethyl ether backbone, which is completely soluble in either the aqueous *tert*-butyl alcohol or acetone solvent systems used for the vast majority of catalytic enantioselective dihydroxylation reactions. This solvent compatibility allows the use of either the NMO or ferricyanide counteroxidants in the reaction. The solubility of the polymer requires an additional precipitation step to allow recovery of the ligand by filtration. Typically, *tert*-butyl methyl ether or diethyl ether is added to the reaction mixture to precipitate the catalyst, which is then recovered by filtration. An important advantage of using soluble polymer-bound ligands is the ability to use them in conjunction with polymer-bound substrates, enabling high-throughput, automated synthesis with recovery of both the ligand and the diol products by separate filtration and precipitation steps.¹⁶⁷ The bis(cinchona)alkaloids **126** and **127**, which are attached to the soluble polymer backbone via either the quinuclidine sidechain or the heteroaryl linker group, are superior ligands for the enantioselective dihydroxylation and offer selectivities and reaction rates that are very similar to those of homogeneous reactions (Eq. 123).^{168,169}

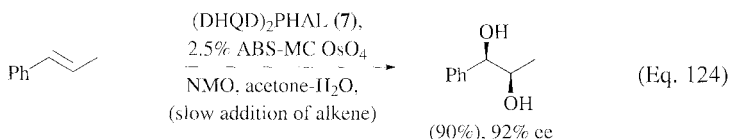


(Eq. 123)

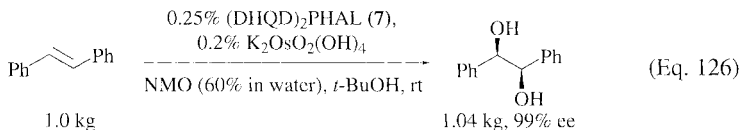
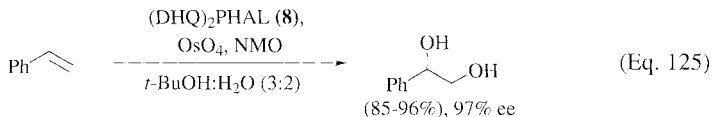
Osmium Sources. Osmium is the only known transition metal for the enantioselective dihydroxylation of alkenes. For many of the stoichiometric enantioselective dihydroxylations using chiral 1,2-diamine complexes of OsO₄, OsO₄ is used directly as the osmium source. Osmium tetroxide is a light yellow, volatile, crystalline solid. It is typically stored in sealed ampoules at 0° to prevent loss to sublimation. It is available as both the free solid as well as a solution either in toluene, *tert*-butyl alcohol, or water. Because solid OsO₄ typically arrives as a single large crystal that must be broken up prior to use, many prefer to use solutions of OsO₄ to minimize exposure during measurement and addition of the reagent. Osmium tetroxide is both expensive (\$110.00 per gram) and toxic. Since many of the enantioselective dihydroxylations using OsO₄-1,2-diamine complexes are carried out under anhydrous conditions, either solid OsO₄ or OsO₄ in toluene is typically used. Osmium tetroxide is also the preferred osmium source for catalytic reactions where NMO is used as the secondary oxidant. Catalytic asymmetric dihydroxylation using potassium ferricyanide as the secondary oxidant allows the use of potassium osmate (VI) dihydrate as the osmium source. This easily handled, free flowing, purple crystalline solid is non-volatile and easily measured, thereby minimizing risk of exposure.

While procedures exist for the recovery and reuse of OsO₄, they can be somewhat cumbersome and result in poor recovery due to the volatility of the reagent. The

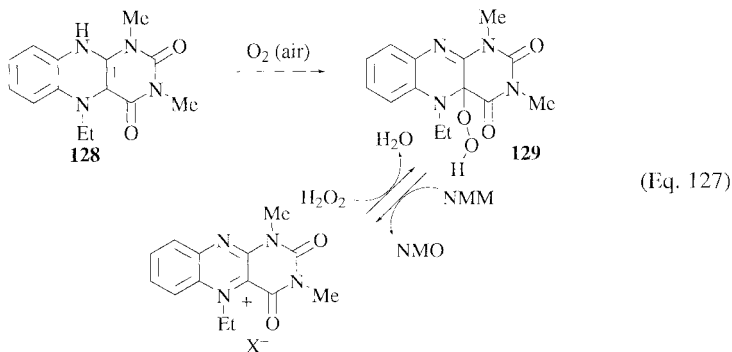
development of polymer-supported osmium catalysts is one approach to allowing convenient recovery and reuse of osmium. Microencapsulation of OsO_4 onto an acrylonitrile-butadiene-polystyrene (ABS) copolymer has been successfully used in both achiral and enantioselective catalytic dihydroxylations.¹⁷⁰ The stability of some of the microencapsulated osmium sources is somewhat dependent on the nature of the substrate. For example, polystyrene microencapsulated OsO_4 (PS-MC OsO_4) dissolves in the presence of styrene. The ABS-MC OsO_4 is stable in the presence of a variety of substrates and is the preferred polymer-supported osmium source for enantioselective dihydroxylation (Eq. 124).¹⁷⁰ This microencapsulated polymer-supported osmium source works well for both the NMO and potassium ferricyanide supported dihydroxylations. Recovery of the osmium source is conveniently accomplished by simple filtration, and no deterioration in either rate or enantioselectivity is noted even after five recyclings.



Secondary Oxidants. Several secondary oxidant systems have been developed for the cinchona alkaloid catalyzed asymmetric dihydroxylation reaction. The first catalytic process that was developed utilized NMO as the stoichiometric oxidant. High conversion and enantioselectivity can be obtained using this oxygen source provided that experimental conditions are carefully selected. Two catalytic cycles exist that result in the conversion of the alkene substrate to the diol product with differing rates and enantioselectivities. The primary catalytic cycle results in highly selective and rapid dihydroxylation, whereas a secondary cycle resulting from alkene oxidation by the Os(VIII) ester intermediate results in a deterioration of the overall reaction rate and enantioselectivity. As discussed previously, the secondary cycle can be circumvented by minimizing both the concentration of alkene and Os(VIII) ester intermediate. Optimum conditions typically utilize a stoichiometric amount of tetraalkylammonium acetate to accelerate hydrolysis of the Os(VIII) ester. In many instances, slow addition of the substrate alkene is also necessary to circumvent the secondary cycle. The use of NMO as the secondary oxidant has significant process advantages for large-scale reactions: (1) high concentrations can be used; (2) there are no large amounts of salts required in the reaction and needing handling in the subsequent workup; and (3) the *N*-methyl morpholine (NMM) byproduct from the reaction is easily removed and can be recycled. Under careful control of substrate addition rate, the reaction can produce diols with very high enantiomeric purity when run in aqueous *tert*-butyl alcohol (Eq. 125).¹⁷¹ A solid to solid process for the highly enantioselective oxidation of stilbene to hydrobenzoin has recently been developed using this oxidant system (Eq. 126).¹⁷²

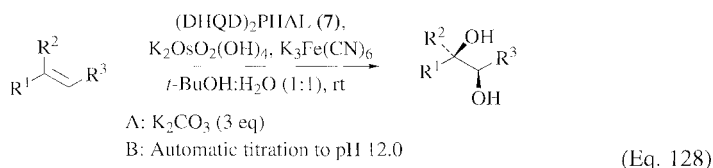


Catalytic amounts of NMO may be used for the asymmetric dihydroxylation in a new coupled catalytic system that utilizes hydrogen peroxide as the terminal oxidant.^{173,174} Oxygen or hydrogen peroxide are attractive terminal oxidants for industrial applications, as they are both inexpensive and environmentally friendly. A flavin catalyst is necessary for the reoxidation of NMM to NMO. The proposed catalytic cycle detailing the transfer of oxygen from H_2O_2 to the flavin catalyst and subsequently to NMM to regenerate NMO is shown in Eq. 127.¹⁷⁴ Initial oxidation of the flavin catalyst **128** by air produces the flavin peroxide **129**, which rapidly recycles NMM to NMO. The system leads to a mild, kinetically-controlled electron transfer from the substrate alkene to hydrogen peroxide at ambient temperature. This oxidant system can be applied to the enantioselective dihydroxylation using cinchona alkaloid ligands. The reaction of both styrene and (*E*)-stilbene was reported using $(\text{DHQD})_2\text{PHAL (7)}$ as the chiral ligand, affording the diol products in 84–87% yield and 88% ee.¹⁷⁴ Slow addition of the alkene substrate is still required with this system in order to achieve optimum reaction rate and enantioselectivity.



Potassium ferricyanide has been successfully used as the stoichiometric oxidant for a wide variety of alkene substrates and is the secondary oxidant of choice for small-scale reactions. Because the second cycle is precluded by obligatory hydrolysis of the Os(VI) ester intermediate prior to oxidation to Os(VIII), there is no need for slow addition of the substrate alkene during the course of the reaction. Enantioselectivities are generally higher with the use of this counteroxidant as compared to

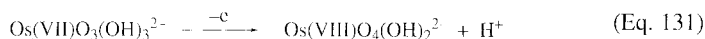
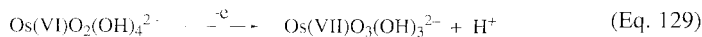
NMO. The reaction medium must be kept basic in order for catalytic turnover to be achieved, and this can result in undesirable side reactions with base-sensitive substrates. Potassium carbonate is typically used to maintain a buffered alkaline medium during the course of the reaction. With sensitive substrates, the pH can be slightly lowered with the use of a mixed bicarbonate-carbonate buffer. No turnover is observed when bicarbonate is used as the sole buffer. In general, there is no need to add a catalyst to accelerate the hydrolysis of the Os(VI) ester intermediate when the substrate has one unsubstituted alkene carbon atom. However, when both carbon atoms of the substrate double bond bear a substituent, it is typically necessary to add a stoichiometric equivalent of methanesulfonamide to accelerate the hydrolysis step. In cases where the hydrolysis step is exceptionally slow (e.g. with tetrasubstituted alkenes with all-carbon substituents), it is necessary to add three equivalents of methanesulfonamide to achieve reasonable substrate conversion. Presumably methanesulfonamide functions as a nucleophilic catalyst under the basic conditions of the reaction. Alternatively, the rate of hydrolysis may be accelerated for these substrates by careful control of the pH. Thus, under conventional conditions (3 equivalents of $\text{K}_3\text{Fe}(\text{CN})_6$, 3 equivalents of K_2CO_3), the pH of the reaction mixture slowly decreases from 12.2 at the start of the reaction to a final value of 9.9. However, with the use of an automatic titration apparatus to maintain a pH of 12.0, the overall reaction rate can be dramatically increased without the need for methanesulfonamide. Thus, for the catalytic enantioselective dihydroxylation of α -methylstilbene, complete conversion of the alkene is observed after only 1.5 hours of reaction at pH 12.0, whereas 21 hours are required under the conventional reaction conditions. There is a slight reduction in enantioselectivity at the higher pH, and this lower selectivity presumably results from competition of hydroxide ion with the chiral ligand for binding to OsO_4 . These results are summarized in Eq. 128.⁷¹ This decrease in enantioselectivity can be overcome by increasing the loading of chiral ligand from 1 mol% to 4 mol%. Over-oxidation of diols derived from substituted styrenes and stilbenes to benzoin is sometimes problematic under these more basic reaction conditions.⁷¹



R ¹	R ²	R ³		Time		% ee
<i>n</i> -Bu	H	<i>n</i> -Bu	A	3 h	(95%)	93
<i>n</i> -Bu	H	<i>n</i> -Bu	B	1.8 h	(95%)	90
Ph	Me	Ph	A	21 h	(82%)	99
Ph	Me	Ph	B	1.5 h	(62%)	99

While the use of potassium ferricyanide as the counteroxidant has advantages of convenience, disposal issues associated with large quantities of iron salts and cyanide have prompted several investigations into the use of coupled oxygen sources. In these systems, a catalytic amount of potassium ferricyanide is used as

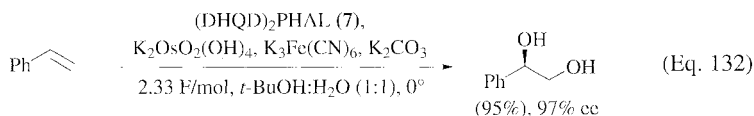
the secondary oxidant, and the oxidative regeneration of Fe(III) is mediated either electrochemically or by a tertiary oxidant. The direct electrochemical oxidation of Os(VI) to Os(VIII) occurs in two stages with potentials of $E_{\text{pa}}(\text{O}_1) = -0.115\text{V}$ (Eq. 129) and $E_{\text{pa}}(\text{O}_2) = +0.225\text{V}$ (Eq. 130), respectively.¹⁷⁵ The first oxidation produces a species that is adsorbed at the electrode surface, and therefore the rate of the second electron transfer is not diffusion-controlled. The species resulting from the first electron transfer is also reduced at $E_{\text{pc}}(\text{R}_1) = -0.225\text{V}$ (Eq. 131).¹⁷⁵



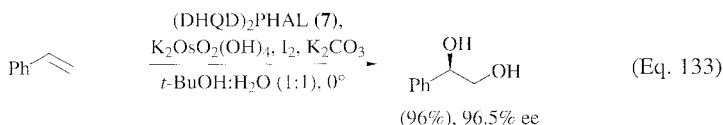
It is not necessary to use a divided cell when the electrochemical oxidation is conducted in the presence of a mediator, such as $\text{K}_3\text{Fe}(\text{CN})_6$, as the direct electrochemical oxidation of $\text{K}_2\text{OsO}_2(\text{OH})_4$, which results in electrodeposition of Os, is slow relative to its oxidation by the mediator.¹⁷⁵ A detailed investigation of the electrochemical dihydroxylation of stilbene revealed that an anodic potential of 400 mV or larger is necessary to regenerate either ferricyanide or perosmate ion.¹⁷⁶ Direct electrochemical oxidation of hydrobenzoin to benzaldehyde can occur at these potentials, but does not significantly contribute to the observed current inefficiency. The perosmate-catalyzed oxidation of hydrobenzoin to benzil is a more significant side reaction. Preparative oxidation of stilbene was reported using 1.6 mol% OsO_4 and 40 mol% $\text{K}_3\text{Fe}(\text{CN})_6$ with the DHQD-*p*-chlorobenzoate (**4**) ligand in aqueous *tert*-butyl alcohol-water. A broad maximum in yield is noted when 85–90% of the theoretical charge is passed, corresponding to 80–95% alkene conversion and 17 turnovers of ferricyanide ion. The yield of hydrobenzoin decreases beyond this point, presumably as a result of competitive perosmate-catalyzed oxidation of hydrobenzoin. Under optimum conditions, hydrobenzoin is produced in 94% yield with 90–95% ee using this system.

The enantioselectivity and scope of the electrochemical osmium-catalyzed enantioselective dihydroxylation is dramatically enhanced by the use of the PHAL-class ligands.¹⁷⁷ The reaction is conducted in an undivided cell using platinum electrodes, and the diol product may be obtained in high yield and enantiomeric purity using as little as 10 mol% of potassium ferricyanide. Preparative runs are conducted at a constant current of 2 mA/cm² (applied voltage 1–3 V) until 2.33 F/mol (1.17 equivalents) of electricity are passed. Yields and enantioselectivities for the dihydroxylation of several alkenes of the terminal, E-1,2-disubstituted and trisubstituted alkene classes are comparable to those obtained under the conventional reaction conditions with potassium ferricyanide as the counteroxidant. Thus, the electrochemical oxi-

ation of styrene affords the corresponding glycol in 95% yield and 97% ee (Eq. 132).¹⁷⁷



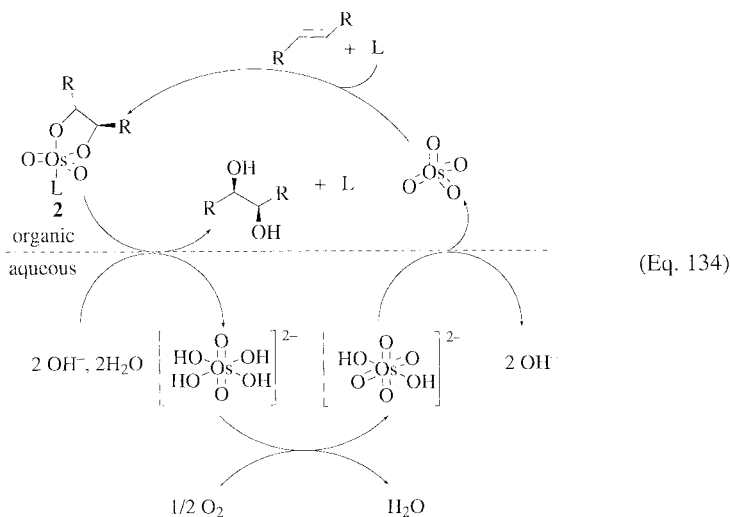
Iodine has been successfully used in both chemical and electrochemical dihydroxylations of alkenes using cinchona alkaloid catalysts and potassium osmate.¹⁷⁵ The reaction must be conducted under suitably basic conditions using either potassium carbonate or potassium phosphate as the buffer salt, since hydrolysis of the osmate ester precedes oxidation of Os(VI) to Os(VIII) and requires an alkaline pH (>11.0). Optimum conversion for the chemical oxidation using iodine is observed when 1.5 equivalents of the counteroxidant are used, and yields and enantioselectivities for the dihydroxylation of substrates belonging to a variety of alkene classes are generally very high (Eq. 133).^{176,177} The yield for the oxidation of several α,β -unsaturated esters under these conditions is somewhat lower than that observed for reactions using $\text{K}_3\text{Fe(CN)}_6$ and can be optimized by using a more weakly basic mixed buffer system (K_2CO_3 - KHCO_3).



Electrochemical regeneration of I_2 from I^- is also possible, and as little as 0.5 equivalents of I_2 based on substrate can be used.¹⁷⁵ The use of iodide rather than iodine as the initial mediator results in lower conversions and isolated yields. This is because the lower redox potential of the Os(VI)-Os(VIII) couple relative to the I^- - I_2 couple precludes oxidation of I^- to I_2 in the presence of Os(VI). As indicated earlier, this direct electrochemical oxidation of Os(VI) to Os(VIII) can result in electrodeposition of the osmium catalyst, resulting in lower turnover; however, when iodine is used as the initial mediator, it rapidly oxidizes Os(VI) to Os(VIII), resulting in a low concentration of Os(VI) in the diffusion layer that is replenished with I^- ions that can be oxidized at the electrode. Thus, under optimum electrolysis conditions, $\text{K}_2\text{Os(VI)O}_2(\text{OH})_4$ undergoes a two-electron oxidation mediated by the electrochemically produced active iodine oxidizing species. The resultant $\text{K}_2\text{Os(VIII)O}_6(\text{OH})_2$ is in equilibrium with OsO_4 , which is transferred to the organic phase and oxidizes the substrate.

The most attractive reagents for the reoxidation of Os(VI) species are air or oxygen, since they are the least expensive and most environmentally friendly oxidants. Oxygen can be used as a secondary oxidant for the catalytic enantioselective dihydroxylation without the use of an intermediate oxygen transfer reagent. Alkene substrates in five of the six alkene classes have been successfully oxidized without

the use of methanesulfonamide or other additives to accelerate the hydrolysis of the intermediate osmium ester species. Substrates possessing hydrogen atoms alpha to an aromatic substituent are prone to osmium-catalyzed over-oxidation of the diol product, giving benzaldehyde, benzoic acid, and other oxygenated products.¹⁷⁸ There is a strong dependence of reaction rate, chemoselectivity, and enantioselectivity on the pH of the aqueous phase. Under optimum conditions, the reaction is conducted with a 3:1 ratio of ligand to potassium osmate, and the pH is maintained between 10.4 and 11.2. More alkaline conditions result in sharply lower enantioselectivity, presumably due to competition of hydroxide with the cinchona alkaloid for coordination to osmium. *The reaction rate can be enhanced by increasing the oxygen pressure, but reactions run under a pure oxygen atmosphere should never be conducted under >10 bar of pressure due to the risk of explosion.* For each of the substrate classes that were evaluated, the enantioselectivity of the reaction is generally lower than that obtained using the conventional $\text{K}_3\text{Fe}(\text{CN})_6\text{-K}_2\text{CO}_3$ system. The observed substrate functional group compatibility, direction of enantioselectivity, optimum ligand, and substrate structure-enantioselectivity relationships are similar to those observed under conventional conditions. The proposed catalytic cycle is shown in Eq. 134 and is similar to that of the potassium ferricyanide based oxidant system.¹⁷⁸



Solvents and Concentration

Catalytic oxidations of alkenes with OsO_4 require an aqueous medium to effect hydrolysis of the intermediate osmate ester. Asymmetric dihydroxylations using potassium ferricyanide as the counteroxidant are typically triphasic at 0° (solid, aqueous, and organic phases), with the hydrolysis and reoxidation steps occurring in the aqueous phase, while the dihydroxylation step occurs in the organic phase. Oxidations using NMO as the counteroxidant are typically homogeneous due to the absence of salts. Dramatic effects of organic solvent on enantioselectivity have been

shown, and *tert*-butyl alcohol is by far the preferred solvent for highly enantioselective dihydroxylations. A survey of other solvents, such as toluene, methylene chloride, acetone, acetonitrile, and chloroform in the enantioselective dihydroxylation of simple substituted styrenes indicated that each of these solvents was inferior to *tert*-butyl alcohol with regard to the enantiomeric purity of the diol product.⁵⁸ Oxidations with NMO as the secondary oxidant are typically performed in mixtures of acetone and water, although the enantioselectivity of the reaction is dramatically improved when conducted in aqueous *tert*-butyl alcohol.¹⁷¹ The concentration of alkene in the enantioselective dihydroxylation using potassium ferricyanide as the counteroxidant is typically 0.1 M. For industrial scale applications, higher concentrations are desired, and reactions using NMO as the stoichiometric oxidant can be carried out at concentrations as high as 2.5 M.¹⁷²

Reaction Temperature and Catalyst Loading

The enantioselectivity of the catalytic enantioselective dihydroxylation can be sensitive to temperature, and reactions are typically conducted at 0 to 4°, except in cases where catalyst turnover is slow, in which case the reaction is conducted at room temperature (e.g. tetrasubstituted alkenes with all carbon substituents). The aqueous *tert*-butyl alcohol mixture typically used for the potassium ferricyanide secondary oxidant system freezes at temperatures lower than 0°.

Typical loadings for laboratory scale reactions are 1 mol% of ligand and 0.2 mol% of osmium. Interestingly, enantioselectivity is markedly insensitive to the relative amounts of ligand and osmium. Successful dihydroxylations have been conducted with as little as 0.01 mol % of ligand without a catastrophic reduction in enantioselectivity. Thus for the dihydroxylation of *trans*-stilbene using (DHQD)₂PHAL (7), use of 0.01 mol % of (DHQD)₂PHAL (7) affords the diol product with 96% ee as opposed to 99.8% ee under normal conditions.¹⁹ Alternatively, it is possible to increase the amount of osmium in cases where catalytic turnover is slow. For sluggish substrates, such as unactivated tetrasubstituted alkenes and α,β -unsaturated amides, the catalyst loading is typically increased to 5 mol% of ligand and 1 mol% of osmium. The enantioselective dihydroxylation of *cis*-1,2-disubstituted alkenes requires 2 mol% of the IND ligand and 0.2 mol% of osmium.

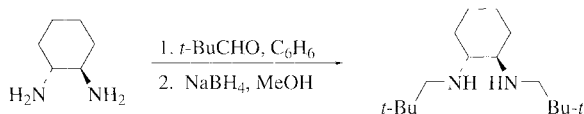
Premixed Reagents for Catalytic Enantioselective Dihydroxylation

Premixed reagents are available for the catalytic enantioselective dihydroxylation reaction and are sold as AD-mix α and AD-mix β corresponding to dihydroxylation of the α or β alkene faces according to the mnemonic for prediction of enantioselectivity (Figure 2). These commercially available mixtures are adjusted to provide 0.4 mol% of osmium and 1 mol% of ligand when used in the recommended ratio of 1.4 g of AD-mix for each millimole of alkene substrate.²⁰ For particularly sluggish reactions, additional ligand (ca. 5 mol%) and osmium (ca. 1 mol%) are used, and pre-mixed solid reagents at these ratios are sometimes referred to as Super AD-mix. These AD-mixes are pre-mixed PHAL-based ligand, potassium osmate, potassium ferricyanide, and potassium carbonate and are sold as AD-mix α , containing (DHQ)₂PHAL (8) or AD-mix β , containing (DHQD)₂PHAL (7). The recommended contents of 1 kg of AD-mix are as follows: K₃Fe(CN)₆: 699.6 g; K₂CO₃: 293.9 g;

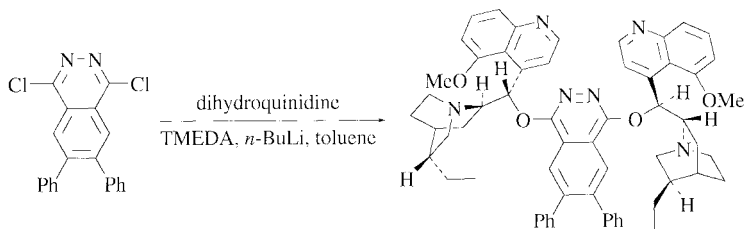
(DHQD)₂PHAL (**7**) or (DHQ)₂PHAL (**8**): 5.52 g; and K₂OsO₂(OH)₄: 1.04 g.²⁰ This mixture should be thoroughly mixed in a blender and can be stored indefinitely at ambient temperature in a dry environment. There are no pre-mixed reagents available at present containing other cinchona alkaloid ligands.

EXPERIMENTAL PROCEDURES

Procedures for the Synthesis of Ligands for Enantioselective Dihydroxylation

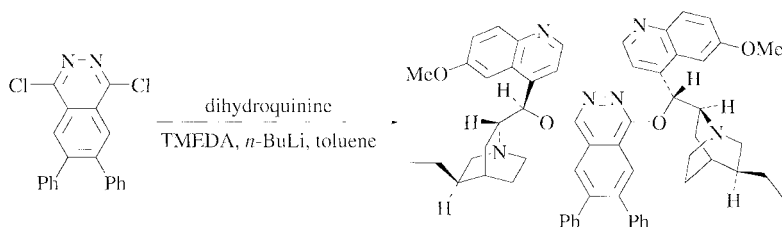


(1*R*,2*R*)-*N,N'*-Bis(3,3-dimethylpropyl)cyclohexane-1,2-diamine.⁹ To a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (1.45 g, 12.7 mmol) in benzene (50 mL) was added freshly distilled 3,3-dimethylbutyraldehyde (2.8 g, 28 mmol). The flask was fitted with a Dean-Stark apparatus, and the mixture was refluxed for 1 hour. The solution was then evaporated to dryness, and the residue was dissolved in methanol (50 mL). Sodium borohydride (1.92 g, 50.8 mmol) was added portionwise at 0°. The mixture was stirred overnight, the solution was acidified with 10% HCl to pH 2, concentrated, and extracted with CH₂Cl₂. The aqueous solution was basified to pH 12 with 10% NaOH and extracted three times with CH₂Cl₂. The organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was distilled using a Kugelrohr apparatus to obtain 2.66 g (75%) of (1*R*,2*R*)-*N,N'*-bis(3,3-dimethylpropyl)cyclohexane-1,2-diamine as a colorless solid: mp 67–68°; [α]_D²⁰ –91.7° (*c* 2.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 2.73 (td, *J* = 5.7 Hz, 10.5 Hz, 2H), 2.40 (td, *J* = 5.7 Hz, 10.5 Hz, 2H), 2.12–2.03 (m, 4H), 1.75–1.65 (m, 2H), 1.45–1.17 (m, 8H), 1.05–0.90 (m, 2H), 0.89 (s, 18H).



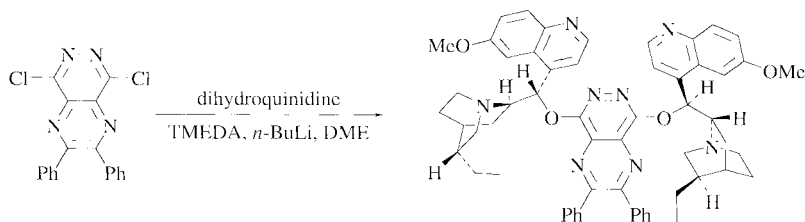
1,4-Bis(9-*O*-dihydroquinidyl)-6,7-diphenylphthalazine [(DHQD)₂DP-PHAL (119**)].**¹⁵⁷ In an oven-dried 50-mL round-bottom flask, a 2.5 M solution of *n*-BuLi in hexanes (1.1 mL, 2.75 mmol) was added dropwise under N₂ to a suspension of dihydroquinidine (0.815 g, 2.5 mmol) and TMEDA (0.58 g, 0.75 mL, 5.0 mmol) in toluene (25 mL) at 0°. After 40 minutes, 6,7-diphenyl-1,4-dichlorophthalazine¹⁵⁷ (0.35 g, 1.0 mmol) was added, and the mixture was heated to reflux. After 6 hours, the mixture was cooled to room temperature, water (15 mL) and ethyl acetate

(10 mL) were added, and the layers were separated. The organic phase was washed with water (10 mL), and the combined aqueous layers were extracted with ethyl acetate (10 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated to give a solid which was purified by flash chromatography ($\text{CH}_2\text{Cl}_2 + 5\% \text{CH}_3\text{OH} + 1\% \text{NH}_4\text{OH}$) to give the title compound (0.45 g, 48%) as a colorless solid: mp $154\text{--}157^\circ$; R_f 0.32 (CH_2Cl_2 , 5% CH_3OH , 1% NH_4OH); $[\alpha]_D^{23} -273.3^\circ$ (c 0.99, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.63 (d, $J = 4.5$ Hz, 2H), 8.34 (s, 2H), 7.98 (d, $J = 9.2$ Hz, 2H), 7.56 (d, $J = 2.6$ Hz, 2H), 7.41 (d, $J = 4.6$ Hz, 2H), 7.37–7.31 (m, 8H), 7.26–7.23 (m, 4H), 7.06 (d, $J = 5.3$ Hz, 2H), 3.86 (s, 6H), 3.40 (q, $J = 8.5$ Hz, 2H), 2.83–2.71 (m, 8H), 2.04 (br s, 2H), 1.71 (br s, 2H), 1.58–1.39 (m, 12H), 0.73 (t, $J = 7.0$ Hz, 6H).



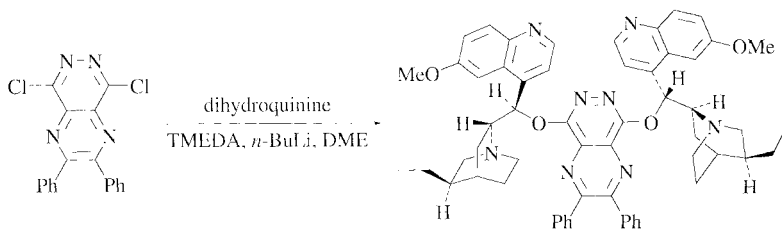
1,4-Bis(9-*O*-dihydroquinyl)-6,7-diphenylphthalazine [(DHQ)₂DP-PHAL].¹⁵⁷

Using dihydroquinine (0.815g, 2.5 mmol) and the identical procedure used to prepare 1,4-bis-(9-*O*-dihydroquinidyl)-6,7-diphenylphthalazine, a crude solid was produced which was purified by flash chromatography ($\text{CH}_2\text{Cl}_2 + 5\% \text{CH}_3\text{OH} + 1\% \text{NH}_4\text{OH}$) to give the title compound (0.64 g, 68%) as a white solid. This solid could be further purified by crystallization from methylene chloride:hexane (1:5): mp $231\text{--}234^\circ$; R_f 0.32 ($\text{CH}_2\text{Cl}_2 + 5\% \text{CH}_3\text{OH} + 1\% \text{NH}_4\text{OH}$); $[\alpha]_D^{23} +320.1^\circ$ (c 0.95, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.64 (d, $J = 4.5$ Hz, 2H), 8.29 (s, 2H), 7.99 (d, $J = 9.2$ Hz, 2H), 7.62 (d, $J = 2.5$ Hz, 2H), 7.45 (d, $J = 4.5$ Hz, 2H), 7.37–7.30 (m, 8H), 7.25–7.20 (m, 4H), 7.07 (d, $J = 5.9$ Hz, 2H), 3.87 (s, 6H), 3.49 (q, $J = 6.3$ Hz, 2H), 3.18 (m, 2H), 3.02 (dd, $J = 13.6, 9.7$ Hz, 2H), 2.59 (m, 2H), 2.33 (d, $J = 15.4$ Hz, 2H), 1.78 (br s, 6H), 1.44–1.22 (m, 10H), 0.81 (t, $J = 7.3$ Hz, 6H).



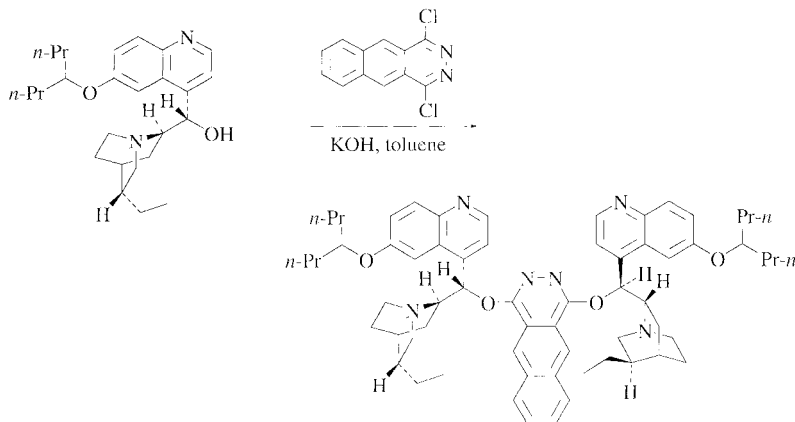
5,8-Bis(9-*O*-dihydroquinidyl)-2,3-diphenylpyrazino[2,3-*d*]pyridazine [(DHQD)₂DPP (35)].¹⁵⁷ A solution of dihydroquinidine (13.9 g, 42.7 mmol) and

N,N,N',N'-tetramethylethylenediamine (TMEDA) (17.1 mL, 95 mmol) in dimethoxyethane (300 mL, distilled from sodium) was cooled to -50° , and *n*-butyllithium (2.5M in hexanes, 17.1 mL, 42.7 mmol, 2.25 equiv) was added slowly. The mixture was stirred for 15 minutes, warmed to room temperature, and 5,8-dichloro-2,3-diphenylpyrazino[2,3-*d*]pyridazine (6.70 g, 18.95 mmol) was added. After heating at reflux for 4 hours, the mixture was cooled to room temperature, and H_2O (20 mL) was added together with ethyl acetate (500 mL). The organic phase was washed with saturated aqueous NaHCO_3 solution (100 mL). The aqueous layers were extracted with ethyl acetate (3×100 mL), and the combined organic phases were dried over MgSO_4 and concentrated in vacuo. The residue was purified by flash chromatography (5 cm \times 15 cm pad of silica, $\text{CHCl}_3 + 0.5\%$ MeOH + 0.5% NH_4OH) and was dried overnight in vacuo at 50° to afford 16.8 g (18.0 mmol, 95%) of the title product as a pale yellow solid: mp $173\text{--}177^{\circ}$; R_f 0.15 ($\text{CHCl}_3 + 5\%$ MeOH + 0.5% NH_4OH); $[\alpha]_D^{23} 345.6^{\circ}$ (c 1.022, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.64 (d, $J = 4.5$ Hz, 2H), 7.97 (d, $J = 9.2$ Hz, 2H), 7.63–7.58 (m, 6H), 7.50–7.44 (m, 4H), 7.42–7.38 (m, 4H), 7.31 (d, $J = 9.2, 2.6$ Hz, 2H), 7.00 (d, $J = 4.0$ Hz, 2H), 3.74 (s, 6H), 3.43 (m, 2H), 2.82–2.78 (m, 6H), 2.70–2.65 (m, 2H), 2.15 (t, $J = 10.6$ Hz, 2H), 1.71 (br s, 2H), 1.56–1.33 (m, 12H), 0.67 (t, $J = 7.2$ Hz, 6H).

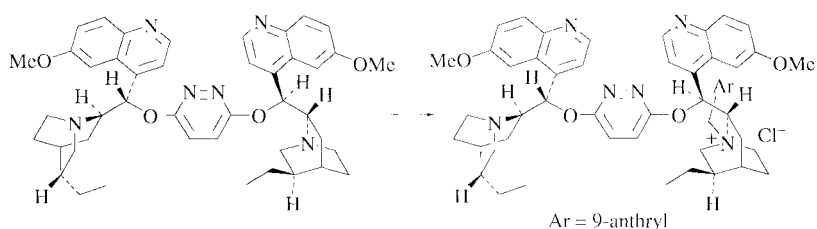


5,8-Bis(9-*O*-dihydroquinyl)-2,3-diphenylpyrazino[2,3-*d*]pyridazine [(DHQ)₂DPP].¹⁵⁷ The title compound was prepared analogously to (DHQD)₂DPP (35) (procedure above) using 5,8-dichloro-2,3-diphenylpyrazino[2,3-*d*]pyridazine (1.035 g, 2.93 mmol), dihydroquinine (2.39 g, 7.32 mmol, 2.5 equiv), *n*-butyllithium (2.5 M in hexanes, 2.93 mL, 7.32 mmol, 2.5 equiv) and TMEDA (2.21 mL, 14.7 mmol, 5 equiv) in dimethoxyethane (100 mL, distilled from sodium). After a reaction time of 3 hours, analogous workup, flash chromatography (2.5 cm \times 15 cm pad of silica, $\text{CHCl}_3 + 5\%$ MeOH + 0.5% NH_4OH), and drying overnight under high vacuum at 50° , 2.554 g (2.74 mmol, 95%) of the title compound was obtained as a pale yellow solid: R_f 0.16 ($\text{CHCl}_3 + 5\%$ MeOH + 0.5% NH_4OH); mp $175\text{--}180^{\circ}$; $[\alpha]_D^{23} +441.7^{\circ}$ (c 1.037, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.64 (d, $J = 4.5$ Hz, 2H), 7.97 (d, $J = 9.2$ Hz, 2H), 7.65 (br s, 2H), 7.61–7.58 (m, 4H), 7.51–7.45 (m, 4H), 7.43–7.38 (m, 4H), 7.29 (dd, $J = 9.2, 2.7$ Hz, 2H), 6.93 (d, $J = 5.5$ Hz, 2H), 3.73 (s, 6H), 3.56–3.52 (m, 2H), 3.29–3.19 (m, 2H), 3.04 (dd, $J = 13.5, 9.8$ Hz, 2H),

2.61-2.52 (m, 2H), 2.33-2.27 (m, 2H), 1.96-1.71 (m, 8H), 1.49-1.23 (m, 8H), 0.83 (t, $J = 7.3$ Hz, 6H).



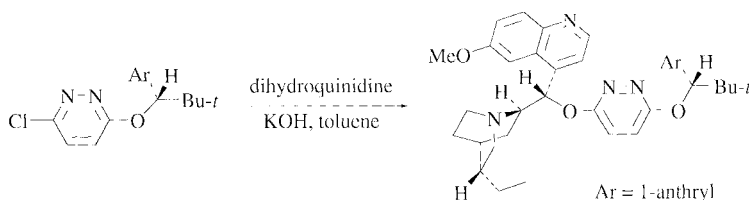
1,4-Bis[*O*-6'-(4-heptyl)hydrocupreidyl]naphthopyridazine (92).⁶² To a solution of *O*-6'-(4-heptyl)hydrocupreidine (1.7g, 4.2 mmol) in 140 mL of toluene was added 1,4-dichloronaphthopyridazine¹⁷⁹ (0.51 g, 2.1 mmol) and powdered KOH (1.7g, 30 mmol). The mixture was heated to reflux with azeotropic removal of water using a Dean-Stark trap. After 3 hours, the mixture was cooled to room temperature, diluted with 100 mL of H₂O, and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by radial chromatography (8 mm silica plate, 10 mL/minute, CHCl₃, followed by 97:3:0.3 CHCl₃+MeOH+NH₄OH) to afford 1.55 g (75%) of (92) a colorless syrup: R_f 0.37 (CHCl₃+MeOH+NH₄OH 9:1:0.1); $[\alpha]_D^{23} -275^\circ$ (c 0.51, CHCl₃).



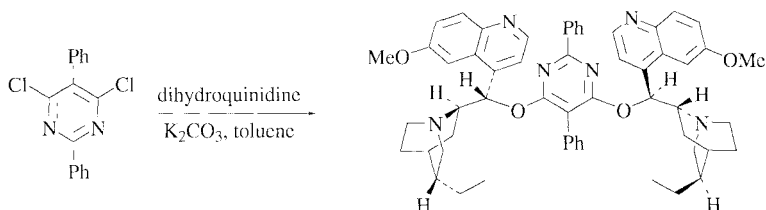
3,6-Bis(hydroquinidyl)pyridazine-mono-9-anthracenylmethyl Chloride.⁸²

To a solution of 3,6-bis(hydroquinidyl)pyridazine (1.6 g, 2.2 mmol) in 4.4 mL of acetonitrile was added 9-chloromethylanthracene (0.50 g, 2.2 mmol), and the resulting mixture was stirred for 12 hours at 40°. After concentration in vacuo, the

residue was purified by flash column chromatography ($\text{CHCl}_3 + \text{MeOH} + \text{NH}_4\text{OH}$, 90:10:1), followed by radial chromatography (4 mm plate, $\text{CHCl}_3 + \text{MeOH} + \text{NH}_4\text{OH}$, 98:2:0.2 to 90:10:1), giving 0.85 g (40%) of a light yellow solid; R_f 0.28 ($\text{CHCl}_3 + \text{MeOH} + \text{NH}_4\text{OH}$, 85:15:1.5); $[\alpha]_D^{23} +48^\circ$ (c 0.18, CHCl_3); ^1H NMR (400 MHz, CD_3OD) δ 8.73 (d, $J = 4.6$ Hz, 1H), 8.67 (s, 1H), 8.39 (d, $J = 9.0$ Hz, 1H), 8.34 (d, $J = 4.6$ Hz, 1H), 8.27 (s, 1H), 8.10 (m, 3H), 7.88-7.82 (m, 2H), 7.72-7.66 (m, 2H), 7.64 (d, $J = 9.3$ Hz, 1H), 7.61 (d, $J = 2.2$ Hz, 1H), 7.58-7.52 (m, 3H), 7.51 (d, $J = 4.6$ Hz, 1H), 7.44 (t, $J = 8.2$ Hz, 1H), 7.34 (d, $J = 1.9$ Hz, 1H), 7.17 (dd, $J = 2.5, 9.2$ Hz, 1H), 7.00 (t, $J = 7.4$ Hz, 1H), 6.91 (s, 1H), 5.96 (d, $J = 14.0$ Hz, 1H), 5.66 (d, $J = 14.0$ Hz, 1H), 4.53 (m, 1H), 4.09 (s, 3H), 4.05 (m, 1H), 3.75 (s, 3H), 3.59 (m, 1H), 3.18 (m, 1H), 2.92-2.67 (m, 6H), 2.28 (m, 1H), 1.94 (s, 1H), 1.79 (m, 2H), 1.67-1.53 (m, 11H), 1.37 (m, 1H), 0.94 (t, $J = 7.1$ Hz, 3H), 0.79 (t, $J = 7.3$ Hz, 3H).



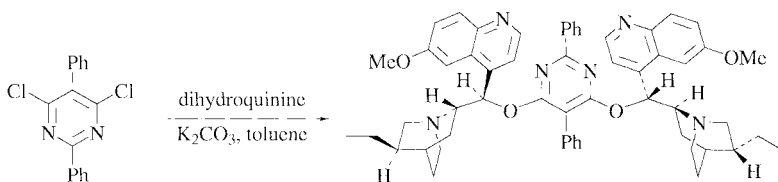
6-Dihydroquinidyl-3-[1(*S*)-anthracen-1-yl-2,2-dimethylpropoxy]pyridazine [DHQD-PYDZ-(*S*)-Anthryl Ligand].⁷³ To a suspension of dihydroquinidine (0.114 g, 0.350 mmol) in toluene (3 mL) was added KOH (0.070 g, 1.3 mmol, pulverized prior to use) and 3-[(*S*)-1-anthracen-1-yl-2,2-dimethylpropoxy]-6-chloropyridazine⁷³ (0.12 g, 0.32 mmol). The resulting mixture was heated at reflux (140° bath temperature) for 45 minutes (larger scale reactions require azeotropic removal of water using a Dean-Stark trap). After the mixture was cooled to room temperature, 15 mL of H_2O was added, and the mixture was extracted three times with ethyl acetate (30 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by flash chromatography ($\text{MeOH} + \text{CHCl}_3 + \text{NH}_4\text{OH}$, 3:97:0.3) to give 0.19 (88%) of a light yellow syrup: $[\alpha]_D^{23} +188.5^\circ$ (c 0.20, MeOH); ^1H NMR (CDCl_3 , 500 MHz) δ 8.85 (s, 1H), 8.53 (dd, $J = 1.5, 4.4$ Hz, 1H), 8.37 (s, 1H), 8.06 (d, $J = 5.7$ Hz, 1H), 7.95 (d, $J = 7.4$ Hz, 1H), 7.84 (m, 2H), 7.56 (d, $J = 4.9$ Hz, 1H), 7.45 (m, 2H), 7.36 (m, 2H), 7.27 (d, $J = 7.2$ Hz, 1H), 7.18 (d, $J = 8.5$ Hz, 1H), 7.08 (s, 1H), 7.00 (d, $J = 8.9$ Hz, 1H), 6.91 (d, $J = 9.4$ Hz, 1H), 6.88 (s, 1H), 3.50 (s, 3H), 3.35 (m, 1H), 2.81 (m, 2H), 2.63 (m, 2H), 1.90 (m, 1H), 1.71 (s, 1H), 1.47 (m, 6H), 1.08 (s, 9H), 0.89 (t, $J = 7.2$ Hz, 3H).



2,5-Diphenyl-bis(9-O-dihydroquinidyl)pyrimidine [(DHQD)₂PYR (25)].⁷⁷

Hydroquinidine hydrochloride (75 g) was added to concentrated aqueous NH_4OH (500 mL). The resulting suspension was extracted with CH_2Cl_2 (3×200 mL). The combined organic extracts were washed with aqueous NH_4OH (200 mL) and H_2O (200 mL), dried over MgSO_4 , filtered, and concentrated in vacuo, affording dihydroquinidine (54 g) as a colorless solid.

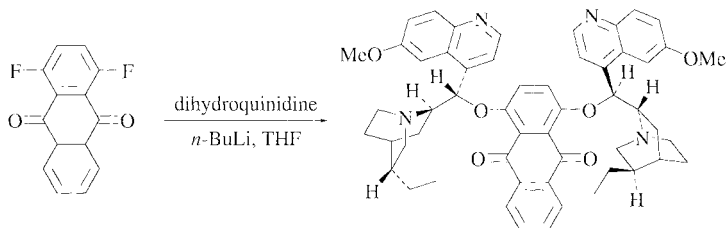
A 50-mL flame-dried one-neck round-bottom flask was charged with dihydroquinidine (2.58 g, 7.66 mmol), 2,5-diphenyl-4,6-dichloropyrimidine (1.15 g, 3.83 mmol)⁷⁷, K_2CO_3 (1.6 g, 11.5 mmol), and anhydrous toluene (30 mL). The flask was flushed with nitrogen and equipped with a Dean-Stark condenser. After the mixture was stirred at reflux (oil bath temperature 135°) for 2 hours, KOH pellets (729 mg, 13.0 mmol) were added, and the mixture was refluxed with azeotropic removal of water for an additional 12 hours. The light orange solution was cooled to room temperature, diluted with H_2O (100 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. The crude, pale yellow solid was crystallized from acetonitrile (100 mL), affording the title compound as fluffy white crystals (2.6 g, 77%): mp $253\text{--}254^\circ$; ^1H NMR (400 MHz, CDCl_3) δ 8.72 (d, $J = 4.4$ Hz, 2H), 8.01 (d, $J = 9.2$ Hz, 2H), 7.59–7.44 (m, 9H), 7.40–7.37 (m, 4H), 7.20 (t, $J = 7.3$ Hz, 1H), 7.03–6.97 (m, 4H), 3.82 (s, 6H), 3.13–3.11 (m, 2H), 2.81–2.55 (m, 8H), 1.81–1.75 (m, 2H), 1.59 (br s, 2H), 1.47–1.25 (m, 8H), 0.97 (m, 4H), 0.69 (t, $J = 7.2$ Hz, 6H).



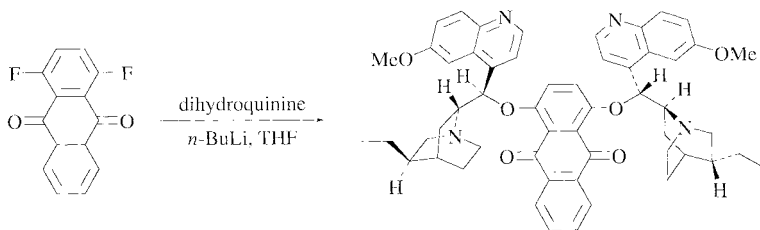
2,5-Diphenyl-4,6-bis(dihydroquinyl)pyrimidine [(DHQ)₂PYR (26)].⁷⁷

This ligand was prepared following the same procedure described in the section above. Starting from dihydroquinine (1.0 g), the title compound (0.98 g, 72%) was obtained as white crystals after crystallization from ethyl acetate (10 mL): ^1H NMR (400 MHz, CDCl_3) δ 8.69 (d, $J = 4.5$ Hz, 2H), 8.01 (d, $J = 9.2$ Hz, 2H), 7.59–7.55

(m, 4H), 7.50–7.46 (m, 5H), 7.39 (dd, $J = 2.6, 9.2$ Hz, 2H), 7.33 (d, $J = 4.5$ Hz, 2H), 7.18 (t, $J = 7.3$ Hz, 1H), 6.97 (t, $J = 7.6$ Hz, 2H), 6.90 (br s, 2H), 3.83 (s, 6H), 3.15–3.09 (m, 4H), 2.96 (dd, $J = 10.0, 13.4$ Hz, 2H), 2.56–2.49 (m, 2H), 2.29 (d, $J = 12.7$ Hz, 2H), 1.63–1.54 (m, 6H), 1.30 (br s, 2H), 1.24–1.15 (m, 8H), 0.75 (t, $J = 7.3$ Hz, 6H).

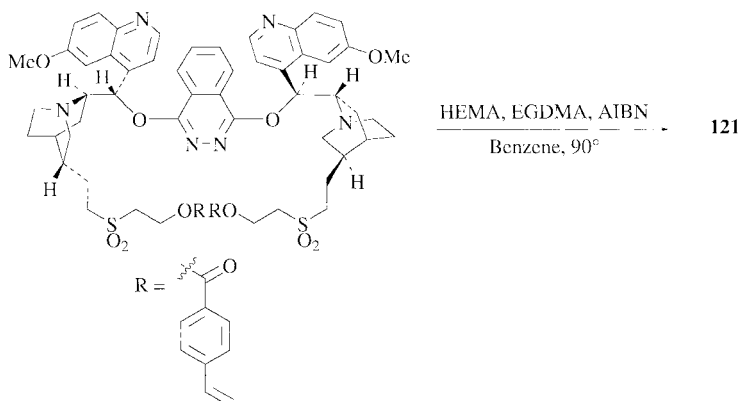


1,4-Bis(dihydroquinidyl)benzo[g]phthalazine-5,10-dione [(DHQD)₂AQN (30)].⁸⁶ A solution of dihydroquinidine (3.33 g, 10.3 mmol) in dry THF was cooled to -50° , and a solution of *n*-butyllithium in hexane (1.6 M, 6.4 mL, 10.25 mmol) was added slowly over 10 minutes. The pale red solution was stirred for 15 minutes, warmed to 0° , and difluoroanthraquinone⁸⁶ (1.00 g, 4.10 mmol) was added as a solid. The mixture was warmed to room temperature and was stirred for 15 hours. After warming to 40° , the mixture was stirred for another 2 hours. For reactions conducted on a larger scale, the solvent was removed in vacuo at this point. Ethyl acetate (200 mL) was added along with saturated aqueous NaHCO_3 solution (100 mL). The aqueous phase was extracted twice with 100 mL of ethyl acetate, and the combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (4×15 cm, $\text{CHCl}_3 + \text{MeOH} + \text{NH}_4\text{OH}$, 95:5:0.5) afforded (DHQD)₂AQN (30) as yellow solid (3.107 g, 3.625 mmol, 88%); mp $152\text{--}157^{\circ}$; $[\alpha]_{\text{D}}^{25} -487^{\circ}$ (c 1.1, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 8.65 (d, $J = 4.5$ Hz, 2H), 8.22 (dd, $J = 5.8, 3.3$ Hz, 2H), 8.02 (d, $J = 9.4$ Hz, 2H), 7.79 (dd, $J = 5.7, 3.3$ Hz, 2H), 7.49 (d, $J = 4.2$ Hz, 2H), 7.36 (dd, $J = 9.4, 2.2$ Hz, 4H), 6.65 (s, 2H), 5.87 (br s, 2H), 3.92 (s, 6H), 3.24 (br s, 2H), 2.81–2.41 (m, 8H), 2.41 (br s, 2H), 1.77–1.25 (m, 14H), 0.84 (t, $J = 7.3$, 6H).



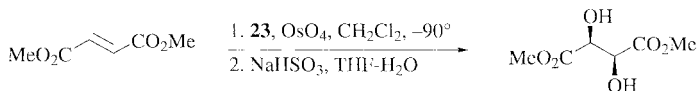
1,4-Bis(dihydroquinyl)benzo[g]phthalazine-5,10-dione [(DHQ)₂AQN (31)].⁸⁶ The synthesis is analogous to that of (DHQD)₂AQN (30) described above. Dihydroquinine (3.35 g, 10.25 mmol), *n*-butyllithium in hexane (1.6 M, 6.4 mL, 10.25 mmol), and difluoroanthraquinone (1.00 g, 4.10 mmol) afforded (DHQ)₂AQN (31) (2.967 g, 3.462 mmol, 84%) as a yellow solid: mp $177\text{--}180^{\circ}$; $[\alpha]_{\text{D}}^{25} +579^{\circ}$ (c 1.18, CHCl_3); ^1H

NMR (CDCl_3 , 400 MHz) δ 8.64 (d, $J = 4.5$ Hz, 2H), 8.28 (dd, $J = 5.7$, 3.3 Hz, 2H), 8.03 (d, $J = 9.2$ Hz, 2H), 7.79 (dd, $J = 5.7$, 3.3 Hz, 2H), 7.43 (d, $J = 4.5$ Hz, 2H), 7.37 (dd, $J = 9.2$, 2.5 Hz, 2H), 7.32 (br s, 2H), 6.61 (br s, 2H), 5.95 (br s, 2H), 3.92 (s, 6H), 3.23 (br s, 4H), 3.05 (dd, $J = 13.4$, 10.0 Hz, 2H), 2.35–2.61 (m, 6H), 2.05 (br s, 2H), 1.92 (br s, 2H), 1.59 (br s, 2H), 1.14–1.44 (m, 8H), 0.80 (t, $J = 7.3$ Hz, 6H).



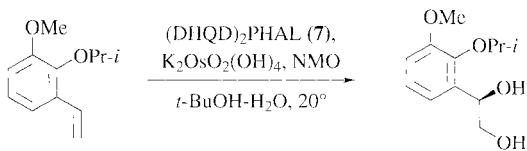
(DHQD)₂PHAL—EGDMA—HEMA Block Copolymer Ligand (121).¹⁶² A solution of 1,4-bis-[12-(4-vinylbenzoyloxyethanesulfonyl)-9-*O*-dihydroquinidyl]-phthalazine (0.32 g, 0.25 mmol), hydroxyethyl methacrylate (HEMA, 0.22 mL, 1.7 mmol), and ethylene glycol dimethacrylate (EGDMA, 0.1 mL, 0.5 mmol) in benzene (10 mL) was added to benzene (90 mL) at 80°. The polymerization was initiated by the addition of AIBN (0.063 g, 0.038 mmol) and the mixture was stirred for 24 hours. The precipitated polymer was filtered, extracted with methanol and acetone using a Soxhlet extractor, and concentrated in vacuo, affording a 76% yield of the title compound. Nitrogen analysis indicated a 9.51 mol% loading of chiral alkaloid.

Procedures for the Enantioselective Dihydroxylation of Alkenes

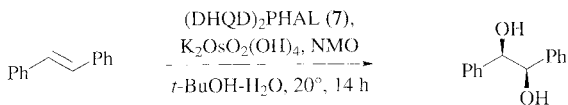


***S,S*-Diethyl Tartrate [Stoichiometric Enantioselective Dihydroxylation Using a Chiral 1,2-Diamine Ligand].**⁹ To a solution of (1*R*,2*R*)-*N,N'*-bis(3,3-dimethylbutyl)cyclohexane-1,2-diamine (117 mg, 0.416 mmol) in CH_2Cl_2 (4 mL) at -90° was added OsO_4 (4.1 mL of a 25 mg/mL CH_2Cl_2 solution, 0.403 mmol). After the resulting mixture was stirred for 30 minutes at -90° , dimethyl fumarate (50 mg, 0.347 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 30 minutes. The resulting mixture was stirred at -90° for 5 hours. Sodium bisulfite (1.15 g) was then added, and the mixture was concentrated in vacuo. The residue was dissolved in THF

(8 mL) and H₂O (0.5 mL), and the solution was refluxed for 2 hours. Evaporation of the solvents afforded a black residue that was dissolved in CH₂Cl₂ (20 mL), and the solution was dried with Na₂SO₄. Flash column chromatography (ethyl acetate:hexanes, 55:45) gave (*S,S*) diethyl tartrate (41 mg, 67%); [α]_D²³ = -16.4° (*c* 1.28, H₂O) of 96% ee based on both the ¹H NMR and ¹⁹F NMR of its Mosher's ester derivative.

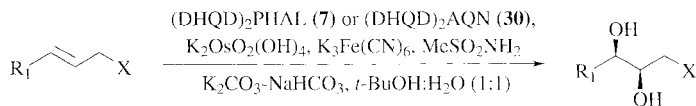


2-(2'-Isopropoxy-3'-methoxyphenyl)-2-hydroxyethanol [Catalytic Asymmetric Dihydroxylation Using NMO as the Secondary Oxidant].¹⁷¹ To a 50-L three-neck flask was added K₂OsO₂(OH)₄ (34.5 g, 0.09 mol), (DHQD)₂PHAL (7) (81.6 g, 0.10 mol), NMO (60 wt% in H₂O, 3.0 L, 17.4 mol), *tert*-butyl alcohol (14 L), and H₂O (10 L). The flask was fitted with a mechanical stirrer, and the reaction mixture was stirred until the solution cleared. 2-Isopropoxy-3-methoxystyrene (2.5 kg, 2.2 L, 13.0 mol) was then added at a rate of 5.6 mL/minute using a peristaltic pump, such that the tip of the tubing was immersed in the solution. The temperature of the solution was kept at 20 ± 5° by an external temperature control. Samples were taken at 1-hour intervals and checked to make sure that the alkene content did not exceed 3% and the enantiomeric purity did not fall below 92% by GC and HPLC (chiral column), respectively. At this rate of addition, the alkene content never exceeded 0.7%, and the enantiomeric purity was never below 95%. After addition of the alkene, the resulting orange solution was stirred until the alkene content was less than 0.5%, after which time were added toluene (12 L) and a solution of Na₂SO₃ (1.9 kg) in H₂O (4.7 L). After stirring overnight, the phases were separated and the organic phase was washed with an aqueous solution of Na₂SO₄ (0.8 kg in 5 L of H₂O). The chiral ligand was extracted from the organic phase using H₂SO₄ (0.38 L) in aqueous Na₂SO₄ (1.6 kg in 10 L of H₂O), and the resulting acidic solution was made basic with NaOH and then extracted with toluene (0.70 L). The ligand (61 g) was recovered pure (98% according to HPLC) as a white powder after drying of the solution and evaporation of the solvent. The organic phase remaining after acid extraction was dried with K₂CO₃ (1.0 kg), and the solvent was evaporated under vacuum at 60° to yield 2.5 kg of a light brown oil (94% pure according to GC and an enantiomeric purity of 95%), which crystallized upon standing. ¹H NMR (500 MHz, CDCl₃) δ 7.05-6.80 (m, 3H), 5.15 (m, 1H), 4.65 (m, 1H), 3.85 (s, 3H), 3.75 (m, 1H), 3.65 (m, 1H), 3.10 (br s, 1H), 2.50 (br s, 1H), 1.30 (dd, 6H).

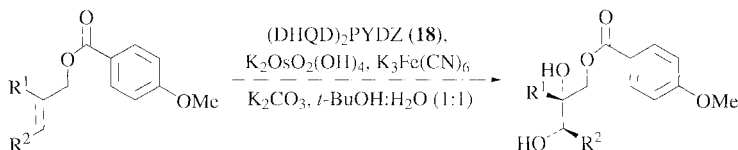


(*R,R*)-(+)-1,2-Diphenyl-1,2-ethanediol [Solid to Solid Asymmetric Dihydroxylation with NMO].¹⁷² A 5-L round-bottomed flask, equipped with a large magnetic stir bar, was charged with (DHQD)₂PHAL (7) (10.89 g, 0.25 mol%),

trans-stilbene (1 kg, 5.6 mol), NMO (1.4 L of 60% aqueous, NMO, Aldrich), and *tert*-butyl alcohol (2.24 L). The flask was placed in a water bath (initially at about 20°, and no further efforts were made to control the temperature). Potassium osmate(VI) dihydrate (4.12 g, 0.2 mol%) was added under stirring. (*Caution: substitution of OsO₄ results in a substantial exotherm which reduces the yield and enantiomeric purity of the product.*) The reaction mixture was then stirred until all the stilbene was consumed as monitored by TLC (about 14 hours). The reaction was quenched by the addition of 4,5-dihydroxy-1,3-benzenedisulfonic acid disodium salt monohydrate (Tiron, Aldrich, 10 g) followed by stirring at room temperature for 3 hours. The resulting mixture was poured into H₂O (3 L) and stirred for another 3 hours. The crude product was collected by filtration, washed with H₂O until colorless, and dried under vacuum, yielding (*R,R*)-1,2-diphenyl-1,2-ethanediol as a colorless powder (910 g, 76%, 99% ee). To recover the ligand, the largely aqueous filtrate was stirred with ethyl acetate (2 L) for 1 hour. The resulting organic phase was separated and then extracted with 0.5 M H₂SO₄ (2 × 250 mL). To these combined acidic extracts was added CH₂Cl₂ (500 mL), and this mixture was stirred while sodium carbonate was added until the pH of the aqueous phase was *ca.* 10 or 11. The organic phase was washed with H₂O, dried over MgSO₄, and concentrated to give (DHQD)₂PHAL (**7**) (10 g, 95% recovery). An additional 130 g of (*R,R*)-1,2-diphenyl-1,2-ethanediol was obtained from the ethyl acetate phase after evaporation of the solvent (11% yield, 99% ee), for an overall yield of 87% (1.04 kg). The enantiomeric excess was determined by HPLC analysis of the bis(MTPA) ester of the diol using a Chiralcel® OD column: mp 148–150°; [α]_D²⁵ +95° (*c* 0.87, EtOH); ¹H NMR (400 MHz, CDCl₃) δ 7.22 (m, 6H), 7.11 (m, 4H), 4.67 (s, 2H), 3.00 (br s, 2H).

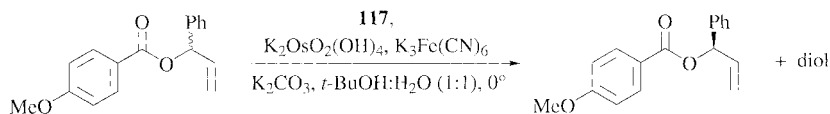


Buffered Asymmetric Dihydroxylation Protocol.¹⁵⁴ To a well-stirred solution of (DHQD)₂PHAL (**7**) (8 mg, 1 mol%), K₂OsO₂(OH)₄ (1.8 mg, 0.5 mol%), K₃Fe(CN)₆ (988 mg, 3 mmol), K₂CO₃ (415 mg, 3 mmol), NaHCO₃ (252 mg, 3 mmol), and CH₃SO₂NH₂ (95 mg, 1 mmol) in *tert*-butyl alcohol:water (1 : 1, 10 mL) at 0° was added the appropriate allylic halide (1 mmol). After the reaction was finished (TLC), 1.0 g of Na₂S₂O₄ was added and stirring was continued for 30 minutes. The layers were separated, and the aqueous layer was extracted with ethyl acetate (30 mL). The combined organic layers were washed with 1 N KOH (5% aqueous), HCl, and brine, and then dried over MgSO₄ and concentrated. The crude halo diol was purified by flash chromatography on silica gel.



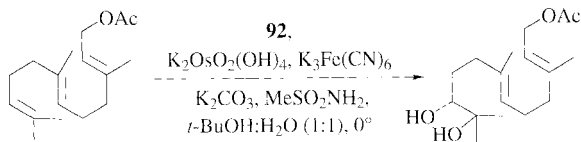
General Procedure for the Asymmetric Dihydroxylation of Allylic 4-Methoxybenzoates.⁶¹ A mixture of K₂CO₃ (3.00 equiv), K₃Fe(CN)₆ (3.00 equiv),

$\text{K}_2\text{OsO}_2(\text{OH})_4$ (0.005 equiv), and $(\text{DHQD})_2\text{PYDZ}$ (0.01 equiv) in *tert*-butyl alcohol:water (1:1) was cooled to 0° . The resulting suspension was treated with the corresponding alkene (1 equiv, 0.08 M alkene concentration with respect to total reaction volume), stirred until the reaction was complete (TLC), and was quenched by addition of Na_2SO_3 (12 equiv). The resulting mixture was stirred for 5 minutes, warmed to room temperature over 5 minutes, and was partitioned between ethyl acetate and minimal H_2O . The organic extract was washed twice with brine, dried with Na_2SO_4 , and concentrated in vacuo. The residue was filtered through a silica gel plug eluting with ethyl acetate, and the filtrate was concentrated in vacuo to afford the product.



(*R*)-(-)-1-Phenyl-2-propen-1-yl 4-Methoxybenzoate [Kinetic Resolution].⁶³

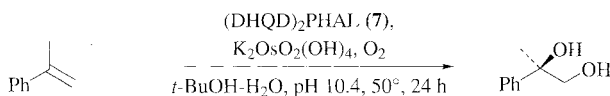
A mixture of $\text{K}_3\text{Fe}(\text{CN})_6$ (0.24 g, 0.73 mmol), K_2CO_3 (0.10 g, 0.73 mmol), DHQD-PYDZ-(*S*)-anthryl ligand (1.6 mg, 0.0024 mmol), (+/-)-1-phenyl-2-propen-1-yl 4-methoxybenzoate (0.065 g, 0.24 mmol), and dibutyl phthalate (0.05 mL, added as an internal standard) in *tert*-butyl alcohol:water (1:1, 3 mL) was stirred for 20 minutes at 0° . Approximately 0.025 mL of this mixture was quenched with saturated aqueous Na_2SO_3 (0.05 mL) and extracted with ethyl acetate (0.1 mL). The organic layer was concentrated (reduced pressure, 23° bath temperature) and analyzed by HPLC (Regis Whelk O1 column at 23° , 5% 2-propanol-hexane, 1 mL/minute flow rate; λ_{235} nm; retention times (*R*) 9.9 minutes, (*S*) 16.6 minutes, dibutyl phthalate 11.9 minutes). The reaction was initiated by addition of $\text{K}_2\text{OsO}_2(\text{OH})_7$ (0.45 mg, 0.0012 mmol) to the reaction mixture, and aliquots were taken and analyzed using the above procedure every 5–10 minutes. After all of one enantiomer had reacted, the mixture was quenched with 2 mL of saturated aqueous Na_2SO_3 , and was extracted with ethyl acetate (3 x). The combined organic layers were washed with brine (2×10 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuo. Flash chromatography [ethyl acetate:hexane (1:1) to elute alkene, followed by ethyl acetate to elute diols] gave recovered (*R*)-(-)-1-phenyl-2-propen-1-yl 4-methoxybenzoate (0.026 g; $[\alpha]_D^{23} -21.7^\circ$ (*c* 0.35, EtOH), and diol (0.036 g, 50%).



(10*R*)-10,11-Dihydroxy-10,11-dihydrofarnesyl Acetate [Asymmetric Dihydroxylation of Non-Conjugated Polyalkenes].^{62,142}

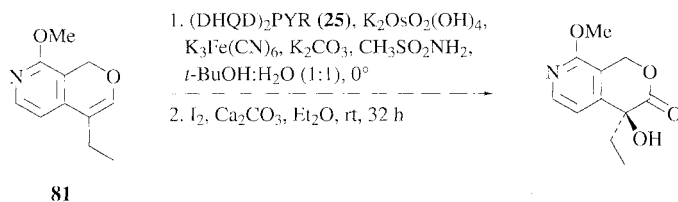
A mixture of 1,4-bis[*O*-6'-(4-heptyl)hydrocupreidyl]naphthopyridazine (**92**) (46 mg, 0.040 mmol), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (7.4 mg, 0.0020 mmol), $\text{K}_3\text{Fe}(\text{CN})_6$ (1.98 g, 12 mmol), K_2CO_3 (1.07 g, 12 mmol), $\text{CH}_3\text{SO}_2\text{NH}_2$ (0.38 g, 4.0 mmol), 2,6-*E,E*-farnesyl acetate (1.06 g, 4.0 mmol), and *tert*-butyl alcohol:water (1:1, 40 mL) was stirred at 0° for 19 hours. The mixture was

treated with saturated Na_2SO_3 solution (15 mL) and then aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (15 mL) at 0° , and was warmed to room temperature over 45 minutes. The resulting mixture was extracted with ethyl acetate (4x20 mL), and the combined extracts were washed with 3 M aqueous KOH, brine, dried over Na_2SO_4 , and concentrated in vacuo. The residue was separated by silica gel chromatography (1:1 ethyl acetate:hexane) to give unreacted farnesyl acetate (195 mg, 20%), 6,7-dihydroxy-6,7-dihydrofarnesyl acetate (6 mg, 0.5%), and the title compound (754 mg, 80%; 64% uncorrected for recovered farnesyl acetate; 96% ee): $[\alpha]_{\text{D}}^{23} +20^\circ$ (c 0.72, MeOH). Elution with ethyl acetate:ethanol (5:1) afforded 6,7,10,11-tetrahydroxy-6,7,10,11-tetrahydrofarnesyl acetate (184 mg, 14%). The ligand (35 mg, 76%) was recovered by eluting the column with $\text{CHCl}_3 + \text{MeOH} + \text{NH}_4\text{OH}$, 20:1:0.1.



2-Phenyl-1,2-propanediol [Asymmetric Dihydroxylation Under Atmospheric Oxygen Pressure].¹⁸⁰

In a 100-mL Schlenk tube, $\text{K}_2\text{OsO}_2(\text{OH})_4$ (3.7 mg, 0.01 mmol) and $(\text{DHQD})_2\text{PHAL}$ (**7**) (23.4 mg, 0.03 mmol) were dissolved in a mixture of *tert*-butyl alcohol (10 mL) and an aqueous buffer solution (25 mL, pH 10.4). The Schlenk tube was then purged with O_2 , and the biphasic mixture was warmed to 50° in an oil bath. Then α -methylstyrene (260 μL , 2 mmol) was added in one portion by a syringe and the tube was connected to a graduated gas buret filled with O_2 . The reaction mixture was stirred vigorously with a magnetic stirring bar, and the O_2 uptake was observed to follow the reaction. After 24 hours, 22 mL (*ca.* 1 mmol) of O_2 had been consumed. A small amount of Na_2SO_3 was added, and the mixture was cooled to room temperature while stirring. The mixture was then extracted with ethyl acetate (2×20 mL). The combined organic layers were dried over MgSO_4 , concentrated under reduced pressure, and the crude diol was purified by column chromatography (hexane:ethyl acetate 2:1) to give 2-phenyl-1,2-propanediol (257 mg, 93%, 88% ee) as a colorless solid: ^1H NMR (CDCl_3) δ 7.23–7.41 (m, 5H), 3.74 (d, $J = 11.1$ Hz, 1H), 3.58 (d, $J = 11.1$ Hz, 1H), 2.39 (br s, 2H), 1.50 (s, 3H); HPLC (diol): (R,R)-Whelk-O1, 2% EtOH in hexane, flow rate 1.0 mL/minute, $t_{\text{R}} = 14.4$ minutes (S), 16.7 minutes (R).

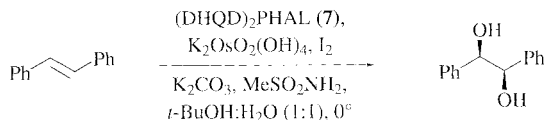


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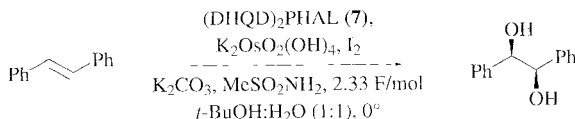
(4S)-4-Ethyl-4-hydroxy-8-methoxy-1,4-dihydropyrano[3,4-c]pyridin-3-one [Asymmetric Dihydroxylation of Enol Ethers].^{134,135}

A 500-mL flask was charged with $(\text{DHQD})_2\text{PYR}$ (**25**) (230 mg, 0.261 mmol) as a solution in *tert*-butyl alcohol (126 mL), followed by successive addition of deionized H_2O (131 mL), $\text{K}_3\text{Fe}(\text{CN})_6$ (25.8 g, 78.4 mmol), anhydrous K_2CO_3 (10.8 g, 78.4 mmol), potassium

osmate (VI) dihydrate (19.2 mg, 0.0522 mmol), and $\text{CH}_3\text{SO}_2\text{NH}_2$ (2.49 g, 26.1 mmol). After stirring for 3 minutes at room temperature, the nearly homogeneous mixture was cooled to 0° , at which temperature it turned into a red slurry. A solution of **81** (5.00 g, 26.1 mmol) in *tert*-butyl alcohol (5 mL) was added, and the thick slurry was vigorously stirred for 48 hours at 0° . The mixture was treated with iodine (33.2 g, 131 mmol) and calcium carbonate (13.1 g, 131 mmol). After being warmed to room temperature, the brown mixture was stirred for 48 hours. The mixture was subsequently cooled to 0° and sodium sulfite (25 g) was added in three portions over 5 minutes. The stirring was continued for 30 minutes. The now green mixture was filtered by suction through a pad of Celite[®] 545 and the pad washed with ethyl acetate:methanol (90:10, 250 mL). The filtrate was washed with brine (2 x), dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give crude product (5.79 g) as a yellow oil. The oil had a higher than 90% chemical purity by HPLC: Chiral HPLC (Chiralcel[®] OD, ethanol:hexane 2:99, λ 276 nm, 1.0 mL/minute) showed an S/R ratio of 34:1 (t_R for S-enantiomer 14.92 minutes, R-enantiomer 16.26 minutes). An analytical sample was obtained by flash chromatography on silica gel eluting with 3% $\text{MeOH}-\text{CH}_2\text{Cl}_2$; ^1H NMR (400 MHz, CDCl_3) δ 8.21 (d, $J = 5$ Hz, 1H), 7.16 (d, $J = 5$ Hz, 1H), 5.58 (d, $J = 16$ Hz, 1H), 5.27 (d, $J = 16$ Hz, 1H), 3:99 (s, 3H), 3.62 (s, 1H), 1.80 (m, 2H), 0.96 (t, $J = 7$ Hz, 3H).

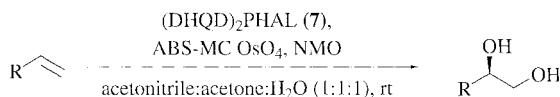


(1*R*,2*R*)-1,2-Diphenyl-1,2-ethanediol (Asymmetric Dihydroxylation with Iodine as Secondary Oxidant).¹⁷⁵ To a stirred solution of *tert*-butyl alcohol:H₂O (1:1, 100 mL), K_2CO_3 (30 mmol), iodine (15 mmol), $\text{CH}_3\text{SO}_2\text{NH}_2$ (10 mmol), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (0.02 mmol), and $(\text{DHQD})_2\text{PHAL}$ (**7**) (0.1 mmol) was added *trans*-stilbene (10 mmol) in one portion at 0° . The mixture was stirred vigorously for more than 30 hours (monitored by TLC), and was then quenched with solid sodium sulfite (10 g). The two phases were separated, and the aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phases were washed with 2 M NaOH and dried over MgSO_4 . Concentration and flash chromatography afforded the title compound in 98.4% yield: $[\alpha]_D^{25} +91^\circ$ (CDCl_3). The enantiomeric excess of the R,R-diol was determined by HPLC analysis [Chiralcel[®] OB-H column (Daicel), 10% *i*-PrOH in hexane, 0.5 mL/min] to be 99.5%.



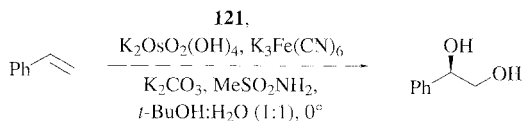
(1*R*,2*R*)-1,2-Diphenyl-1,2-ethanediol [Electrochemical Asymmetric Dihydroxylation].¹⁷⁵ A mixture of *tert*-butyl alcohol:H₂O (1:1, 50 mL), $\text{CH}_3\text{SO}_2\text{NH}_2$ (5 mmol), K_2CO_3 (15 mmol), iodine (2.0 mmol), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (0.01 mmol), $(\text{DHQD})_2\text{PHAL}$ (**7**) (0.05 mmol), and *trans*-stilbene (5 mmol) was electrolyzed in an undivided flow cell (Micro-Flow Cell) equipped with two platinum electrodes

(3 × 4 cm). After passage of 2.33 F/mol of electricity at room temperature (progress was monitored by TLC), solid sodium sulfite (5 g) was added, and the solution was stirred for 40 minutes. The two phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 25 mL). The combined organic phases were washed with 2 M NaOH and dried over MgSO₄. Concentration and flash chromatography afforded the title compound in 82.4% yield, $[\alpha]_D^{25} +91^\circ$ (CDCl₃). The enantiomeric excess was determined by HPLC analysis [Chiralcel® OB-H column (Daicel), 10% *i*-PrOH in hexane, 0.5 mL/min] to be 99.5%.

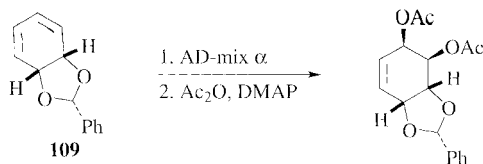


Asymmetric Dihydroxylation using ABS-MC OsO₄.¹⁷⁰ ABS-MC OsO₄ (76.7 mg, 5 mol%), (DHQD)₂PHAL (7) (21.5 mg, 5 mol%), and NMO (0.72 mmol) were combined in water:acetone:acetonitrile (1:1:1, 3.5 mL) at room temperature. To this mixture was added the alkene (0.55 mmol) slowly over a period of about 24 hours. Methanol (10 mL) was added, and the mixture was stirred for 10 minutes. ABS-MC OsO₄ was separated by filtration. After washing with methanol, the combined filtrates were concentrated under reduced pressure. The chiral ligand was recovered from the aqueous layer after acidification with 1N HCl. The concentrated organic layer was purified by chromatography on silica gel to afford the *cis*-diol product.

Preparation of ABS-MC OsO₄.¹⁷⁰ ABS polymer [Stylac® 200 (Asahi Chemical), 1.00 g] was dissolved in THF (20 mL) at 70–80°, and to this solution was added OsO₄ (0.200 g). The mixture was stirred for 1 hour at this temperature and then slowly cooled to 0°. Coacervates (phase separation) were found to envelop the core dispersed in the medium, and methanol (30 mL) was added to harden the capsule walls. After 8 hours, the capsules were washed with methanol several times and dried at room temperature for 24 hours to afford ABS-MC OsO₄ (1.18 g). Based on the recovered weight, 0.180 g of OsO₄ was microencapsulated according to the above procedure. Unencapsulated OsO₄ was recovered from the washings.



(*R*)-1-Phenyl-1,2-ethanediol [Asymmetric Dihydroxylation Using a Polymer-Bound Ligand].¹⁶² To a solution of K₃Fe(CN)₆ (3 equiv) and K₂CO₃ (3 equiv) in *tert*-BuOH:H₂O (1:1, 6 mL), was added OsO₄ (0.0125 equiv) and polymeric ligand **121** (0.25 equiv). After 30 min, styrene (2 mmol) was added, and the heterogeneous mixture was stirred at 0° for 24 hours. After addition of H₂O (3.0 mL), the mixture was centrifuged, and the centrifugate was extracted with CH₂Cl₂. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography, affording the title compound in 86% yield and 91% ee.



(2*R*,3*aR*,4*R*,5*R*,7*aR*)-2-Phenyl-3*a*,4,5,7*a*-tetrahydrobenzo[1,3]dioxole 4,5-Diacetate [Asymmetric Dihydroxylation Using AD-mix].^{147,148} A mixture of **109** (261 mg, 1.31 mmol), AD-mix α (1.8 g), and $\text{CH}_3\text{SO}_2\text{NH}_2$ (125 mg, 1.31 mmol) in *tert*-butyl alcohol: H_2O (1:1, 13.2 mL) was stirred at 0° for 38 hours. To the mixture were added Na_2SO_3 (1.97 g) and KOH (720 mg), and stirring was continued for 1 hour at room temperature. The mixture was diluted with ethyl acetate, and the organic layer was washed with brine, dried over MgSO_4 , and evaporated under reduced pressure to leave the crude diol (383 mg) as a colorless oil. This material was then stirred with acetic anhydride (0.37 mL, 3.93 mmol), triethylamine (0.64 mL, 4.59 mmol), and 4-(*N,N*-dimethylamino)pyridine (DMAP) (16 mg, 0.13 mmol) in CH_2Cl_2 (10 mL) at room temperature for 10 minutes. The mixture was washed with brine, dried over MgSO_4 , evaporated under reduced pressure, and chromatographed on a silica gel column (20 g, elution with 1:2 v/v ether-hexane) to give unreacted **109** (25 mg, 10%) and the title compound (336 mg, 81%) as a colorless oil: $[\alpha]_{\text{D}}^{25} -256^\circ$ (*c* 1.32, CHCl_3); 87% ee by chiral HPLC: (Chiralcel[®] OD, elution with 1:9 v/v *i*-PrOH:hexane); FTIR (neat) 1745 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.47-7.45 (m, 2H), 7.39-7.36 (m, 3H), 6.17 (dd, $J = 9.76, 3.66\text{ Hz}$, 1H), 6.03 (ddd, $J = 9.77, 5.49, 1.22\text{ Hz}$, 1H), 5.90 (s, 1H), 5.55 (dd, $J = 5.49, 3.66\text{ Hz}$, 1H), 5.27 (dd, $J = 8.54, 3.66\text{ Hz}$, 1H), 4.81 (ddd, $J = 9.16, 3.67, 1.22\text{ Hz}$, 1H), 4.57 (dd, $J = 8.55, 6.71\text{ Hz}$, 1H), 2.09 (s, 3H), 2.08 (s, 3H).

TABULAR SURVEY

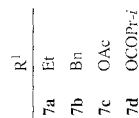
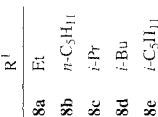
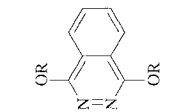
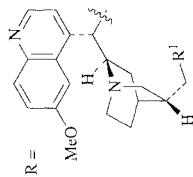
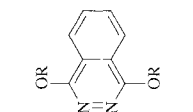
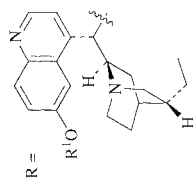
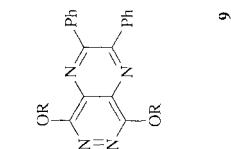
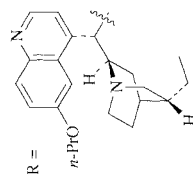
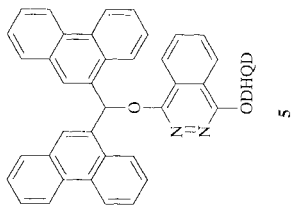
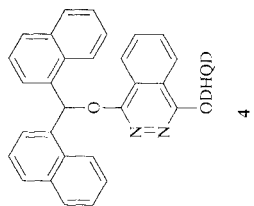
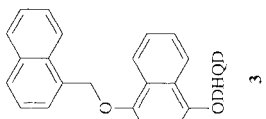
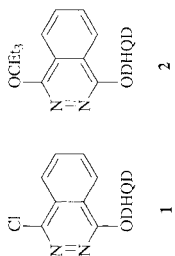
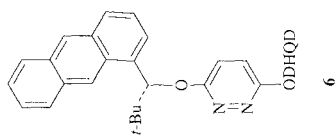
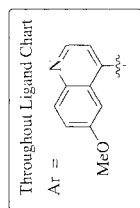
Tables 1–9 include examples of stoichiometric and catalytic asymmetric dihydroxylation reactions that have appeared in the literature up to the end of 2000. Supplementary Table 10 is a survey of the literature from 2001 through 2004. The tables are arranged in the same order as the text discussion. Entries in the tables are in the order of increasing number of carbon atoms, although some exceptions occur when a single structure covers a series with different R groups. Polymeric substrates are listed at the end of a section under the category C_n . The symbol (—) indicates that no yield was reported.

There are a number of entries where an absolute configuration of the diol is given but for which the authors did not report ee or de values. These entries are faithful to the original literature. For some products, absolute configurations were assigned in the original literature using the mnemonic of Figure 2. Such examples are marked with an asterisk by the product. OsO_4 was used in stoichiometric amounts unless otherwise indicated, or unless a secondary oxidant is listed in the conditions. There are some polymeric ligands (see Ligand Charts) for which no values are given for the number of repeating units; for conditions including these ligands, additional information (mol% of one or more components of these polymers) may be found in the original literature.

Abbreviations used in the charts and tables are as follows:

ABS MC	acrylonitrile-butadiene-polystyrene microencapsulated copolymer
Ac	acetyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
Chz	benzyloxycarbonyl
DHQ	dihydroquininyl
DHQD	dihydroquinidinyl
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DME	1,2-dimethoxyethane
DMPM	3,4-dimethoxyphenylmethyl
Ether	diethyl ether
LAH	lithium aluminum hydride
LDH	layered double hydroxide supported (for catalyst)
MOM	methoxymethyl
PMB	<i>p</i> -methoxybenzyl
NMM	<i>N</i> -methylmorpholine
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
Os EnCat	polyurea microencapsulated osmium tetroxide
PEG	polyethylene glycol
PEM-MC	poly(phenoxyethoxymethylstyrene)co-styrene
Piv	pivaloyl
PMP	<i>para</i> -methoxyphenyl
Phth	phthaloyl
SEM	trimethylsilylethoxymethyl
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TEAA	tetraethylammonium acetate
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
T _f	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	tri-iso-propylsilyl
TMS	trimethylsilyl
TON	turnover number
Tr	triphenylmethyl (trityl)
Troc	trichloroethoxycarbonyl
Ts	<i>p</i> -toluenesulfonyl
XAD	prefix for a series of Amberlite™ resins

CHART 1. LIGANDS USED IN TABLES 1-9



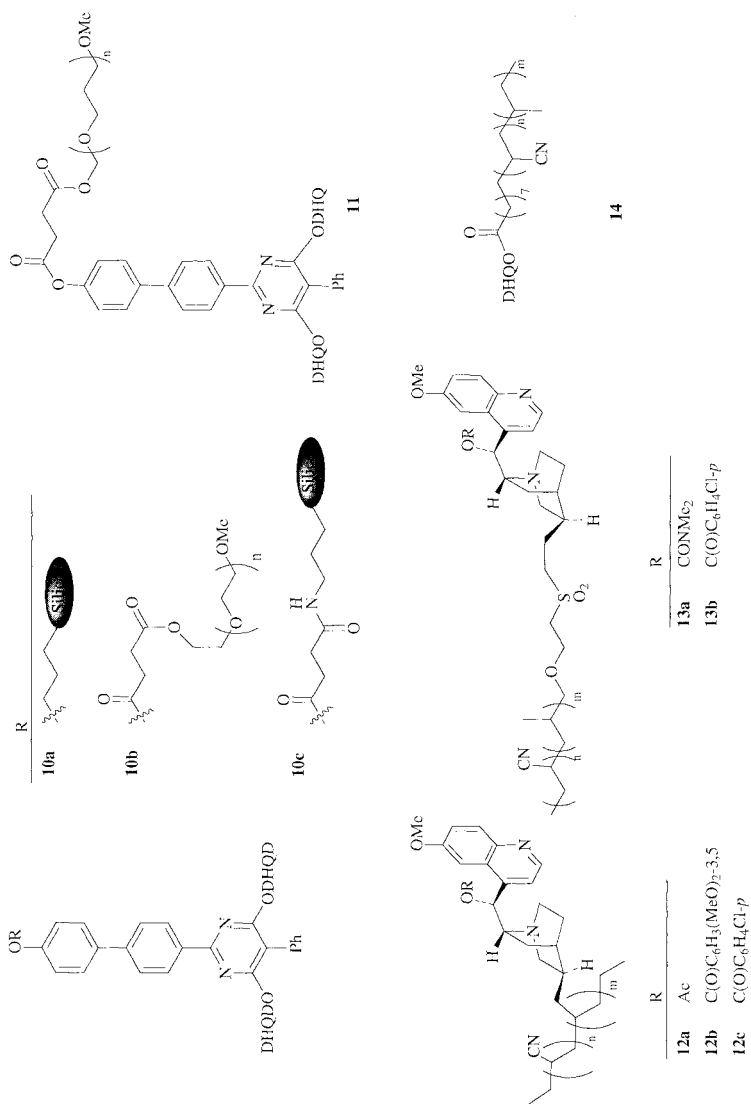
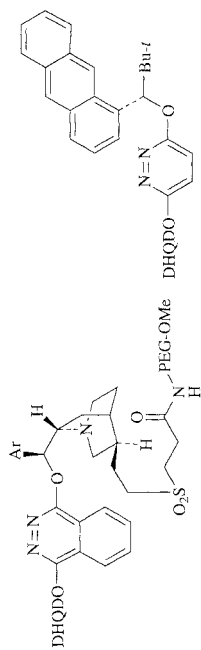
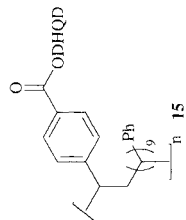
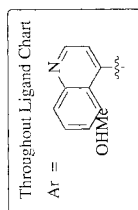
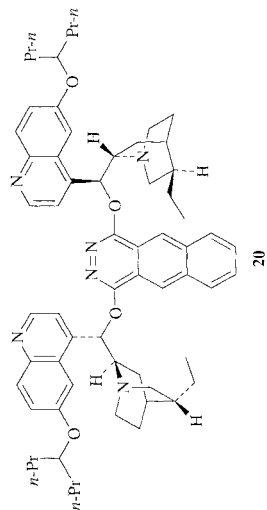
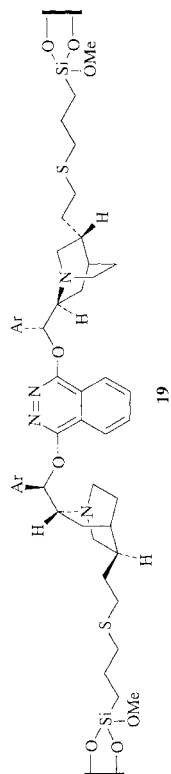
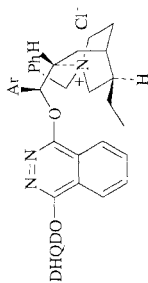
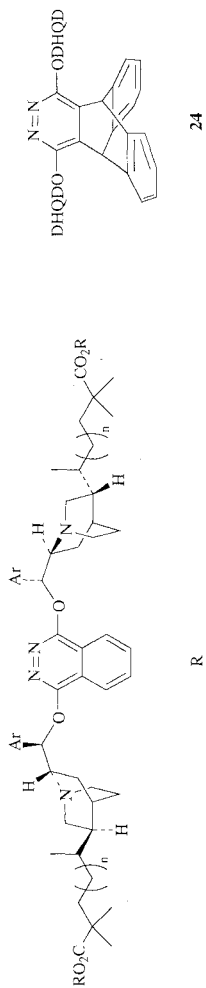
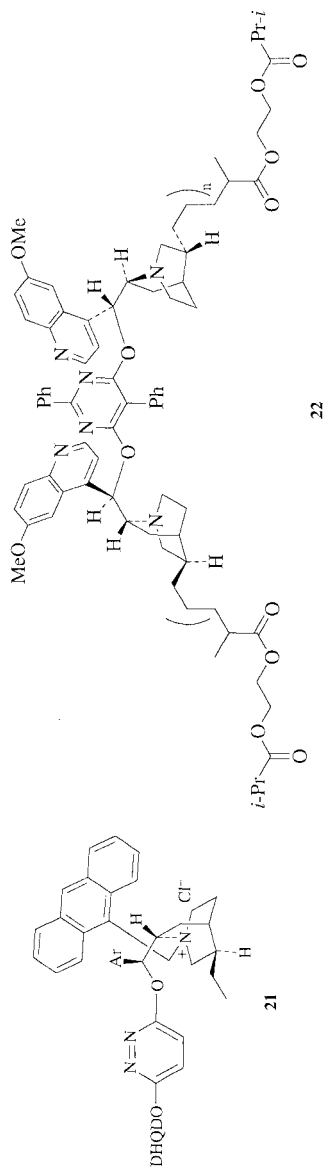


CHART 1. LIGANDS USED IN TABLES 1-9 (Continued)



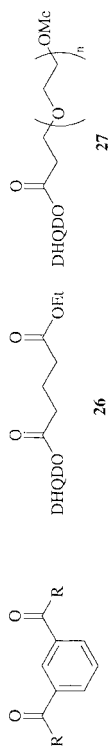
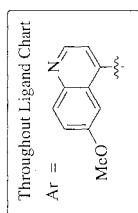
17



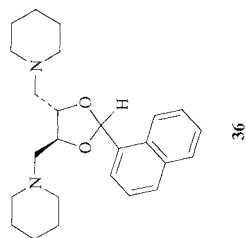
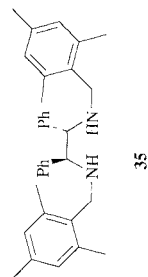
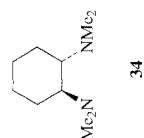
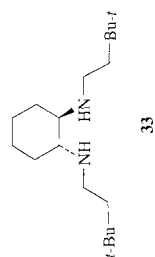
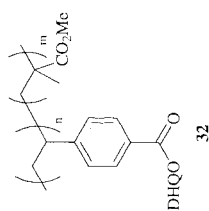
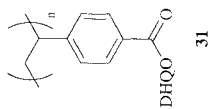
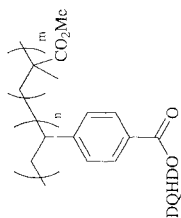
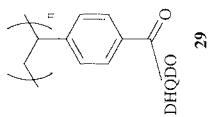
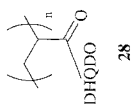


	R
23a	Me
23b	CH ₂ CH ₂ OH

CHART 1. LIGANDS USED IN TABLES 1-9 (Continued)



R = O-9-quininy!



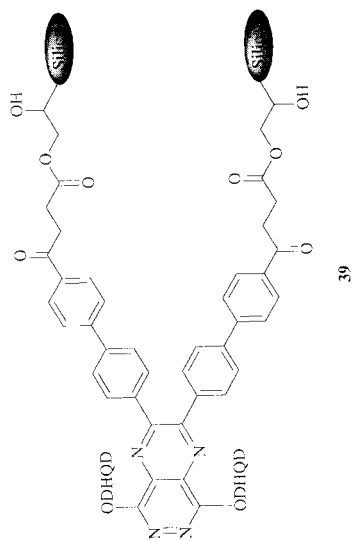
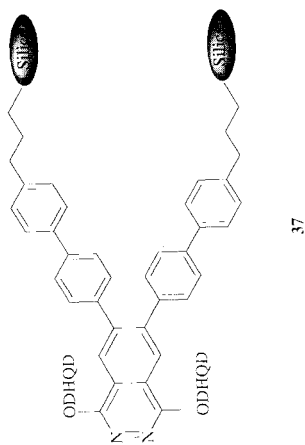
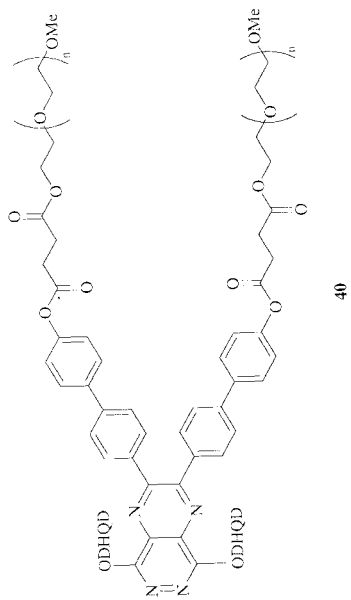
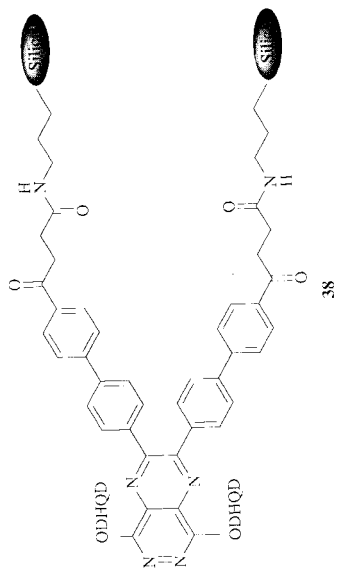
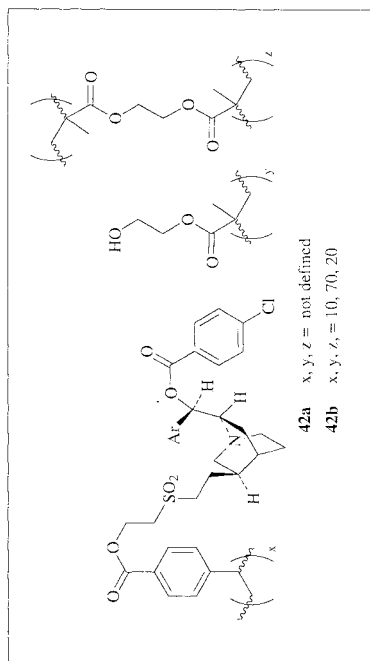
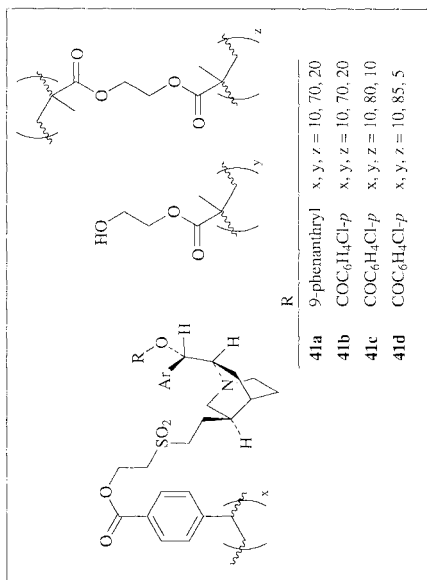
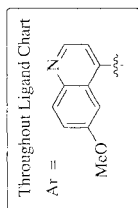


CHART 1. LIGANDS USED IN TABLES 1-9 (Continued)
Block Co-Polymers



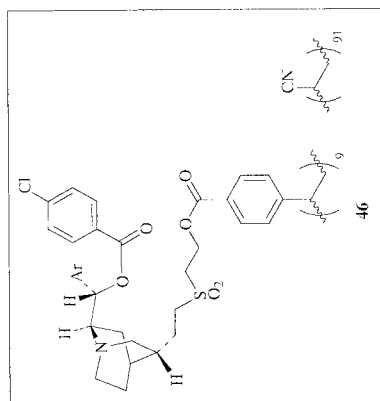
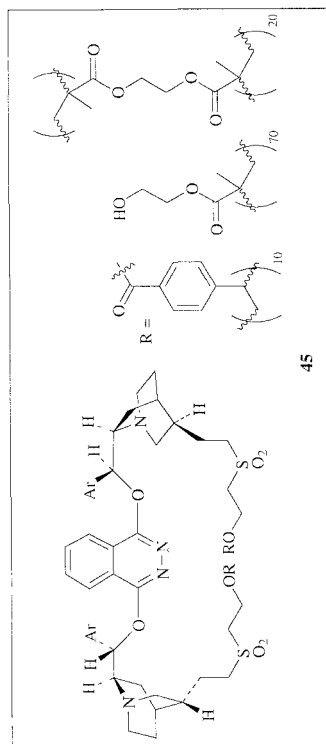
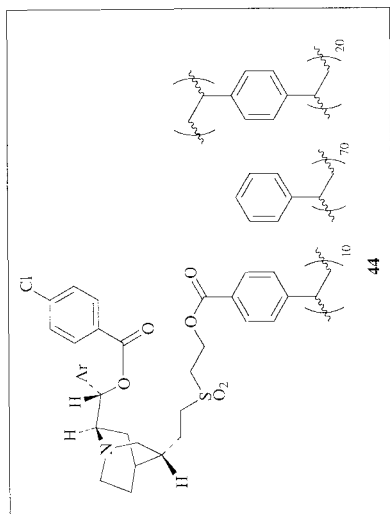
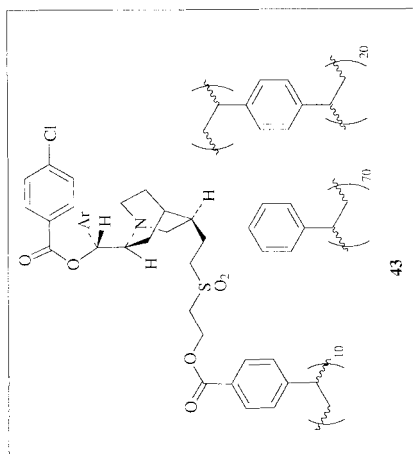


CHART 1. LIGANDS USED IN TABLES 1-9 (Continued)

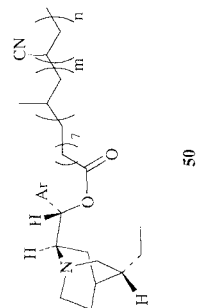
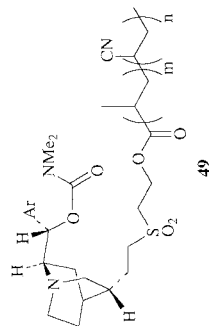
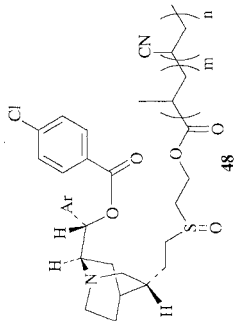
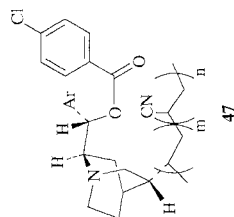
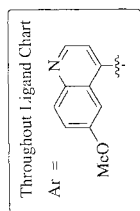
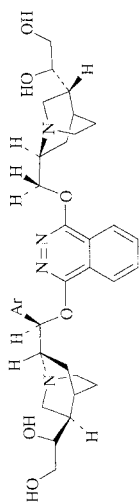
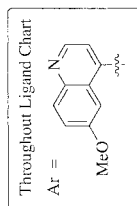
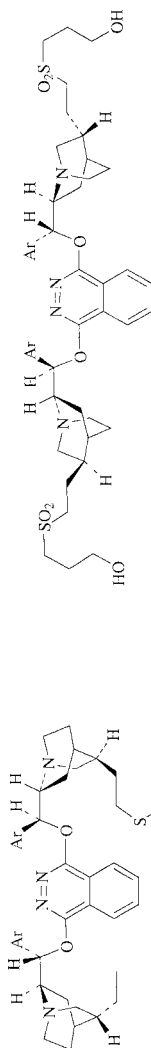


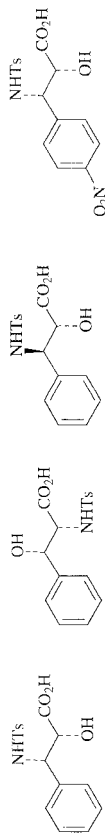
CHART 2. LIGANDS AND ADDITIVES USED IN TABLE 10



51



52



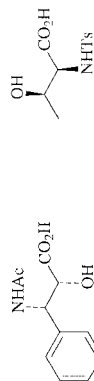
53

54

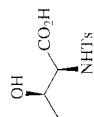
55

56

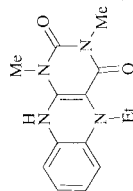
57



58

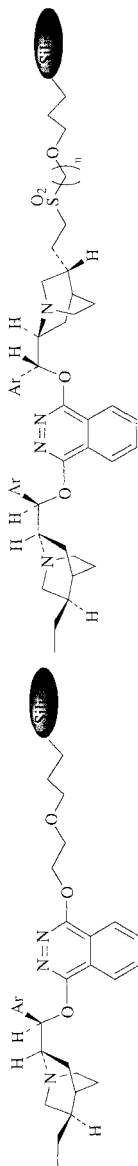


59



60

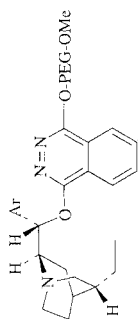
CHART 2. LIGANDS AND ADDITIVES USED IN TABLE 10 (Continued)



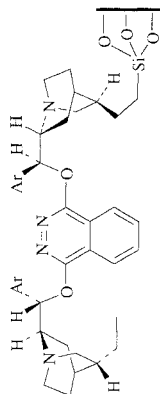
61

62 n = 2

63 n = 6

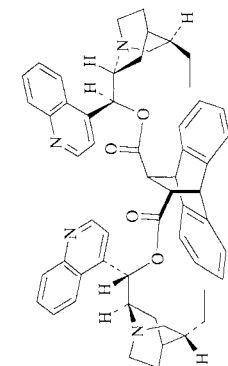


64

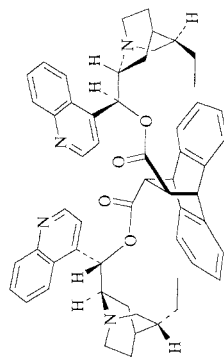


65 Support = mesoporous silica

66 Support = silica gel



67



68

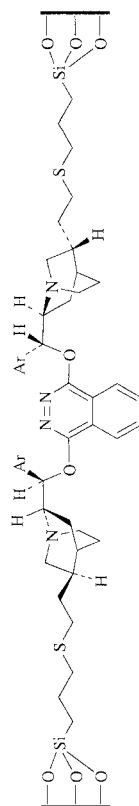
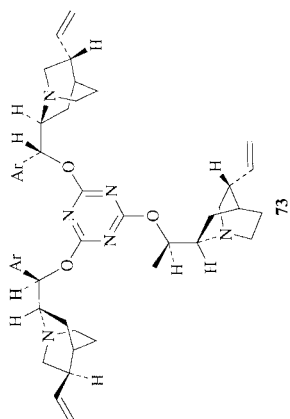
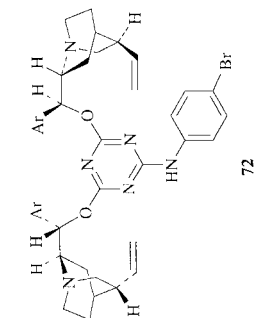
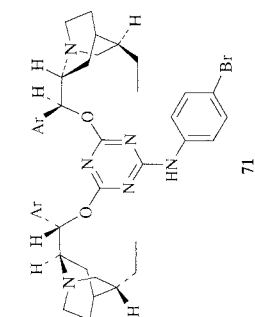
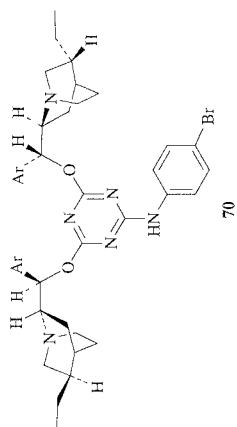
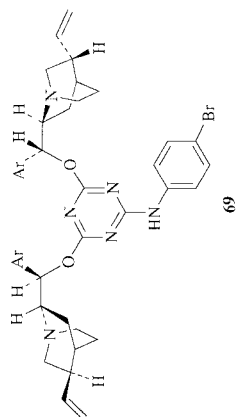
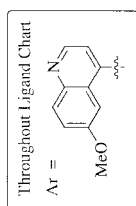
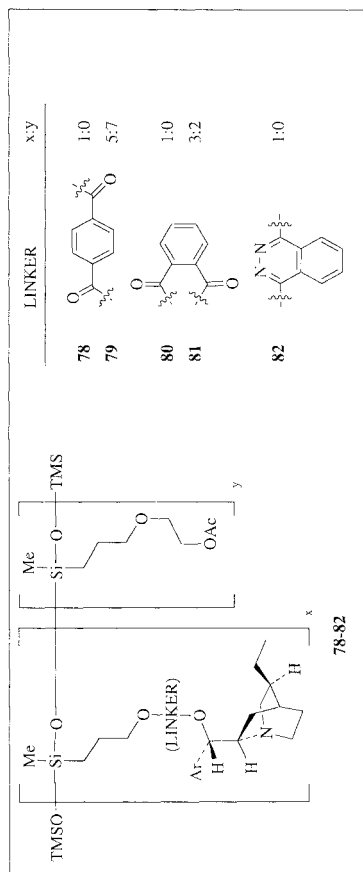
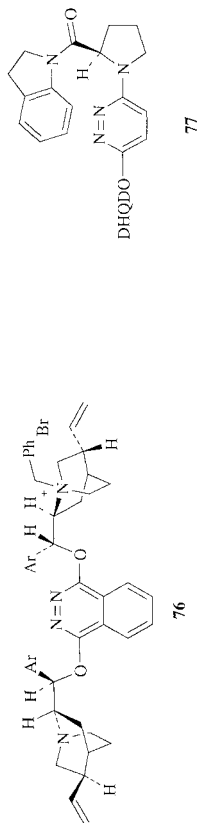
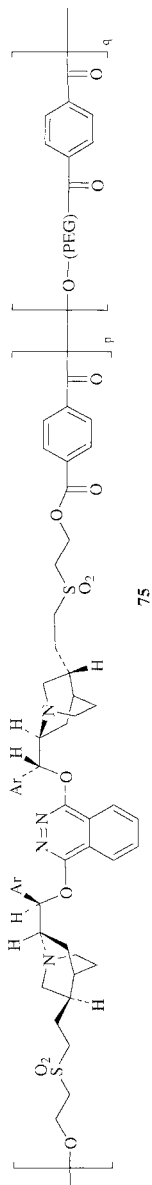
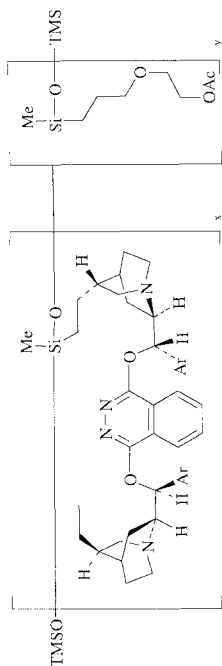
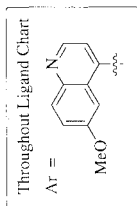


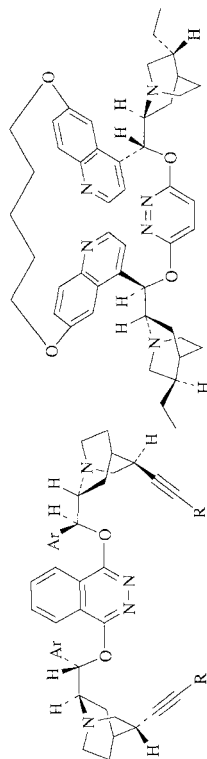
CHART 2. LIGANDS AND ADDITIVES USED IN TABLE 10 (Continued)





83 $xy = 1:0$

84 $xy = 5:7$

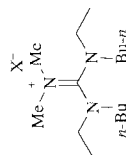


85 R = Ph

86 R = I

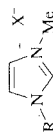
87 R = quinolyl

88



100 X = PF₆

101 X = N(Tf)₂



89 R = *n*-Bu, X = PF₆

90 R = *n*-Bu, X = BF₄

91 R = *n*-Bu, X = N(Tf)₂

92 R = *n*-Bu, X = SbF₆

93 R = *n*-Bu, X = OCOCF₃

94 R = *n*-Oct, X = PF₆

95 R = *n*-Oct, X = BF₄

96 R = *n*-C₁₀H₂₁, X = PF₆

97 R = *n*-C₁₀H₂₁, X = BF₄

98 R = MeO(CH₂)₂O(CH₂)₂, X = PF₆

99 R = MeO(CH₂)₂O(CH₂)₂, X = BF₄

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