THREE NEW $C_2$ SYMMETRIC CHIRAL AUXILIARIES FOR METAL MEDIATED
ASYMMETRIC REACTIONS: STUDIES IN ASYMMETRIC CARBON–HYDROGEN,
CARBON–NITROGEN, AND CARBON–OXYGEN BOND FORMATION

by

JOEL MICHAEL HAWKINS

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY IN
ORGANIC CHEMISTRY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

January 1986
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Submitted to the Department of Chemistry on January 27, 1986 
in partial fulfillment of the requirements for the degree of 
Doctor of Philosophy in Organic Chemistry

ABSTRACT

Three new C₂ symmetric chiral auxiliaries were synthesized and 
applied in asymmetric reactions. three-\(\alpha\)-N,\(\alpha\)'-Bis(\(\alpha\)-methylbenzyl)sulfamide, 
readily prepared from \(\alpha\)-methylbenzylamine and sulfur chloride, was 
employed as a chiral ligand for asymmetric reductions with lithium aluminum 
hydride. The optimized system employing N-benzylmethylamine as an additive 
at -20°C reduced aryl ketones with a maximum of 87% ee (for n-butyl 
2-naphthyl ketone), and fully saturated dialkyl ketones with a maximum of 
71% ee (for cyclohexyl methyl ketone). At lower temperatures, the 
enantiomeric excess increased as a function of conversion.

3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine, synthesized from 
2,2'-bis(bromomethyl)-1,1'-binaphthyl by annulation with 2,2,2-trifluoro-
acetamide, and resolved via the dibenzoyl tartrate salt, was studied as a 
chiral nucleophile in asymmetric Michael reactions with methyl crotonate. 
Thermally, an initial diastereomer ratio of 4.1:1 decreased with time and 
leveled off at 1.0:1. Michael addition of the corresponding lithium amide 
gave the isomeric adduct with a 94:1 and 61:1 ratio of diastereomers from 
the racemic and homochiral amides, respectively. The relative 
stereochemistry in the adducts were correlated by an independent synthesis.

three-\(\alpha\),\(\alpha\)'-Di-tert-butyl-2,6-pyridinedimethanol and related 
pyridinediols were synthesized from 2,6-dibromopyridine by reiterative 
bromine-lithium exchange and electrophilic trapping; and the three-di-tert-
butyl isomer was resolved via the dibenzoyl tartrate salt. Molybdenum(VI)-
dioxo complexes of these ligands were found to possess novel five-coordi-
nate MoO₃NO₂ structures in solution, and five-coordinate or polymeric 
structures in the solid state. A crystal structure of five-coordinate 
(-)-(three-2,6-bis(2,2-dimethyl-1-oxypropyl)pyridinato)dicymolybdenum(IV) 
was determined. This complex catalyzed the epoxidation of an isolated 
olefin with hydrogen peroxide and an allylic alcohol with tert-butylhydro-
peroxide (TBHP), but the epoxides showed little or no enantiomeric excess. 
In situ generated titanium(IV) complexes of the pyridinediols catalyzed the 
epoxidation of allylic alcohols with alkyl hydroperoxides. Epoxidation of 
(E)-\(\alpha\)-phenylcinnamyl alcohol with the monomeric three-\(\alpha\),\(\alpha\)'-di-tert-butyl-
2,6-pyridinedimethanol complex gave opposite face selections with TBHP 
(41% ee) and trityl hydroperoxide (64% ee). (E)-1-cyclohexyl-2-butene-1-ol 
gave erythro/threo ratios ranging from 80:20 to 50:50 depending on the 
pyridinediol and the alkyl hydroperoxide used. Analogies with titanium-
tartrate catalysts are discussed.

Thesis Supervisor: Dr. K. Barry Sharpless 
Title: Professor of Chemistry
Acknowledgements

I am grateful to the Fannie and John Hertz Foundation for a graduate fellowship (1982-1986). Preliminary portions of Part III were conducted by Mr. Gregory Fu under the author’s direction. I am grateful to Greg for his diligent experimentation, and to Professor Sharpless for allowing me to conduct this independent project in his laboratory. Helpful discussions with numerous colleagues, most notably Drs. M. G. Finn, Steven Pedersen, Robert Hanson, and Hiroko Masamune, have greatly assisted me in the preparation of this thesis. Finally, I thank Professor Sharpless for the rare and valuable experience of studying chemistry under his direction.

For Mary.
Preface

Parts of this thesis have been adapted from previous writings by the author:


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PART I. INTRODUCTION

1. Chiral Auxiliaries: Classification and Symmetry

Asymmetric reactions\(^1\) are gaining significance and recognition for the preparation of homochiral pharmaceutical and agricultural chemicals,\(^2\) and for reagent-controlled diastereoselection.\(^3\) Excluding certain weak physical phenomena, asymmetric reactions require chemical chiral auxiliaries to interact with the substrate and induce diastereomeric transition states. These auxiliaries can be attached to the substrate directly (in a previous step), or transiently (in situ). Direct attachment of the chiral auxiliary enforces proximity to the substrate but requires additional synthetic steps. Transient attachment via kinetically labile interactions can require a stoichiometric chiral auxiliary, or, in the event that these interactions survive turnover cycles, a catalytic chiral auxiliary.

Kinetically labile chiral auxiliary-substrate interactions often involve a chiral ligand-metal-substrate ligand relationship. Many of the more successful chiral ligands are bidentate with \(C_2\) symmetry. This concept was partly realized in 1953 when Wright noted the importance of the "bifunctional nature of 2,3-dimethoxybutane [1]" as opposed to monofunctional chiral ether ligands in an asymmetric Grignard reaction.\(^4\) However, it was not until 1972 that the importance of symmetry was specifically cited. For the development of diop [2], Kagan noted the need for "equivalent phosphorus atoms [to] avoid the possibility of geometric isomerism about the rhodium."\(^5\)

\[\text{MeO} \quad \text{OMe} \]
\[\text{Ph}_2\text{P} \quad \text{PPh}_2\]

\(1\)

\(2\)
2. Structural Features of \textit{threeo-}N,N'-Bis(\textit{\alpha-}\textit{methylbenzyl})sulfamide, 3,5-Dihydro-4\textit{H}-dinhaphth[2,1-\textit{c}:1',2'-\textit{e}]azepine, and \textit{threeo-}\textit{\alpha,\alpha'}-Di-\textit{tert}-butyl-2,6-pyridinedimethanol

This thesis describes the synthesis of three new chiral auxiliaries and their applications in asymmetric reactions. The title compounds, \textit{threeo-}N,N'-bis(\textit{\alpha-}\textit{methylbenzyl})sulfamide (3), 3,5-dihydro-4\textit{H}-dinhaphth[2,1-\textit{c}:1',2'-\textit{e}]azepine (4), and \textit{threeo-}\textit{\alpha,\alpha'}-di-\textit{tert}-butyl-2,6-pyridinedimethanol (5), were each conceived with certain useful features in mind. \textit{C}_2 symmetry is common to all three structures; additional features are detailed below.

Chiral ligands with \textit{C}_2 symmetry have generally been prepared by the derivation of tartaric acid or by resolution. An alternative process is to couple two chiral molecules of \textit{C}_1 symmetry in such a way as to produce a molecule of \textit{C}_2 symmetry.\textsuperscript{6-8} Section II-3 describes the facile preparation of sulfamide 3 by the coupling of two equivalents of \textit{\alpha-}methylbenzylamine. Homochiral \textit{\alpha-}methylbenzylamine is quite inexpensive in either enantiomeric form allowing the homochiral sulfamide to be prepared on a large scale. The synthesis leads directly to a single isomer; neither the resolution of enantiomers, nor the separation of diastereomers is required.

In addition to coupling the \textit{\alpha-}methylbenzylamine fragments, the SO\textsubscript{2} moiety increases the acidity of the remaining protons on nitrogen. Furthermore, the NSO\textsubscript{2}N unit positions large N,N'-dialkyl substituents in a \textit{C}_2 conformation producing an axially dissymmetric structure (see Section II-1). This provides the potential for chiral groups on nitrogen to influence the configuration at sulfur. Section II-4 describes the application of 3 with lithium aluminum hydride in the asymmetric reduction
of prochiral ketones.

Dihydroazepine 4 employs the rigid and symmetric 1,1′-binaphthyl moiety which has found extensive use in chiral auxiliaries. Most commonly, chelates of structure 6 have been used, where the X's are donor sites and ML$_n$ is the metallic site of reaction.$^9$ Alternatively, fixed rings such as dihydroazepines of structure 7 have been applied. The latter include Cram's chiral catalyst for the addition of alkyllithiums to aldehydes, 7a,$^{10}$ and Mazaleyrat's chiral acyl anion equivalent for aldehyde additions, 7b.$^{11}$ Dihydroazepine 4 is the simplest member of this class, and Section III-4 describes diastereoselective Michael additions of 4 and the corresponding lithium amide to methyl crotonate. Structurally, 4 is distinguished from other C$_2$ symmetric chiral secondary amines (Section III-1) in that it has only two stereoisomers; i.e., there is no corresponding meso isomer which must be separated from the d,l-isomers.

Pyridinediol 5 is a potentially tridentate ligand which, when bound to a metal, blocks diagonal quadrants of the coordination sphere. This steric arrangement led to novel molybdenum complexes in Section IV-5, and found analogy to titanium-tartrate asymmetric epoxidation catalysts in Section IV-7. The synthesis of 5 required the separation of the threo from the meso isomer, followed by resolution (Section IV-4).
PART II. threo-N,N'-Bis(α-methylbenzyl)sulfamide
HISTORICAL

1. Sulfamides

The synthesis, physical properties, and reactions of sulfamides (diamides of sulfuric acid) have been reviewed. Structural studies of sulfamides have shown that the geometry at nitrogen is intermediate between planar and tetrahedral, but closer to planar. The plane defined by nitrogen and its two non-sulfur substituents is approximately orthogonal to the nitrogen-sulfur-nitrogen plane. In N,N'-di-tert-butylsulfamide, the tert-butyl groups reside on opposite sides of the nitrogen-sulfur-nitrogen plane giving the axially dissymmetric structure 9.

The ligative behavior of the parent sulfamide, SO$_2$(NH$_2$)$_2$, has been examined with a number of metals. The sodium salt was generated in warm aqueous sodium carbonate. The rhodium chelate Na[(H$_2$O)$_2$Rh(N$_2$H$_2$SO$_2$)$_2$], formed from the sodium salt and Na$_2$RhCl$_6$·2H$_2$O, was the second carbon-free octahedral complex to be resolved. A crystal structure of disilver sulfamide AgNH$_2$SO$_2$NHAg, formed in aqueous silver nitrate, showed discrete SO$_2$N$_2$ tetrahedra with each silver atom bonded to two nitrogen atoms of different tetrahedra. Sulfamide has also acted as a weak donor ligand in copper(II), nickle(II), and zinc(II) complexes.

Davis recently reported the synthesis of a series of unsymmetrical chiral sulfamides and studied the utility of the corresponding sulfamylloxaziridines in the asymmetric oxidation of sulfides to sulfoxides. In his best case, sulfamylloxaziridine 10 oxidized 9-anthryl methyl sulfide with 68% ee.
2. Asymmetric Reduction of Carbonyl Compounds with Hydridic Reagents: 
A Review of the Literature with Respect to Substrate Classification

Chiral secondary alcohols are important intermediates and targets for the synthetic organic chemist. In the racemic mode, the reduction of ketones with lithium aluminum hydride and other hydridic reagents provides an efficient and general route to these compounds. These facts, combined with the ease of modifying these reagents in situ by simply adding protic acids, Lewis bases, or olefins, depending on the type of reagent, have spurred the development of a large number of asymmetric reducing agents over the last thirty years. Homochiral alcohols, diols, amines, diamines, amino alcohols, and terpenes have been applied in aluminate, boronate, and borane based reagents with varying degrees of success.\textsuperscript{18-20} Although none of these reagents have universal scope, the combined range of the best reagents now allows for many classes of ketones to be reduced with high enantiomeric excess.

The primary literature and recent reviews of this field are organized according to the reagents.\textsuperscript{18-20} Since each reagent is described separately, it is difficult to tell which are the most synthetically useful. In contrast, this chapter is organized according to the substrates. For each class of ketone, the most useful reagents are described and compared. Usefulness is judged not only by enantioselectivity, but also by practicality. Reagents of outdated utility are not discussed.

The asymmetric reduction of a prochiral ketone inevitably involves the differentiation of the two groups bound to the carbonyl carbon. These groups can be divided into eight types: proton, methyl, primary alkyl, secondary alkyl, tertiary alkyl, aryl, olefinic, and acetylenic. "Square" this list then gives a table of ketone classes (Table I). The bottom left hand portion of the table is omitted to avoid redundancy. Aldehydes are included as "ketones" with $\text{R} = \text{H}$. Deleting formaldehyde and acetone then leaves thirty four classes of substrates. These are combined under five main headings which are covered below: aldehydes, saturated dialkyl ketones, alkyl-aryl ketones, olefinic ketones, and acetylenic ketones.

13
Table I. Ketone Classification Scheme with Highest Recorded % ee’s per Class

<table>
<thead>
<tr>
<th></th>
<th>1° alkyl</th>
<th>2° alkyl</th>
<th>3° alkyl</th>
<th>Aryl</th>
<th>Olefinic</th>
<th>Acetylenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>83</td>
<td>70</td>
<td>100</td>
<td>88</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Me</td>
<td>XX</td>
<td>79</td>
<td>83</td>
<td>95</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46</td>
<td>100</td>
<td>97</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>1° alkyl</td>
<td>--</td>
<td>--</td>
<td>78</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2° alkyl</td>
<td>--</td>
<td>--</td>
<td>86</td>
<td>--</td>
<td>--</td>
<td>92</td>
</tr>
<tr>
<td>3° alkyl</td>
<td>--</td>
<td>--</td>
<td></td>
<td>--</td>
<td>98</td>
<td>--</td>
</tr>
<tr>
<td>Aryl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Olefinic</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylenic</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table I also shows the highest enantiomeric excesses recorded to date for each of the substrate classes. Not all of the ketones within a given class can be reduced so selectively as shown in subsequent tables. No ee’s are given for classes which have not been studied or which have not been reduced with greater than 20% ee. This chapter concentrates on boron and aluminum based hydridic reagents. Enzyme catalyzed reductions and the transition metal catalyzed asymmetric hydrogenation and hydrosilation of ketones are not covered.

Introduction to Key Reagents

Before the individual classes of ketone substrates are discussed, four key asymmetric reducing agents applicable under two or more of the main substrate headings will be introduced below. The less general but still useful reagents will be discussed with their respective substrates.

**BINAL-H**

In 1979, Noyori and co-workers reported the asymmetric reducing agent BINAL-H (11), prepared by combining equimolar quantities of lithium aluminum hydride, ethanol, and (R)- or (S)-2,2’-dihydroxy-1,1’-binaphthol (12) in tetrahydrofuran at room temperature (eq 1). Clear solutions of lithium aluminum hydride were used to prepare cloudy milk-white
"near-solutions" of the reagent which were used in two to three (generally three) fold excess with respect to ketone. Reductions were conducted at very low temperatures (typically starting out at -100°C and then warming to -78°C), and good to excellent enantioselectivities resulted for aldehydes and aromatic, olefinic, and acetylenic ketones.\textsuperscript{22,23}

\[
3 \text{LiAlH}_4 + 3 \text{EtOH} + 3 \quad \text{[11]} \quad \xrightarrow{\text{R Un}} \quad \text{HOH} \quad \text{R Un} \quad \text{(R)-12}
\]

The chiral auxiliary 12 is commercially available in both enantiomeric forms. Unfortunately, it is very expensive. This is due to the need for classically resolving (±)-12 via salts of the corresponding acid phosphate.\textsuperscript{24,25} Binaphthol 12 can be recovered (with care to prevent racemization) and reused. Even so, the expense of 12, coupled with the need for performing the reductions at very low temperatures limits the application of BINAL-H on a large scale.

The enantioselectivity is highly sensitive to unsaturated groups at the carbonyl carbon. A given enantiomer of BINAL-H reduces unsaturated ketones to alcohols with the same configuration of R and Un (eq 1), independent of the type of unsaturation (aromatic, olefinic, or acetylenic), or the size of R (from proton to secondary and even tertiary alkyl). The magnitude of the enantioselectivity, however, depends on the size of R. For aryl, olefinic, and acetylenic ketones, best results occur with primary R groups; secondary and tertiary groups decrease the optical yield.

Noyori chose the binaphthol auxiliary 12 in order to minimize the number of possible reactive species by giving a rigid, symmetric chelate. Although various hydride species were observed in the reagent, a single species appeared to be reacting, at least in one of the cases studied. This apparent simplicity of the system and the general configurational correlation with unsaturated substituents tempted mechanistic speculation. Noyori proposed a set of four six-membered ring chair transition states with steric and electronic factors that caused one to be favored. His
model was consistent with the observed chemistry, but reaction via more complicated species such as aggregates or even particle surfaces could not be ruled out.

N-Methylephedrine - Lithium Aluminum Hydride Systems

Both enantiomers of N-methylephedrine are available from the corresponding enantiomers of ephedrine by treatment with formaldehyde and formic acid (Eschweiler-Clarke reaction). Both ephedrine enantiomers are inexpensive; and (-)-N-methylephedrine (13) is commercially available directly at a moderate price.

In 1974, Vigneron and co-workers reported the asymmetric reducing agent 14, prepared by combining lithium aluminum hydride with one equivalent of N-methylephedrine and two equivalents of 3,5-xylenol in ether at room temperature (eq 2). Reductions were performed at -15°C with 1.2 to 3.0 equivalents of reagent, and good to very good enantioselectivities resulted with acetylenic and unhindered aromatic ketones. Like BINOL-H, aryl and acetylenic groups have the same directing effect on the absolute configuration of the products. The ready availability of the chiral auxiliaries and reduction at higher temperature make this system attractive for larger scale operation.

\[
\text{LiAlH}_4 + \text{Ph} - \text{NMe}_2 + 2 \text{OH} \rightarrow \text{[14]} \tag{2}
\]

(-)-13

Terashima and co-workers reported a second N-methylephedrine system in 1980. Their asymmetric reducing agent, 15, was prepared by combining lithium aluminum hydride with one equivalent of N-methylephedrine and two equivalents of N-ethylaniline in ether at room temperature to reflux (eq 3, X=CH). Reductions performed at -78°C with 1.8 to 3.3 equivalents of reagent resulted in good to very good enantioselectivities with aromatic ketones, and very good to excellent enantioselectivities with acyclic olefinic ketones.
\[
\text{LiAlH}_4 + 13 + 2 \rightleftharpoons [15], \, X=\text{CH} \\
\text{[16], } X=\text{N}
\]

In 1984, Terashima reported a third \( N \)-methylephedrine system 16, prepared and applied similarly to 15, except that 2-ethylaminopyridine was used in place of \( N \)-ethylaniline (eq 3, \( X=N \)).\(^{31}\) This reagent proved especially useful for cyclic enones. With the exception of \( \beta \)-tetralone, the \( N \)-ethylaniline and 2-ethylaminopyridine modified reagents gave opposite carbinol configurations using the same enantiomer of \( N \)-methylephedrine.

\underline{1,1-Diphenylvalinol – Borane}

In 1983, Itsuno and co-workers reported the borane based asymmetric reducing agent 17, prepared by adding two equivalents of borane to one equivalent of 1,1-diphenylvalinol (18) in tetrahydrofuran at \(-78^\circ \text{C}\) and then stirring at \(30^\circ \text{C}\) (eq 4).\(^{32}\) Reductions performed at \(30^\circ \text{C}\) with 1.25 equivalents of reagent gave impressive results with aromatic and dialkyl ketones.\(^{33}\)

\[
\text{[18]} + 2 \text{BH}_3 \rightleftharpoons [17]
\]

The chiral auxiliary, 18, was prepared from valine by esterification followed by reaction with excess phenyl Grignard. Both enantiomers of valine are commercially available. The natural isomer is quite inexpensive, and the unnatural isomer, while nearly twenty times as much, is still only moderately priced. The auxiliary is readily recovered during work up via the hydrochloride salt.

\underline{B-(3-Pinanyl)-9-borabicyclo[3.3.1]nonane}

The reagents discussed above transfer hydride from the metal (aluminum or boron) to the carbonyl carbon. \( B-(3\text{-pinanyl})-9\text{-borabicyclo[3.3.1]nonane} \)
(19), in contrast, transfers hydride from C-2, beta to boron, to the substrate. While it had been known since the 1960's that trialkylboranes can reduce aldehydes at elevated temperature, it was not until Midland combined the attributes of the less hindered 9-borabicyclo[3.3.1]nonane framework and $\beta$-substitution on the third alkyl group that reductions could be performed under mild conditions. Midland used this combination in the asymmetric reducing agent 19, which he reported in 1977.

Midland and co-workers prepared 19 by hydroborating $\alpha$-pinene with 9-BBN in refluxing tetrahydrofuran (eq 5). Both (+)$\alpha$ and (-)$\alpha$-pinene are commercially available, but the inexpensive grades are only 91.3 and 81.3–87% ee respectively. (-)$\alpha$-Pinene of 92% ee can be prepared by isomerizing commercial (-)$\beta$-pinene; and this material, as well as the cheap commercial (+)$\alpha$-pinene, can be purified to 99% ee by a two step procedure. Purified (+)$\alpha$-pinene of 98% ee is now available at a moderate price. Solutions of the preformed boranes made from the unpurified commercial pinenes are also available (Aldrich trade name Alpine–borane).

\[
\begin{align*}
\text{+} & \quad 9\text{-BBN} \\
\ll \longrightarrow \quad \text{B} & \quad \ll
\end{align*}
\]

(5)

19

Midland found that solutions of 19 gave very good to excellent enantioselectivities in the reduction of aldehydes and acetylenic ketones using the enantiomerically pure reagent; correspondingly lower selectivities were found with the impure reagent. More hindered ketones reacted only slowly with solutions of 19, and achiral reduction by 9-BBN (formed by the reverse of eq 5) competed. Brown then made the simple but important contribution of removing the solvent. His group subsequently applied Midland's reagent in neat form to the reduction of dialkyl, olefinic, acetylenic, $\alpha$-halo, and carboalkoxy ketones. Acetylenic and aromatic groups directed differently here, unlike the lithium aluminium hydride based reagents 11 and 14 above.

The neat reagent is more reactive and more selective, presumably by favoring bimolecular reduction and by driving the equilibrium of eq 5 to

18
the right. Midland then found that these effects can be intensified by running the reaction at extremely high pressure. Neat 19 prepared from commercial α-pinene and run at atmospheric pressure is a very practical reagent for acetylenic ketones as documented in a 0.285 mole scale Organic Syntheses preparation. Reductions performed between 0°C and room temperature with 1.4 equivalents of reagent often gave useful levels of induction. Other ketones required long reaction times, but also yielded useful levels of induction in many cases. The reagent prepared from purified α-pinene is still reasonably practical, especially considering that the α-pinene can be easily recovered.

Survey of Asymmetric Reductions According to Substrates

Aldehydes

Since the asymmetric reduction of aldehydes competes R versus H in the transition state, they should give, a priori, greater induction than ketones, which must compete two different kinds of R groups. This has not been found to be a general phenomenon, however, probably because aldehydes have not been studied as much as ketones. The asymmetric reduction of an aldehyde, of course, requires isotopic labeling at either the aldehydic or hydridic proton. Both techniques have proved successful (Table II).

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>n</th>
<th>11</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>n-Pr</td>
<td>1</td>
<td>—</td>
<td>83&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2.</td>
<td>tert-Bu</td>
<td>1</td>
<td>—</td>
<td>70&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3.</td>
<td>Ph</td>
<td>1</td>
<td>—</td>
<td>70&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4.</td>
<td>&quot;</td>
<td>2</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>5.</td>
<td>&quot;</td>
<td>1</td>
<td>—</td>
<td>58&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6.</td>
<td>&quot;</td>
<td>2</td>
<td>84</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup> 93% ee α-pinene was used.  <sup>b</sup> 87-90% labled 9-BBN-9-d was used.
Noyori reduced benzaldehyde-1-d and several 1-deuterated olefinic aldehydes with BINAL-H (11) and obtained 72-88% ee. Midland applied B-(3-pinanyl)-9-BBN (19) in labeled form (made from 9-BBN-9-d) to the reduction of various unlabeled aldehydes. Although the inductions he observed (listed) were not extremely high, after correcting for the optical purity of the α-pinene and the isotopic purity of the 9-BBN-9-d used, they correspond to excellent values. The unlabeled, optically pure reagent gave quantitative asymmetric induction with benzaldehyde-1-d (entry 4).

Saturated Dialkyl Ketones

Saturated dialkyl ketones have proven much more difficult to asymmetrically reduce than their unsaturated aromatic, olefinic, and acetylenic counterparts (Table III). Of the reagents discussed above, Itsuno’s amino alcohol - borane system, 17, gave the best results, yielding good induction even with the tertiary alkyl ketone 3,3-dimethyl-2-butanone (entry 5). Midland’s reagent, 19, gave quite high induction with 3-methyl-2-butanone (entry 4), although extremely high pressure was required.

Table III. Asymmetric Reduction of Dialkyl Ketones, RC=OR’ (% ee)

<table>
<thead>
<tr>
<th>R</th>
<th>R’</th>
<th>17</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Et</td>
<td>—</td>
<td>40a</td>
<td>76</td>
<td>4</td>
<td>5b</td>
</tr>
<tr>
<td>Me</td>
<td>n-Hex</td>
<td>58</td>
<td>44-58a,c</td>
<td>79</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Me</td>
<td>iso-Bu</td>
<td>61</td>
<td>—</td>
<td>30</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Me</td>
<td>iso-Pr</td>
<td>60</td>
<td>57-83a,c</td>
<td>68</td>
<td>32</td>
<td>4b</td>
</tr>
<tr>
<td>Me</td>
<td>tert-Bu</td>
<td>78d</td>
<td>1</td>
<td>2</td>
<td>95</td>
<td>8b</td>
</tr>
<tr>
<td>CH2Br</td>
<td>iso-Pr</td>
<td>—</td>
<td>66</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Et</td>
<td>iso-Pr</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>46b</td>
</tr>
</tbody>
</table>

a 92% ee α-pinene was used. b 83% ee α-pinene was used. c The higher figure was obtained at 6000 atm. d Reaction at 0°C.

A second reagent developed by Midland, 20, works very well for the less hindered members of this group (entries 1, 2). The reagent was prepared from nopol benzyl ether by hydroborating with 9-BBN (THF, reflux) to give
the borane 23, followed by reduction with tert-butyllithium (−78°C) to give
the ate complex 20 (eq 6). Ketone reductions were performed at −100°C with
1.2 equivalents of reagent. Cheap commercial (−)-nopol (ca. 94% ee) was
resolved to higher enantiomeric purity in order to obtain the results
listed. The intermediate borane, 23, has a similar structure to
\[ \text{B-(3-pinanyl)-9-BBN (19)} \] and has accordingly been used for acetylenic
ketone reductions (vide infra). Preformed solutions of the borane 23 and
boronate 20 prepared from (−)-nopol of ca. 94% ee are commercially
available (Aldrich trade names NB-Enantrane and NB-Enantride,
respectively).

\[ \text{OBzI} \quad \rightarrow \quad \text{OBzI} \quad \text{OBzI} \quad \text{OBzI} \]

\[ \text{9-BBN} \quad \text{tert-BuLi} \quad \text{tert-BuLi} \quad \text{tert-BuLi} \]

\[ \text{23} \quad \text{20} \quad \text{20} \quad \text{20} \]

Brown recently reported a chloroborane reducing agent, diisopinocam-
phey1chloroborane (21), prepared by the reaction of diisopinocamphey1-
borane (\( \text{Ipc}_2\text{BH} \)) with dry hydrogen chloride.\(^4\) Since \( \text{Ipc}_2\text{BH} \) can be prepared
in 99% ee from the commercial grades of pinene (via a crystallization), 21
is readily available in high optical purity. It reduced 3,3-dimethyl-2-
butanone at room temperature with 95% ee (entry 5), the best indution
reported for a tertiary alkyl ketone. The other reductions with this
reagent were conducted at −25°C.

In contrast to the results obtained for the methyl ketones in entries
1–5, primary alkyl ketones have yielded limited success. Two isolated
cases are given in entries 6 and 7 for reagents 19 and 22, respectively.
Reagent 22 was prepared from \( \text{Ipc}_2\text{BH} \) and methyllithium, and reacted at 0°C
to room temperature (2.6 equivalents).\(^4\) The case of primary alkyl—
tertiary alkyl ketones is even more limited; no reasonable ee’s have been
reported to date.
Alkyl–Aryl Ketones

Alkyl-ary1 ketones have received a great deal of attention and a great
deal of progress has been made, especially for the less hindered phenyl
ketones (Table IV). Acetophenone (entry 1) can be reduced with nearly
quantitative asymmetric induction using Midland’s reagent (19) at high
pressure, or, more practically with somewhat lower ee, using the Brown
(21), Itsuno (17), or Vigneron (14) reagents. The Noyori (11),
Itsuno, and Brown reagents all gave excellent induction with primary alkyl
phenyl ketones (entry 2), the latter two being more suitable for large
scale operation.

Table IV. Asymmetric Reduction of Alkyl-Aryl Ketones, RC=QAr (% ee)

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>Ar</th>
<th>11</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>19</th>
<th>21</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Me</td>
<td>Ph</td>
<td>95</td>
<td>84</td>
<td>84-88</td>
<td>54</td>
<td>94</td>
<td>98.4</td>
<td>98</td>
<td>51</td>
</tr>
<tr>
<td>2.</td>
<td>1° alkyl</td>
<td>Ph</td>
<td>98-100</td>
<td>78-89</td>
<td>80-90</td>
<td>—</td>
<td>94-100</td>
<td>—</td>
<td>98</td>
<td>68</td>
</tr>
<tr>
<td>3.</td>
<td>iso–Pr</td>
<td>Ph</td>
<td>71</td>
<td>17</td>
<td>78</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>77</td>
</tr>
<tr>
<td>4.</td>
<td>tert–Bu</td>
<td>Ph</td>
<td>44</td>
<td>31</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>79</td>
<td>86</td>
</tr>
<tr>
<td>5.</td>
<td>α–tetralone</td>
<td>74</td>
<td>57</td>
<td>51</td>
<td>96</td>
<td>—</td>
<td>82</td>
<td>82</td>
<td>—</td>
<td>88</td>
</tr>
</tbody>
</table>

a 88% ee was obtained at -100°C. b 98.5% ee α-pinene was used. c Reaction
at 6000 atm. d 92% ee α-pinene was used.

The more hindered secondary and tertiary alkyl phenyl ketones cannot be
reduced as selectively. Terashima’s N-methylephedrine – N-ethylaniline
system, 15, gave the best result with iso–propyl phenyl ketone (entry 3),
and reagent 24 gave the best result with tert–butyl phenyl ketone (entry
4). The latter reagent was prepared from lithium aluminum hydride and
diamino alcohol 25 in tetrahydrofuran (eq 7), 25 having been derived from aspartic acid in several steps. Three equivalents of 24 were used at -100°C for the results listed.

\[
\text{LiAlH}_4 + \text{HO-} \text{NHPh} \xrightarrow{\text{[24]}} \text{NHMe}
\]

25

α-Tetralone (entry 5) is another special case. Terashima's N-methylephedrine - 2-ethylaminopyridine system, 16, is the most selective here. 31

Olefinic Ketones

Many types of olefinic ketones can now be reduced with excellent enantioselectivity (Table V). Three reagents stand out: Terashima's reagent with N-ethylaniline, 15, is best for methyl enones (entries 1-4); 30 Noyori's BINAL-H, 11, is best for n-alkyl enones (entry 5); 23 and Terashima's reagent with 2-ethylaminopyridine, 16, is best for cyclic enones (entries 6-8). 31

Table V. Asymmetric Reduction of Olefinic Ketones, RC=OR' (% ee)

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>11 (%)</th>
<th>15 (%)</th>
<th>16 (%)</th>
<th>19 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>79-100</td>
<td>88</td>
<td>—</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>—</td>
<td>98</td>
<td>34</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>—</td>
<td>78</td>
<td>—</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>—</td>
<td>&gt;90</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>n-Pent</td>
<td>91-97</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>o-Cymene</td>
<td>—</td>
<td>45</td>
<td>98</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>o-Cymene</td>
<td>—</td>
<td>58</td>
<td>96</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>o-Cymene</td>
<td>—</td>
<td>34</td>
<td>90</td>
<td>—</td>
</tr>
</tbody>
</table>

a 92% ee α-pinene was used. b Reaction at 6000 atm.
Acetylenic Ketones

Like aromatic ketones, acetylenic ketones have received considerable attention (Table VI). They tend to be more useful than the aromatic substrates due to the further transformations available to the triple bond.

Table VI. Asymmetric Reduction of Acetylenic Ketones,

RC=OC=CR’ (% ee)

<table>
<thead>
<tr>
<th>R</th>
<th>R’</th>
<th>11^a</th>
<th>14</th>
<th>19</th>
<th>23</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>H</td>
<td>---</td>
<td>79</td>
<td>73^b</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>R</td>
<td>84</td>
<td>---</td>
<td>71--92^b</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>1º alkyl</td>
<td>H</td>
<td>84-96</td>
<td>75-86</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Me, 1º</td>
<td>90</td>
<td>---</td>
<td>77-78^c</td>
<td>91-94</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>CO2Et</td>
<td>---</td>
<td>---</td>
<td>85-88^b</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>iso-Bu</td>
<td>H</td>
<td>---</td>
<td>88</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Me</td>
<td>---</td>
<td>88</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>iso-Pr</td>
<td>H</td>
<td>57</td>
<td>86</td>
<td>91^b</td>
<td>---</td>
</tr>
<tr>
<td>9</td>
<td>c-Hex</td>
<td>n-Pent</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>tert-Bu</td>
<td>H</td>
<td>---</td>
<td>90</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>R</td>
<td>---</td>
<td>---</td>
<td>92^b,d</td>
<td>---</td>
</tr>
<tr>
<td>12</td>
<td>Th</td>
<td>R</td>
<td>---</td>
<td>89-92^c</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>CO2Et</td>
<td>---</td>
<td>98</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

^a Methanol was used in place of ethanol in the reagent. ^b 92% α-pinene was used. ^c Different substrates, the latter was with 92% ee α-pinene. ^d Reaction at 6000 atm.

As mentioned above, B–(3-pinanyl)–9–BBN (19) is a useful reagent for acetylenic ketones. The nopol benzyl ether derived borane, 23, (see eq 6), works similarly. Commercial nopol (ca. 94% ee, further resolved for the results listed) led to carbinol configurations opposite those from the (+)-α-pinene derived borane. BINAL–H (11) was ineffective for 4-methyl-1–pentyln–3–one (entry 8), but secondary alkyl groups were accommodated by the boranes 19 and 23, in addition to Vigneron’s reagent 14 (entries 8, 9). Tertiary alkyl ketones reacted with 19 only under high pressure (entry 11), but they were effectively asymmetrically reduced by
14 and 26 (entries 10, 11). Reagent 26, like 14, was prepared from lithium aluminium hydride and a homochiral amino alcohol (eq 8). Reductions were performed in ether at -78°C with 1.1 equivalents of reagent. The R-selective auxiliary, (+)-Darvon alcohol 27, is commercially available at a moderate price.

\[
\text{LiAlH}_4 + 2.3 \quad \text{Me}_2\text{N} \quad \text{Ph} \quad \rightarrow \quad [26] \quad (8)
\]

27

Entries 12 and 13 are significant because both of the ketonic substituents are unsaturated. The ability of B-(3-pinanyl)-9-BBN (19) to asymmetrically reduce these substrates is consistent with the opposite directing effects of acetylenic and aryl groups with this reagent.
RESULTS AND DISCUSSION

3. Preparation of \( \text{three-} N,N'-\text{Bis(} \alpha\text{-methylbenzyl}) \text{sulfamide} \)

Condensation of \((S)\)-\(\alpha\)-methylbenzylamine with sulfuryl chloride cleanly produced \((S,S)\)-sulfamide 3 in 89% yield after recrystallization (eq 9). A 0.5 mole scale was easily accommodated. The \((R,R)\)-sulfamide was similarly obtained from \((R)\)-\(\alpha\)-methylbenzylamine in 87% yield. Dichloromethane proved a superior solvent to petroleum ether, which had been used in previous \(N,N'\)-dialkylsulfamide preparations,\(^{51}\) in that the reaction mixture remained stirrable and higher yields were obtained.

\[
\begin{align*}
2 \quad & \quad \begin{array}{c}
\text{H}_2\text{N} \\
\text{Me}
\end{array} \quad \text{Ph} \\
\text{Me} \\
\text{H}_2\text{N} \quad \begin{array}{c}
\text{Ph}
\end{array}
\quad \text{SO}_2\text{Cl}_2
\quad \frac{2 \quad \text{NET}_3}{\text{CH}_2\text{Cl}_2, \ -78^\circ\text{C}} \\
\text{SO}_2\left(\text{NH} \quad \begin{array}{c}
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Ph}
\end{array} \right)_2
\end{align*}
\]

\((S,S)-3\)

4. Asymmetric Reductions Employing \(\text{three-} N,N'-\text{Bis(} \alpha\text{-methylbenzyl}) \text{sulfamide} \)

with Lithium Aluminum Hydride and Additives

Treatment of lithium aluminum hydride with one equivalent of sulfamide 3 at 0°C and one equivalent of \(N\)-benzylmethylamine at room temperature in tetrahydrofuran produced a reagent effective in the asymmetric reduction of prochiral ketones (eq. 10). The optimum achiral additive (\(N\)-benzylmethylamine) and reduction temperature (-20°C) were determined empirically. Preliminary studies with acetophenone at a low temperature (-98°C) showed that lithium aluminium hydride with the sulfamide alone gave poor induction (28% ee \((S)\) with \((R,R)-3\)). Addition of one equivalent of ethanol to the reagent (in analogy to Noyori’s BINAL-H, \textit{vide supra}) increased the induction to 75% ee \((S)\). However, this system failed with \(n\)-butyl 2-naphthyl ketone, giving only 23% ee \((S)\).
Secondary amines were explored as alternatives to ethanol (Table VII). (Achiral amine additives had been used in Terashima’s N-methylephedrine systems, vide supra.) n-Butyl 2-naphthyl ketone was employed as a model substrate due to ready measurement of the resulting enantiomeric excess by Pirkle’s chiral stationary phase HPLC. Reductions were started at low temperature (−100 or −78°C) and warmed to between −55 and 25°C over an extended reaction time (12 to 76 h).

Table VII. Optimization of Secondary Amine Additive

<table>
<thead>
<tr>
<th>entry</th>
<th>HNRR'</th>
<th>conversion</th>
<th>ee (confign)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>diethylamine</td>
<td>88%</td>
<td>60% (R)</td>
</tr>
<tr>
<td>2.</td>
<td>diisopropylamine</td>
<td>94%</td>
<td>36% (R)</td>
</tr>
<tr>
<td>3.</td>
<td>pyrroldidine</td>
<td>48%</td>
<td>87% (R)</td>
</tr>
<tr>
<td>4.</td>
<td>piperidine</td>
<td>74%</td>
<td>79% (R)</td>
</tr>
<tr>
<td>5.</td>
<td>morpholine</td>
<td>23%</td>
<td>45% (R)</td>
</tr>
<tr>
<td>6.</td>
<td>HNMe(CH₂)₂NMMe₂</td>
<td>80%</td>
<td>77% (R)</td>
</tr>
<tr>
<td>7.</td>
<td>HNMe(CH₂)₃NMMe₂</td>
<td>56%</td>
<td>81% (R)</td>
</tr>
<tr>
<td>8.</td>
<td>(S)-HNMeCHMePhe</td>
<td>81%</td>
<td>66% (R)</td>
</tr>
<tr>
<td>9.</td>
<td>(R)-HNMeCHMePhe</td>
<td>94%</td>
<td>81% (R)</td>
</tr>
<tr>
<td>10.</td>
<td>HNMeDec</td>
<td>76%</td>
<td>85% (R)</td>
</tr>
<tr>
<td>11.</td>
<td>HNMeBn</td>
<td>76%</td>
<td>89% (R)</td>
</tr>
</tbody>
</table>
The sense of induction [(R)-alcohol with (S,S)-3] remained constant, but the extent of conversion and the enantiomeric excess varied with the structure of the amine additive. Changing the steric requirements of simple symmetric secondary amines (entries 1-4) gave results ranging from low induction with high conversion (entry 2) to high induction with low conversion (entry 3). Other heteroatoms that might offer binding sites to lithium or aluminum (entries 5-7) had either small or detrimental effects. Chirality had a significant effect (entries 8-9); still, only 81% ee was obtained in the "matched" case. Simple secondary methyl amines produced the best results; first with N-decylmethylamine (entry 10), and then with N-benzylmethylamine (entry 11). Commercially available N-benzylmethylamine provided the best induction with good conversion and was thus employed in subsequent studies.

The use of amines may result in the formation of alane type species via the alane extraction mechanism of Ashby. Ashby showed that the addition of diethylamine to an ether solution of lithium aluminum hydride resulted in hydrogen evolution and an immediate white precipitate identified as Li₃AlH₆. He proposed the mechanism shown in Scheme I. Preparation of the sulfamide-based reagent with diethylamine in ether (cf. Table VII entry 1 in THF) gave a copious white precipitate. Reaction with n-butyl 2-naphthyl ketone then gave 44% ee (R).

\[ \text{Scheme I. Ashby's Alane Extraction Mechanism} \]

\[
\begin{align*}
\text{LiAlH}_4 + \text{HNET}_2 & \rightarrow [\text{LiH}] + [\text{Et}_2N\cdot\text{AlH}_3] \\
\downarrow 1/2 \text{LiAlH}_4 & \quad \downarrow -\text{H}_2 \\
\text{V} & \quad \text{V} \\
1/2 \text{Li}_3\text{AlH}_6 & \quad [\text{Et}_2\text{NAlH}_2] \\
\downarrow \text{LiAlH}_4 & \\
\text{V} & \\
\text{LiAl}_{2}H_{6}\cdot\text{NET}_{2} & 
\end{align*}
\]
Facile measurement of enantiomeric excess by HPLC allowed monitoring the reactions in Table VII as they proceeded. Interestingly, the enantiomeric excess increased as a function of conversion in the cases studied (entries 4, 6-11). With N-benzylmethylamine as the additive, aliquots showed 71% ee at 2.1 h, 83% ee at 21 h, 89% ee at 47 h, and 88% ee at 63 h (eq 11). (Note that in this case and in subsequent reactions, the sulfamide was added to the lithium aluminum hydride before the amine. This change in the order of addition relative to the reactions in Table VII simplified the reagent preparation, but did not affect the reduction.)

\[
4 \text{LiAlH}_4 + 4 (\text{R,R})-3 + 4 \text{HNMeBn} \rightarrow \text{[reduction]} \rightarrow -100 \text{ to } -55^\circ\text{C}
\]

Graphically, this increase in ee is best represented by plotting the mole percent of each of the alcohol enantiomers relative to the total amount of alcohol plus ketone (Figure 1). From \(t_0\) to the first aliquot, a significant amount of both the (S)- and (R)-alcohols formed. Beyond the first aliquot, the (S)-alcohol continued to form, but the amount of the (R)-alcohol remained about constant. This suggested that reaction occurred initially with a nonselective species followed by a highly selective species.\(^{54}\)

To test this hypothesis, the reagent was first treated with a "sacrificial" ketone in the hope of consuming a nonselective species before adding a second ketone. Two chemically similar but chromatographically different ketones were chosen: ethyl 2-naphthyl ketone and n-nonyl 2-naphthyl ketone. The two ketones and four corresponding alcohols (counting enantiomers) all separated on a Pirkle column. Ethyl 2-naphthyl ketone was added first, followed by n-nonyl 2-naphthyl ketone after 1.3 h (Figure 2). The first ketone reacted similarly to n-butyl 2-naphthyl ketone in Figure 1. The second ketone also reacted in this fashion, yielding a significant amount of the corresponding (S)- and (R)-alcohols during its first hour of contact with the reacting mixture. During this same period, the first ketone yielded some of its (S)-alcohol, but none of
Figure 1. Asymmetric Reduction of n-Butyl 2-Naphthyl Ketone as a Function of Time (eq 11)

Figure 2. Competitive Asymmetric Reduction of Ethyl 2-Naphthyl Ketone and n-Nonyl 2-Naphthyl Ketone
its (R)-alcohol. Thus, the first ketone did not serve the purpose of eliminating a nonselective species. Adding the nonyl ketone first, or waiting 21 h before adding the second ketone, gave the same result.

It appears that the initial nonselective reaction occurred not as the result of a nonselective species in the reaction mixture (which would have also reacted with the first ketone), but due to the environment incurred during the process of addition to the reagent. Neither slow addition of the precooled ketone solution, nor addition of the reagent to the ketone, improved the enantiomeric excess.

Although the phenomenon of the increasing ee’s could not be harnessed to give a more selective reagent, two points became evident from the preceding study. Firstly, the reaction temperatures were too low and the reaction times too long for the ready availability of the sulfamide to have much meaning. Secondly, selective reaction was apparently available at warmer temperatures. Reaction at -20°C was thus tried, and n-butyl 2-naphthyl ketone gave 87% ee with 82% conversion (80% isolated yield) after only 1 hour. Due to the operational simplicity of these conditions with only a slight loss in selectivity, -20°C was chosen for subsequent reactions with other substrates (Table VIII).

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>reaction time</th>
<th>isolated yield</th>
<th>ee (config)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>n-butyl 2-naphthyl ketone</td>
<td>1 h</td>
<td>80%</td>
<td>87% (R)</td>
</tr>
<tr>
<td>2.</td>
<td>acetophenone</td>
<td>1 h</td>
<td>50%</td>
<td>81% (R)</td>
</tr>
<tr>
<td>3.</td>
<td>9-anthryl trifluoromethyl ketone</td>
<td>18 h</td>
<td>97%</td>
<td>55% (S)</td>
</tr>
<tr>
<td>4.</td>
<td>2-octanone</td>
<td>1 h</td>
<td>57%</td>
<td>29% (R)</td>
</tr>
<tr>
<td>5.</td>
<td>cyclohexyl methyl ketone</td>
<td>1 h</td>
<td>71%</td>
<td>71% (R)</td>
</tr>
<tr>
<td>6.</td>
<td>1-adamantyl methyl ketone</td>
<td>18 h</td>
<td>85%</td>
<td>48% (R)</td>
</tr>
<tr>
<td>7.</td>
<td>n-butyl cyclohexyl ketone</td>
<td>18 h</td>
<td>97%</td>
<td>9% (R)</td>
</tr>
<tr>
<td>8.</td>
<td>n-butyl tert-butyl ketone</td>
<td>21 h</td>
<td>99%</td>
<td>1% (R)</td>
</tr>
</tbody>
</table>

Table VIII. Asymmetric Reductions Employing (S,S)-3 According to eq 10
Table VIII reveals that although aryl-alkyl ketones were reduced with greater selectivity (entries 1-3), fully saturated dialkyl ketones could also be asymmetrically reduced. Systems with this capability have only been found recently (vide supra), and the reduction of cyclohexyl methyl ketone with 71% ee (entry 5) compares favorably with known methods for the reduction of secondary alkyl-methyl ketones (Table III), especially considering that sulfamide 3 is very readily available in both enantiomeric forms, and that extremely low temperatures or high pressures are not required.

As a result of this work, (R,R)- and (S,S)-3 are now commercially available from Aldrich.
PART III. 3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine
1. Applications of $C_2$ Symmetric Chiral Secondary Amines in Asymmetric Synthesis

In 1977, Whitesell evaluated Yamada's asymmetric alkylation of proline ester derived chiral enamines with typically 10-30\% ee and at best 55\% ee as follows:\textsuperscript{55}

"... These results, taken together, are consistent with the participation of two sets of transition states differing by geometrical isomerization (represented by A and B). Of the four transition states resulting from the distinct pathways of approach of the alkylation agent (back and front on both A and B), the carboxyl moiety would be expected to exert a significant steric interaction in only one (back on B). Assuming nearly equivalent energies for the three remaining transition states leads to the prediction that induction in this system would be limited to an enantiomeric excess of around 2 : 1 (34\% ee). Clearly what is needed is an amine with a $C_2$ axis of symmetry."

An amine with a $C_2$ axis did indeed lead to greater selectivity. Alkylation of enamine 28, derived from trans-2,5-dimethylpyrrolidine, followed by hydrolysis gave (S)-2-substituted cyclohexanones with 82-93\% ee.\textsuperscript{55}

In 1980, Whitesell used another $C_2$ symmetric amine, threeo-N-(α-methylbenzyl)-α'-methylbenzylamine. He applied the corresponding lithium amide, 29, for the enantioselective deprotonation of cyclohexene oxide.\textsuperscript{56} The rearrangement product, (R)-2-cyclohexen-1-ol, was obtained with 31\% ee. Although low, this was the best induction he obtained from a series of lithium amides.
Katsuki recently reported the functionalized chiral pyrrolidine derivatives trans-2,5-bis(methoxymethyl)- and trans-2,5-bis(methoxy- methoxymethyl)pyrrolidine. He found that the corresponding amides, 30, could be metallated and alkylated\textsuperscript{57} or acylated\textsuperscript{58} with high diastereoselectivity (\textgreek{95}%).

Additionally, Cram and Mazaleyrat have applied the dihydroazepine moiety in chiral auxiliaries (see Section I-2).

2. Asymmetric Michael Reactions

The asymmetric Michael reaction has recently been reviewed\textsuperscript{59}. Various scenarios have been studied, including chiral nucleophiles, chiral Michael acceptors, and chiral ligands. The addition of chiral nucleophiles to prochiral acceptors pertains to subsequent discussion, and Scheme II summarizes the more selective members of this category. In each case, the chiral auxiliary was cleaved after diastereoselective addition, thus giving a synthon to the enantioselective addition of a simpler unit.

In the presence of base, oxazepine 31 (derived from \textgreek{l}-ephedrine) added to cyclic enones and 1-nitrocyclohexene with 44-75\% de. Acidic cleavage of the chiral auxiliary yielded enantiomerically enriched 2-substituted acetic acids.\textsuperscript{60,61} As the corresponding copper azaenolate, imine 32 (derived from the artificial amino acid \textgreek{t}-leucine) added to cyclic enones with 44-75\% de. Hydrolytic cleavage of the chiral auxiliary yielded enantiomerically enriched substituted acetones.\textsuperscript{62} Enamine 33 (derived from proline) added to \textgreek{\beta}-aryl \textgreek{\alpha},\textgreek{\beta}-unsaturated esters yielding, after hydrolysis, 2-substituted cyclohexanones of \textgreek{>90}\% de and \textgreek{>80}\% ee.\textsuperscript{63} And, after lithiation,
hydrazones of structure 34 added to α,β-unsaturated esters with 96-100% de. Oxidative cleavage of the chiral auxiliary yielded enantiomerically enriched substituted methyl ketones. 64

Scheme II. Chiral Michael Donors

31

32

33

34
RESULTS AND DISCUSSION

3. Synthesis and Resolution of
3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine

Retrosynthetically, 3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine (4) implies the simple annulation showed in eq 12. 2,2'-Bis(bromomethyl)-1,1'-binaphthyl (35), known in both racemic and homochiral forms, was chosen as the alkylation agent. Attempted direct annulation of 35 with ammonia gave a complex mixture. Consequently, 2,2,2-trifluoroacetamide (36) was tried as an ammonia synthon. Treatment of (±)-35 with one equivalent of 36 and two equivalents of sodium hydride in dimethylformamide at room temperature for 2.5 h gave amide (±)-37 in 59% yield (eq 13). Facile hydrolysis of (±)-37 with sodium carbonate in aqueous methanol (room temperature, 17 h) then gave (±)-4 in 99% yield. Although the monoalkylation of N-substituted trifluoroacetamides followed by hydrolysis is known, annotation by the bisalkylation of the unsubstituted amide 36 (e.g. 35 to 37 to 4) is new.

\[
\begin{align*}
\text{N} & \quad \rightarrow \quad \text{N} + \text{H}_2\text{NY} \\
(4) & \quad \rightarrow \quad (±)-37
\end{align*}
\]

\[
\begin{align*}
\text{CF}_2\text{CONH}_2 \quad (36) & \quad \xrightarrow{\text{CF}_3\text{CONH}_2} \quad \text{CF}_3\text{CON}\text{CF}_3 \\
(±)-35 & \quad \xrightarrow{2 \text{ NaH, DMF}} \quad (±)-37 & \quad \xrightarrow{\text{Na}_2\text{CO}_3, \text{MeOH/H}_2\text{O}} \quad (±)-4
\end{align*}
\]
Resolution of 4 was accomplished by a single crystallization of the dibenzoyltartrate salt from methanol (eq 14). The homochiral free base from the dibenzoyl-L-tartrate salt, \((\text{S})-4\) (100% ee based on chiral stationary phase HPLC analysis of the corresponding 1-naphthamide\(^7^0\)) was then obtained in 45% yield (90% of theory) from the racemate. The absolute configuration of \((\text{S})-4\) was assigned by comparing its optical rotation with the recently published literature value.\(^1^1\)

\[
\begin{align*}
(\pm)-4 & \xrightarrow{1) \text{ OBz OBz}} \text{HO}_2\text{C} & \begin{array}{c}
\text{CO}_2\text{H}
\end{array} \\
2) \text{NaOH} & \rightarrow (\text{S})-4
\end{align*}
\]

Since both enantiomers of dibenzoyltartaric acid monohydrate are commercially available (Aldrich), \((\text{R})-4\) should be readily isolable from the free base of the mother liquor from the first crystallization. The overall yield of \((\text{S})-4\) from \((\pm)-35\) (26% = 53% of theory) compares favorably with the yields of Mazaleyrat's recently described syntheses of \((\text{S})-4\) (21% = 41% of theory) and \((\text{R})-4\) (15% = 30% of theory) from \((\pm)-35\) via the diastereomers 38 and 39 (Scheme III).\(^1^1\)
Scheme III. Mazaleyrat's Synthesis

(±)-35

1) 2.1
2 TEA, PhH/CH₃CN
Δ, 10 h
2) recrystallization

Ph

H₂N

CONH₂

38 (38%)

39 (23%)

1) Xs POCl₃
DMF, 0-25°C
(94%)
(94%)
2) 10 AgNO₃
THF/H₂O
(59%)
(69%)

(S)-4

(R)-4

V

V
4. Asymmetric Michael Reactions of
3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine with Methyl Crotonate

Diastereoselective Michael additions were first examined thermally with the free amine 4. Methyl crotonate was chosen as a model substrate in order to simplify NMR analysis. Treatment of (±)-4 with a large excess of methyl crotonate at reflux for 21 h gave amino ester (±)-40 as a 3.5 : 1 mixture of diastereomers (55% de) in 68% yield (eq 15).

\[
\begin{align*}
(±)-4 & \xrightarrow{100^\circ \Delta} \text{(15)} \\
(±)-40, 55\% \text{ de}
\end{align*}
\]

The diastereomer ratio was evident from both \textsuperscript{1}H NMR and HPLC analysis. The diastereomers did not separate on silica gel, but the diastereomers (but not the enantiomers) did separate on Pirkle's chiral stationary phase column. Other facile diastereomer separations on this support have been described.\textsuperscript{71} The relative stereochemistry in the adduct was correlated as discussed below.

HPLC analysis of aliquots from an identical reaction showed that the ratio of diastereomers started at 4.1 : 1 and decreased until leveling off at 1.0 : 1 (Figure 3). This behavior is consistent with an initial kinetically controlled addition (4.1 : 1), followed by equilibration to the thermodynamic product (1.0 : 1). Diastereoselective formation of the kinetic product is reasonable considering that the analogous reaction between piperidine and acrylic esters is known to be second order with direct attack of the amine on the β-carbon of the α,β-unsaturated ester as the rate-determining step;\textsuperscript{72} and that the new carbon-nitrogen bond in the analogous reaction between ammonia and mesityl oxide is approximately half-formed in the transition state.\textsuperscript{73} Equilibration of the diastereomers may have occurred by reversible addition,\textsuperscript{72} or by flipping of the binaphthyl configuration.\textsuperscript{74}
Diastereoselective Michael addition to methyl crotonate was next examined with the lithium amide of 4. Michael addition of lithium amides to $\alpha,\beta$-unsaturated esters had precedent in Schlessinger's addition of lithium diisopropyl amide to ethyl crotonate in nearly quantitative yield (tetrahydrofuran, 10 min at $-78^\circ$C). $\gamma$-Deprotonation in this system only occurred in the presence of HMPA.75

For the case at hand, treatment of a tetrahydrofuran solution of four equivalents of (+)-4 at ca. $-78^\circ$C with a precooled tetrahydrofuran/hexane solution of four equivalents n-butyllithium generated a dark solution, which, after 25 min, was treated with a precooled tetrahydrofuran solution of one equivalent of methyl crotonate (eq 16). After 30 min at ca. $-78^\circ$C, quenching and work-up yielded the amino ester (+)-41 with a 94 : 1 ratio of diastereomers (98% de) in 88% yield. An excess of 42 was required. Use of two and one equivalents reduced the yield to 41% and 15%, respectively; and addition of the lithium amide solution to an excess of methyl crotonate gave only a 15% yield.
Similar treatment of (S)-4 gave 41 with a 61:1 ratio of diastereomers (97% de) in 81% yield (eq 16). High selectivity with both the racemic and homochiral modifications of 42 is consistent with primary control of the diastereoselectivity by the chirality of the incoming nucleophile, as opposed to other more complicated scenarios involving aggregated molecules of lithium amide.

The face selectivities of the thermal (4.1:1 favoring α-approach) and lithium amide (61-94:1 favoring β-approach) Michael additions correspond to diastereomeric transition state energy differences of 1.1 and 1.6 - 1.8 kcal/mol at their respective temperatures of 120 and -78°C. These are approaching energy differences which can be discerned by examining molecular models (e.g. the A-value of a methyl group is 1.7 kcal/mol\(^76\)). Furthermore, the rigidity and symmetry of the incoming nucleophile limit the number of transition states which must be considered such that the principal remaining variable is the conformation about the new carbon-nitrogen bond. Even so, examination of CPK models did not provide a definitive explanation of these face selectivities or the reversal thereof.

The relative stereochemistry in 40 and 41 was correlated by converting the thermal Michael adduct (±)-40 (3.5:1) to amino ether (±)-43 by standard chemistry, and comparing with 44, prepared by coupling the homochiral fragments (S)-45 and (S)-4 (Scheme IV). The displacement of a secondary tosylate by a secondary amine with inversion (cf. 45 to 44) had precedent in the steroid literature.\(^77\) Reaction of tosylate (S)-45 with (±)-4 gave a 1:1 ratio of diastereomers, dispelling the notion that diastereomer 44 could have been formed via the selective alkylation of thermally racemized amine. The alkylation conditions (dimethylformamide, high concentration) were indeed chosen to minimize this complication. The
minor diastereomer of (±)-43 was found to correspond to 44 by $^1$H NMR and HPLC analysis. Therefore, the relative stereochemistry in the major diastereomer of 40 is as shown above.

Since the binaphthyl moiety is attached to adducts 40 and 41 by benzylic carbon-nitrogen bonds, it should be removable by reductive techniques. Accordingly, diastereoselective addition of homochiral 42 to a Michael acceptor, followed by reductive cleavage, should correspond to the enantioselective addition of an asymmetric ammonia synthon.

Scheme IV. Correlation of Relative Stereochemistry

(a) 2 LiAlH$_4$, THF, 0°C, 30 min, 86%; (b) 6 CCl$_3$Ph$_3$, 55% DMAP, TEA/CH$_2$Cl$_2$, room temperature, 53 h, 74%; (c) $^{80}$ 1.1 CCl$_3$Ph$_3$, 4% DMAP, TEA/CH$_2$Cl$_2$, room temperature, 13 h, 93%; (d) 2 TsCl, 5% DMAP, py, room temperature, 43 h, 75%; (e) 2 (S)-4, DMF, 86°C, 2 h, 45%.
PART IV. *threo*-α,α′-*Di-tert*-butyl-2,6-pyridinedimethanol and Related Pyridinediols
**HISTORICAL**

1. **Asymmetric Epoxidation of Allylic Alcohols**

   Early work in this field was abruptly overshadowed by Sharpless' 1980 disclosure of the asymmetric epoxidation of allylic alcohols by alkyl hydroperoxides on titanium–tartrate catalysts (eq 17).\(^{81}\) This reaction is distinguished by the combined qualities of high enantioselectivity, substrate generality, predictable face selection, and practical application on a large scale. Since it has recently been reviewed in detail,\(^{82,83}\) it will be described only briefly here.

\[
\text{R''} \text{R'''} \text{OH} \xrightarrow{\text{Ti(OiPr)}_4} \text{R''} \text{O} \text{R'''} \text{OH} \quad \text{(17)}
\]

(typically 70–90%, \(>90\% \text{ ee}\))

In the currently held mechanism,\(^{82}\) the dialkyl tartrate chiral auxiliary and the titanium(IV) isopropoxide precatalyst associate \textit{in situ} generating a dimeric complex,\(^{46}\) which, by the exchange of the remaining monodentate alkoxides for the allylic alcohol and alkyl hydroperoxide, serves as a template for asymmetric epoxidation. Accordingly, transition state\(^{47}\), with a meridional arrangement of the allylic alcohol and bidentate alkyl hydroperoxide, spiro orientation of the olefin and peroxide, and wrapping of the allylic alcohol away from the diagonal quadrants blocked by the ester groups, leads to the favored epoxide enantiomer.

Amazingly, this system, in which the substrate, product, oxidant, and reduced form of the oxidant all belong to the same basic ligand family as the chiral auxiliary (ROH), works on a catalytic level (5%) without simply washing off the chiral auxiliary. By contrast, in the exceedingly catalytic (ca. 0.1%) asymmetric hydrogenation,\(^{84}\) the chiral auxiliary
(diphosphine), substrate (enamide), product (amide), and reducing agent (H₂) are all different types of ligands and not expected to indiscriminately exchange with one another.

![Chemical Structures](image)

46

47

(meridional-spiro)

2. Asymmetric Epoxidation of Isolated Olefins

Lacking a binding site to enhance reactivity and offer rigidity, isolated olefins have eluded the levels of asymmetric induction achieved in the epoxidation of allylic alcohols. Only two systems have been reported which give >50% ee; both employ chiral iron-porphyrin catalysts with iodosylarene oxidants. 85,86
3. Diastereoselective Epoxidation of Secondary Allylic Alcohols

The epoxidation of a secondary allylic alcohol can give one or both of two possible diastereomeric products which differ in the relative stereochemistry between the alcohol and oxirane. Different classes of allylic alcohols and different classes of reagents can favor a particular (erythro or three) diastereomer. Known results for a model substrate, (E)-1-cyclohexyl-2-butene-1-ol, are shown in Scheme V.

**Scheme V**

![Scheme V Diagram]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Erythro/threo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti(OiPr)$_4$</td>
<td>TBHP$^{88}$</td>
<td>38:62</td>
</tr>
<tr>
<td>&quot;</td>
<td>Ph$_3$COOH$^{89}$</td>
<td>17:83</td>
</tr>
<tr>
<td>Ti-DIPT</td>
<td>TBHP$^{88}$</td>
<td>98: 2 (fast reacting enantiomer)</td>
</tr>
<tr>
<td>&quot;</td>
<td>TBHP$^{88}$</td>
<td>38:62 (slow reacting enantiomer)</td>
</tr>
<tr>
<td>VO(acac)$_2$</td>
<td>TBHP$^{88}$</td>
<td>80:20</td>
</tr>
<tr>
<td>Zr(OiPr)$_4$·HOiPr</td>
<td>TBHP$^{89}$</td>
<td>37:63</td>
</tr>
</tbody>
</table>
RESULTS AND DISCUSSION

4. Synthesis of *threo*-α,α'-Di-tert-buty-2,6-pyridinedimethanol and Related Pyridinediols. Resolution of *threo*-α,α'-Di-tert-buty-2,6-pyridinedimethanol

Two routes were initially envisioned to pyridinediols of the general structure 48: reaction of 2,6-pyridinedicarboboxaldehyde with two equivalents of an R⁻ synthon, and reaction of a 2,6-pyridinedianion synthon with two equivalents of the requisite aldehyde (eq 18). Although the addition of alkyllithiums and Grignard reagents to pyridine monoaldehydes and ketones is well-precedented, reaction of 2,6-pyridinedicarboxaldehyde with tert-butyllithium and tert-butylmagnesiumchloride under a variety of conditions yielded only small amounts of the desired bis-adduct. Thus the second route was pursued.

Two 2,6-pyridinedianion synths were studied: Martin’s procedure for the in situ lithiation and trapping of pyridine-N-oxide, and the reiterative bromine-lithium exchange and trapping of 2,6-dibromopyridine. Martin’s procedure is only amenable with non-enolizable aldehydes; and pivalaldehyde was found to work best. A mixture of anhydrous pyridine-N-oxide and an excess of pivalaldehyde in tetrahydrofuran at -78°C was treated with a slight excess of lithium tetramethylpiperide (eq 19). Work-up with dilute acid and flash chromatography yielded the pure *threo* and meso N-oxides 49 and 50 (in addition to a mixture of 49 and 50, 10%). Relative stereochemistry not yet assigned, the two N-oxide isomers were separately reduced with an excess of neat molten triphenylphosphine. The
products were separated from the required large excess of phosphine by extraction into aqueous acid followed by treatment with base. At this point, the racemic three pyridine isomer 5 was distinguished from the meso pyridine isomer 51 by the presence of two (enantiomeric) peaks on Pirkle chiral stationary phase HPLC. 52

\[
\text{N}^+ \text{O}^- + 4 \text{CHO} \xrightarrow{2.5 \text{ LiTMP}, \text{THF, } -78^\circ \text{C}} \text{OH}^+ \text{N}^+ \text{O}^- \text{OH} + \text{OH}^+ \text{N}^+ \text{O}^- \text{OH} (19)
\]

\[
(\pm)-49 \ (16\%) \quad 50 \ (9\%)
\]

\[
10 \text{ PPh}_3 \quad 220^\circ \text{C} \quad \text{V} \quad 10 \text{ PPh}_3 \quad 220^\circ \text{C} \quad \text{V}
\]

\[
(\pm)-5 \ (89\%) \quad 51 \ (85\%)
\]

Alternatively, 2,6-dibromopyridine was metalated with \(n\)-butyllithium. 2,6-Dilithiopyridine and the corresponding bis-Grignard are known to be available from 2,6-dibromopyridine by reaction with \(n\)-butyllithium (tetrahydrofuran, -90°C)\(^{94}\) and magnesium metal (ether, reflux),\(^{95}\) respectively; but the electrophilic trapping agents described in these papers gave only low to moderate yields. Monolithiation (ether, -60 to -40°C) and trapping, in contrast, is known to proceed in good yield.\(^{96}\) For the case at hand, 2,6-dibromopyridine was monolithiated and trapped twice in a one pot reaction (eq 20). A slurry of 2,6-dibromopyridine in tetrahydrofuran at -78°C was treated successively with \(n\)-butyllithium (producing homogeneity), pivalaldehyde, \(n\)-butyllithium, and a slight excess of pivaldehyde. The three and meso isomers 5 and 51, produced in roughly
equal amounts, were readily separated by flash chromatography. The meso isomer, however, was contaminated by an impurity of similar mobility and solubility. This procedure is compatible with enolizable trapping agents, and accordingly, the three-diisopropyl and achiral tetraethyl analogs 52 and 53 were prepared.

\[
\begin{align*}
1) & \text{n-BuLi, THF, } -78^\circ C \\
2) & \text{RCOR'} \\
3) & \text{n-BuLi} \\
4) & \text{1.3 RCOR'} \\
\end{align*}
\]

\[(\pm)-5, R=\text{ttert}-\text{Bu}, R'=\text{H} \ (35\%) \\
(\pm)-52, R=\text{iso}-\text{Pr}, R'=\text{H} \ (21\%) \\
53, R=R'=\text{Et} \ (37\%)
\]

Of the two syntheses, the one pot halogen-metal exchange procedure is preferred for 5. The yield of the purified three isomer is modest but tolerable considering that the starting materials are readily available, and two carbon–carbon bonds are formed. The main scale limitation is the need for chromatography.

three-\(\alpha,\alpha'-\text{Di-tert-butyl-2,6-pyridinedimethanol}\) (5) presents two structural handles for resolution: the basic nitrogen offers the possibility of classical resolution with a homochiral acid;\(^97\) and the alkyl-aryl carbinol substitution offers the possibility of separation by Pirkle chiral stationary phase HPLC.\(^52\) Both of these methods were explored.

Resolution of 5 by HPLC, while analytically viable (vide supra), was limited preparatively by the low enantiomeric separability factor (\(\alpha = 1.08\)).\(^98\) Increased separability (\(\alpha = 1.19\)) was achieved by acetylation (eq 21).\(^99\) Scale with commercial columns was still limited, but usable quantities of 54 were separated. In agreement with Ziffer's observations, the diol and diacetate enantiomers eluted in opposite orders.\(^99\) The absolute configuration of 5 was tentatively assigned according to Pirkle's chiral recognition model to be (R,R)-(+) as shown. This was later confirmed by X-ray crystallography (vide infra).
Classical resolution was accomplished by multiple recrystallizations of the dibenzoyltartrate salt (eq 22). Progress of the resolution was followed by analytical chiral HPLC of base treated samples. Other acids (tartaric, and 10-camphorsulfonic) were less effective. This resolution was applicable on a larger scale than the preparative chiral HPLC, but the HPLC more rapidly provided small quantities of resolved material for initial testing.
5. Dioxomolybdenum(VI)-Substituted 2,6-Pyridinedimethanol Complexes: Synthesis and Characterization of New Five-coordinate Species

three-α,α'-Di-tert-butyl-2,6-pyridinedimethanol (5) and the related pyridinedimethanols 51, 52, and 53 described in the previous section were studied principally as complexes of molybdenum(VI) and titanium(IV) with the aim of developing selective oxidation catalysts. The molybdenum complexes were also structurally pertinent in the context of current interest in dioxomolybdenum(VI) complexes with sterically bulky ligands as molybdoenzyme models.100,101

Dioxomolybdenum(VI) complexes were prepared from the corresponding pyridinediols by reaction with MoO$_2$(acac)$_2$ in dichloromethane followed by removal of volatiles in vacuo and recrystallization from dichloromethane/ether (eq 23). The complexes were stable to manipulation in air, and mobile on thin layer (10% ethyl acetate in dichloromethane).

\[
\begin{align*}
\text{R} & \quad \text{OH} \\
\text{N} & \quad \text{OH} \\
\text{R} & \quad \text{OH}
\end{align*}
\quad \overset{\text{CH}_2\text{Cl}_2}{\longrightarrow}
\quad \begin{bmatrix}
\text{R} & \text{O} \\
\text{O} & \text{Mo} \\
\text{O} & \text{R}
\end{bmatrix}_n
\]

(±)-5 \quad (±)-55, \text{R}=\text{tert-Bu} (64\%)
(+)5 \quad (-)-55, \text{R}=\text{tert-Bu} (88\%)
51 \quad \text{meso} 56, \text{R}=\text{tert-Bu} (83\%)
(±)-52 \quad (±)-57, \text{R}=\text{iso-Pr} (64\%)

Pertinent spectroscopic data are given in Table IX. The solid state IR (KBr) shows a similarity between the racemic tert-Bu and racemic iso-Pr complexes, (±)-55 and (±)-57, with Holm's unsubstituted complex 56.102 The homochiral tert-Bu and meso tert-Bu complexes, (-)-55 and 56, in contrast, do not show the band near 850 cm$^{-1}$. The solution state IR's, taken in bromoform due to its transparency in the $\nu_{\text{MO}}$ region, are the same for the substituted complexes, each lacking the band near 850 cm$^{-1}$. Similar solution state behavior among the substituted complexes is also seen in the $^1$H NMR (CDCl$_3$). The pyridyl and carbynol resonances are shifted downfield relative to the free ligands. The molecular weight of the homochiral
tert-Bu complex (-)-55, measured in dichloromethane by the Signer method, indicated it to be monomeric in solution.

Table IX. Selected Spectroscopic Data for Dioxo Mo(VI) Complexes

<table>
<thead>
<tr>
<th>R</th>
<th>solid</th>
<th>solution</th>
<th>NMR (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tert-Bu</td>
<td>909, 850</td>
<td>---</td>
<td>4-H</td>
</tr>
<tr>
<td>(+)-55</td>
<td>943, 918</td>
<td>8.10</td>
<td>7.57</td>
</tr>
<tr>
<td>(-)-55</td>
<td>943, 918</td>
<td>8.09</td>
<td>7.56</td>
</tr>
<tr>
<td>tert-Bu</td>
<td>940, 914</td>
<td>8.07</td>
<td>7.50</td>
</tr>
<tr>
<td>(+)-57</td>
<td>943, 919</td>
<td>8.14</td>
<td>7.43</td>
</tr>
</tbody>
</table>

Crystals of the homochiral tert-Bu complex (-)-55 suitable for x-ray crystallography were grown by slow evaporation of a dichloromethane solution. Crystallography revealed two discrete mononuclear species of similar structure within the unit cell, (-)-55a and (-)-55b (Figure 4). Selected bond distances and angles are shown in Table X. The molybdenums are five-coordinate with distorted trigonal bipyramidal geometry; the nitrogen and oxo ligands are equatorial and the alkoxides are axial. The absolute configuration of (-)-55 was determined by anomalous dispersion and found to agree with the configuration of (+)-5 predicted by Pirkle’s model (vide supra).
Figure 4. Geometry of the two independent molecules of (-)-55 showing the atomic labeling scheme and 30% probability thermal ellipsoids. Hydrogen atoms are not shown.
Table X. Selected Bond Distances (Å) and Angles (deg)

<table>
<thead>
<tr>
<th></th>
<th>(-)-55a</th>
<th>(-)-55b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mo1-N11</td>
<td>2.163 (5)</td>
<td>Mo2-N21</td>
</tr>
<tr>
<td>Mo1-O11</td>
<td>1.898 (4)</td>
<td>Mo2-O21</td>
</tr>
<tr>
<td>Mo1-O12</td>
<td>1.919 (4)</td>
<td>Mo2-O22</td>
</tr>
<tr>
<td>Mo1-O13</td>
<td>1.696 (4)</td>
<td>Mo2-O23</td>
</tr>
<tr>
<td>Mo1-O14</td>
<td>1.698 (4)</td>
<td>Mo2-O24</td>
</tr>
<tr>
<td>O13-Mo1-O14</td>
<td>109.7 (3)</td>
<td>O23-Mo2-O24</td>
</tr>
<tr>
<td>O13-Mo1-N11</td>
<td>130.5 (3)</td>
<td>O23-Mo2-N21</td>
</tr>
<tr>
<td>O12-Mo1-O13</td>
<td>97.2 (2)</td>
<td>O22-Mo2-O23</td>
</tr>
<tr>
<td>O12-Mo1-N11</td>
<td>72.1 (2)</td>
<td>O22-Mo2-N21</td>
</tr>
<tr>
<td>O12-Mo1-O11</td>
<td>144.8 (2)</td>
<td>O22-Mo2-O21</td>
</tr>
</tbody>
</table>

Dioxomolybdenum(VI) complexes are generally six-coordinate. For MoO₂ (tridentate) complexes, the sixth ligand can be a donor such as DMSO, or a bridging oxo as in 58. The first example of a five-coordinate dioxo Mo(VI) complex was Holm’s pyridinedithiol complex, 59. Complex (-)-55 is the second example of this structural type, the first bis-alkoxide.

![58](image)

![59](image)

The coordination geometries of (-)-55 and 59 are similar. The Mo-Ooxo bond lengths in (-)-55a and (-)-55b (average 1.698 Å) are essentially the same as found in 59 (average 1.694 Å). The O-Mo-O angles in (-)-55a and (-)-55b (average 109.8°) are slightly smaller than in 59 (110.5°). The diolate O-Mo-O angles in (-)-55a and (-)-55b (average 144.9°) are the same as the corresponding O-Mo-O angle in 58 (145.0°) but smaller than the analogous S-Mo-S angle in 59 (156.4°).
The solid state structure of (-)-55 is probably preserved in the solution state since it is also monomeric. The solution IR $\nu_{\text{MoO}}$ bands at 943 and 918 cm$^{-1}$ can thus be correlated with the five-coordinate structure of (-)-55. Accordingly, (±)-55, 56, and (±)-57 must also be five-coordinate in solution. The solid state IR of the meso complex 56 is similar to that of (-)-55 and 59 (59: 950, 915 cm$^{-1}$, mull$^{100a}$), implying that it is also five-coordinate as a solid. The low $\nu_{\text{MoO}}$ bands in the solid state IR's of the racemic complexes (±)-55 and (±)-57 imply that they, like 58, are polymeric in the solid state.$^{102}$ These assignments are summarized in Table XI.

**Table XI. Aggregation States of Dioxo Mo(VI) Complexes**

<table>
<thead>
<tr>
<th></th>
<th>solid</th>
<th>solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-55</td>
<td>polymer</td>
<td>monomer</td>
</tr>
<tr>
<td>(-)-55</td>
<td>monomer</td>
<td>monomer</td>
</tr>
<tr>
<td>56</td>
<td>monomer</td>
<td>monomer</td>
</tr>
<tr>
<td>(±)-57</td>
<td>polymer</td>
<td>monomer</td>
</tr>
</tbody>
</table>

Thus the tendency of these Mo(VI) dioxo pyridinediol complexes to become six-coordinate by polymerizing is subtly dependent on the stereochemistry of the ligands: two like enantiomers of 55 will not associate, but 55 will associate with its mirror image to form the racemic polymer.
6. Dioxomolybdenum(VI)–Substituted 2,6-Pyridinedimethanol Complexes: Catalysis of Epoxidation with Hydrogen Peroxide and TBHP

The dioxomolybdenum(VI) complexes discussed in the previous section were studied as catalysts for the epoxidation of isolated olefins with hydrogen peroxide, and allylic alcohols with TBHP,\(^{106}\) with the goal of developing an enantioselective process.

Treatment of the di-tert-butyl dioxo complex \((\pm)-55\), with an excess of 90% hydrogen peroxide in tetrahydrofuran at room temperature produced a homogeneous yellow solution which, by thin layer \((N,N,N',N'-\text{tetramethyl-1,4-phenylenediamine spray})^{107}\), contained a peroxide in place of the starting complex (eq 24). Removal of volatiles gave a yellow solid which resisted purification by chromatography or recrystallization. The color and IR \((\nu_{O=O} = 896 \text{ cm}^{-1})^{108}\) of the crude material were consistent with a molybdenum peroxo complex. Structure \(60 \ (L = H_2O \ or \ H_2O_2)\), analogous to the known dipicolinate complex,\(^{109}\) was the anticipated product. The NMR, however, implied an unsymmetrical structure, such as \(61\), analogous to the known picolinate complex.\(^{109}\)

\[
\begin{align*}
\text{[} & \text{Mo} \quad \text{Mo} \text{]}_n \\
\text{O-Mo-O} & \\
\downarrow & \\
\text{O-Mo-O} & \\
\end{align*}
\]

\[40 \text{ H}_2\text{O}_2 \quad \text{THF} \]

\[
\text{[} & \text{Mo} \quad \text{Mo} \text{]}_n \\
\text{O-Mo-O} & \\
\downarrow & \\
\text{O-Mo-O} & \\
\end{align*}
\]

\(\pm-55\)

\[
\begin{align*}
\text{[} & \text{Mo} \quad \text{Mo} \text{]}_n \\
\text{O-Mo-O} & \\
\downarrow & \\
\text{O-Mo-O} & \\
\end{align*}
\]

\[60\]

\[
\begin{align*}
\text{[} & \text{Mo} \quad \text{Mo} \text{]}_n \\
\text{O-Mo-O} & \\
\downarrow & \\
\text{O-Mo-O} & \\
\end{align*}
\]

\[61\]

\(\delta 8.10 \ (t, 1H) \quad \delta 8.02 \ (t, 1H)\)

\(7.57 \ (d, 2H) \quad 7.76 \ (d, 1H), 7.59 \ (d, 1H)\)

\(5.70 \ (s, 2H) \quad 5.94 \ (s, 1H), 5.80 \ (s, 1H)\)

\(1.07 \ (s, 18H) \quad 1.21 \ (s, 9H), 1.19 \ (s, 9H)\)

Repeating the reaction of \((\pm)-55\) with hydrogen peroxide in the presence of a trisubstituted olefin, 2-methyl-2-tetradecene \((62)\),\(^{110}\) gave the same bright yellow solution (eq 25). The olefin, however, did not show any signs of epoxidation.
Epoxidation did occur in a two phase system. Exposure of 2-methyl-2-tetradecene to 10% (±)-55 and ten equivalents hydrogen peroxide in dichloromethane/water at room temperature resulted in the near complete conversion of the olefin to the corresponding epoxide with a small amount of the cleavage product, dodecyl aldehyde (eq 26). During the reaction, the organic phase took on the yellow color characteristic of molybdenum peroxo complexes, but, before a significant amount of epoxide had formed, the color faded and the aqueous phase became yellow. Examination of the yellow organic phase from a similar reaction run without the olefin showed by NMR the same complex observed in tetrahydrofuran above, in addition to unreacted dioxo complex and a small amount of the free pyridinediol.

A control reaction with ammonium molybdate, \((NH_4)_6Mo_7O_{24} \cdot 4H_2O\), in place of (±)-55 gave yellow color only in the aqueous phase and no epoxidation (eq 27). Repeating this reaction with the addition of one equivalent of the di-tert-butyl pyridinediol, (±)-5, per molybdenum (eq 28) did not bring color to the organic phase, but significant epoxidation did take place, albeit slower than in eq 26. The pyridinediol ligand is thus involved in the epoxidation process.
When eq 26 was repeated with the homochiral complex (-)-55, the isolated epoxide displayed a small rotation, but was less than 5% ee by shift reagent analysis (eq 29). Since the pyridinediol is involved in the epoxidation but does not impart significant asymmetric induction, it may be acting as a phase transfer catalyst. Phase transfer catalysis in epoxidations has been observed in a tungstic hydrogen peroxide system.\textsuperscript{112}

\[
62 + 10\% (-)-55 \xrightarrow{10 \text{ H}_2\text{O}_2} \overset{\text{H}_2\text{O/CH}_2\text{Cl}_2}{\text{O}} 10 (75\%, <5\% \text{ ee})
\]

Failing to achieve asymmetric induction with hydrogen peroxide, TBHP was tried as the oxidant. Treatment of an allylic alcohol, (E)-\(\alpha\)-phenyl-cinnamyl alcohol, with a full equivalent of (-)-55 and three equivalents of TBHP in dichloromethane at room temperature gave the corresponding epoxide (eq 30). Epoxidation was slower than expected based on known reactions using molybdenum hexacarbonyl as a precatalyst.\textsuperscript{87} Use of a less hindered complex (the diisopropyl dioxo complex (\(\pm\))-57) or of a less hindered allylic alcohol (trans-2-hexen-1-ol) did not improve reactivity.

The epoxylcohol obtained after 111 h showed little or no enantiomeric excess. The lack of induction coupled with the slowness of the reaction suggest that the pyridinediol complexes are not active, and that epoxidation occurred on a molybdenum species freed of the pyridinediol ligand by TBHP or \textit{tert}-butanol.

\[
\text{Ph} \begin{array}{c} \text{Ph} \\ \text{OH} \end{array} + (-)-55 + 3 \text{ TBHP} \xrightarrow{\text{CH}_2\text{Cl}_2} \text{Ph} \begin{array}{c} \text{Ph} \\ \text{O} \\ \text{OH} \end{array} (68\%, 1\% \text{ ee})
\]
7. Titanium(IV)-Substituted 2,6-Pyridinedimethanol Complexes: Enantioselective and Diastereoselective Epoxidations with Alkyl Hydroperoxides

Unable to achieve enantioselective epoxidation with the molybdenum(VI) systems discussed in the previous section, titanium(IV) systems were explored. Titanium(IV) complexes were prepared in situ by mixing the appropriate pyridinediol ligand with titanium(IV) isopropoxide. Equimolar quantities of the racemic di-tert-butyl pyridinediol 5 and titanium(IV) isopropoxide combined in chloroform-d for 7 min at room temperature gave an NMR spectrum consistent with the symmetric complex 63, plus two equivalents of displaced isopropanol (eq 31). Removal of volatiles from the same reaction performed in dichloromethane gave a white solid which displayed the same NMR spectrum minus the free isopropanol. This material was found to be monomeric in dichloromethane by the Signer method ([Ti] = 108 mM at equilibrium).\(^{103,113}\)

\[
\begin{array}{c}
\text{OH} & \text{OH} \\
& &
\end{array}
\xrightarrow{\text{CDCl}_3} \quad
\begin{array}{c}
\text{OH} & \text{OH} \\
& &
\end{array}
\]

(\pm)-5 \quad \text{Ti(OiPr)}_4 \quad + \quad 2 \text{OiPrOH} \quad (31)

\[
\begin{array}{c}
\text{OH} & \text{OH} \\
& &
\end{array}
\xrightarrow{\text{CDCl}_3} \quad
\begin{array}{c}
\text{OH} & \text{OH} \\
& &
\end{array}
\]

(\pm)-63

\begin{tabular}{ll}
$\delta$ 7.61 (t, 1H) & $\delta$ 7.75 (t, 1H) \\
7.13 (d, 2H) & 7.34 (d, 2H) \\
4.37 (d, 2H) & 5.30 (s, 2H) \\
3.73 (d, 2H) & \\
& 4.82 (sept, 2H) \\
& 1.30 (d, 6H) \\
& 1.20 (d, 6H) \\
0.92 (s, 18H) & 0.96 (s, 18H)
\end{tabular}

Exposure of (E)-\(\alpha\)-phenylcinnamyl alcohol to a mixture of the homochiral pyridinediol (\(+\))-5, titanium(IV) isopropoxide, and TBHP in dichloromethane at -5°C for 2.6 to 4.5 h gave the corresponding epoxide in high yield, and 40-41% ee favoring the 2-S enantiomer (eq 32). The enantiomeric excess was independent of the ligand to titanium ratio (x).
from $x = 1.25$ to 2.00.

\[
\begin{align*}
\text{(+)-5} \quad & x \quad \text{OH} \quad \text{N} \quad \text{OH} \quad \text{OH} \quad \text{+ Ti(OiPr)}_4 \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{OH} \\
\text{CH}_2\text{Cl}_2 \quad -5^\circ\text{C} \quad & 3 \quad \text{TBHP} \\
\rightarrow & \quad \text{Ph} \quad \text{Ph} \quad \text{OH} \\
\end{align*}
\]

$x = 1.25$: 93%, 41% ee  
$x = 1.50$: 75%, 40% ee  
$x = 2.00$: 100%, 41% ee

Setting $x$ at 1.50, but switching to trityl hydroperoxide in place of TBHP, gave the corresponding epoxide in high yield, and 52-64% ee, this time favoring the 2-$R$ enantiomer (eq 33). Varying the concentration did not significantly affect the enantioselectivity. The higher value, 64% ee, was obtained at $[\text{Ti}] = 13$ mM (the same concentration as for eq 32), and at one fifth this concentration, $[\text{Ti}] = 3$ mM. Increasing the concentration five fold to $[\text{Ti}] = 65$ mM produced a cloudy reaction mixture and a small decrease in the ee to 52%.

\[
\begin{align*}
1.5 \quad (+)-5 \quad \text{+ Ti(OiPr)}_4 \quad \text{Ph} \quad \text{Ph} \quad \text{Ph} \quad \text{OH} \\
\text{CH}_2\text{Cl}_2 \quad -5^\circ\text{C} \quad & 3 \quad \text{Ph}_3\text{COOH} \\
\rightarrow & \quad \text{Ph} \quad \text{Ph} \quad \text{OH} \\
\end{align*}
\]

$[\text{Ti}] = 3$ mM: 86%, 64% ee  
$[\text{Ti}] = 13$ mM: 90%, 64% ee  
$[\text{Ti}] = 65$ mM: 86%, 52% ee

This system, and in situ generated complexes of the other pyridinediols, were next examined with a secondary allylic alcohol, $\text{(E)}$-1-cyclohexyl-2-butene-1-ol, \textsuperscript{88} in order to explore diastereoselectivity and kinetic resolution (Scheme VI). Epoxidations were conducted as above, maintaining a ligand to titanium ratio of 1.5 and $[\text{Ti}] = 13$ mM. The number of equivalents of oxidant (TBHP or trityl hydroperoxide), $y$, was decreased for
Scheme VI

1.5 L + Ti(OiPr)$_4$ + (±) $\xrightarrow{y \ R_3COOH}$ erythро

$\xrightarrow{CH_2Cl_2}$

$\xrightarrow{-5^\circ C}$ threeо

<table>
<thead>
<tr>
<th></th>
<th>$R = \text{Me}$</th>
<th>$R = \text{Ph}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$Y$</td>
<td>E/T</td>
</tr>
<tr>
<td>(±)-5</td>
<td>0.6</td>
<td>50:50</td>
</tr>
<tr>
<td>(+)-5</td>
<td>0.7</td>
<td>54:46</td>
</tr>
<tr>
<td>51</td>
<td>3</td>
<td>74:26</td>
</tr>
<tr>
<td>53</td>
<td>3</td>
<td>80:20</td>
</tr>
</tbody>
</table>
the kinetic resolutions and parallel reactions with (±)-5. The erythro/threo ratios did not qualitatively vary with conversion according to TLC. The highest diastereoselectivity obtained here (E/T = 80:20 with 53) equals that obtained with this substrate and vanadium(V), \(^{88}\) a reagent known for its erythro selectivity. \(^{87}\)

The product distributions of the preceding titanium catalyzed epoxidations of (E)-α-phenylcinnamyl alcohol and (E)-1-cyclohexyl-2-butene-1-ol necessitate the involvement of the pyridinediols ligands in the epoxidation before or during the rate-determining step, since they differ from the control reaction with free titanium(IV) isopropoxide (0% ee; and E/T = 38:62 with TBHP and 17:83 with trityl hydroperoxide, vide supra). The most reasonable form of involvement is by binding to titanium during the rate-determining oxygen transfer step. \(^{82}\) The most reasonable form of binding to titanium is tridentate and meridional, analogous to the crystal structure of the dioxomolybdenum complex (−)-55.

The NMR and molecular weight determination discussed above support this mode of binding in the ground state for (±)-63. Homochiral 63 must also be monomeric since no new intermolecular interactions are introduced. The consistency of the enantiomeric excess with the concentration in eq 33 supports this notion that dimers or higher order species are not involved. Complexes of the other pyridinediols, 51 and 53, are very likely also monomeric considering that titanium(IV) isopropoxide itself is principally monomeric, \(^{114}\) and that these bulky ligands have displayed the ability to render the MoO₂ unit monomeric in solution (vide supra).

The consistency of the enantiomeric excess upon variation of the ligand to titanium ratio in eq 32 suggests that the tridentate ligand is strongly bound, such that reaction from unbound (achiral) titanium species does not compete. Interestingly, use of two equivalents of (±)-5 did not slow down the reaction significantly, implying that the binding constant for a second equivalent of (±)-5 (which would block sites for epoxidation) is small. Models indicate that this should be the case with the homochiral ligand since the tert-butyl groups point together in a 2:1 complex. (This scenario is in contrast to vanadium(V) catalyzed asymmetric epoxidations with chiral hydroxamate ligands in which sufficient chiral ligand to maximize asymmetric induction stifled the rate of epoxidation. \(^{115}\)

Accordingly, the rigid 2,6-pyridinedimethanol substructure provides a
framework which can be substituted to block various parts of the coordination sphere: opposite (diagonal) quadrants with 5, one side of the meridional plane with 51, and the back of each quadrant with 53. The blocking of opposite quadrants with 5 in 63 invites analogy with the titanium-tartrate system discussed above.

Figure 5 shows a comparison between the crystal structure of the dimeric tartramide complex 64 used as a model for mechanistic proposals for the titanium-tartrate system,82 and a hypothetical octahedral three-di-tert-butyl pyridinediol complex, 65. The absolute configurations shown correspond to natural tartrate for 64, and (−)-5 for 65 (opposite the configuration used above). Each structure contains a meridional plane defined by a tridentate ligand. In 64, this "ligand" contains the two tartramides and the other (equivalent) titanium. This arrangement is analogous to the alkoxide-donor-alkoxide arrangement of 65 if the bridging oxygens in 64 are considered as a donor in the rear, and an alkoxide on the right (in reality, they are both intermediate between these extremes). Furthermore, both ligands sterically congest diagonal quadrants of titanium's coordination sphere.

![Figure 5](image)

If 65 loads its three remaining coordination sites with the allylic alcohol and the bidentate alkyl hydroperoxide, and then serves as a template for asymmetric epoxidation with the same mechanism as depicted in transition state 47, then this quadrant blocking analogy predicts that (−)-5 should behave like natural tartrate, or, conversely, (+)-5 (used above) should behave like unnatural tartrate. For the epoxidation of
(E)-α-phenylcinnamyl alcohol (eq 32, and 33), this prediction held with trityl hydroperoxide as the oxidant (to the extent of 64% ee), but the opposite configuration was obtained using TBHP as the oxidant (41% ee).

Considering that a compilation of results for the epoxidation of (E)-α-phenylcinnamyl alcohol with titanium(IV), TBHP, and 22 non-tartrate or tartramide chiral ligands showed an average of 10% ee and at best 35% ee, the 41-64% ee obtained here reflect more than a sensitivity of titanium(IV) catalyzed epoxidations to perturbation by chiral ligands. The selectivities obtained here with (E)-α-phenylcinnamyl alcohol and (E)-1-cyclohexyl-2-butene-1-ol, however, correspond to only moderate energy differences (up to ΔG^+ = 0.8 kcal/mol), and are thus difficult to interpret with molecular models. The reversal in face selectivity between epoxidation with TBHP and trityl hydroperoxide, however, deserves comment.

The titanium-tartrate system gives high selectivity with the same face selection with both TBHP and trityl hydroperoxide. Keeping with the quadrant blocking scenario of the mechanism summarized in transition state 47, two changes could account for the reversal in face selection with alkyl hydroperoxide in the pyridinediol system: a facial instead of meridional arrangement of the allylic alcohol and bidentate alkyl hydroperoxide as shown in 66, or a planar instead of spiro orientation of the olefin and peroxide as shown in 67.

Of the two situations, a variation between facial and meridional transition states (47 and 66) should be more dependent on the alkyl group of the alkyl hydroperoxide. A facial transition state for the titanium-
tartrate system was ruled out on steric grounds. A view from above the meridional ligand plane, 68, shows that there is no room in the shaded area for either the olefin or the alkyl group of the alkyl hydroperoxide, one of which must be placed there in a facial transition state. The same view of the analogous pyridinediol system, 69 shows that there is more room to accommodate the olefin and the alkyl group of the alkyl hydroperoxide for a facial transition state. If there is sufficient room for a tert-butyl group but not a trityl group, this would account for the reversal in face selection.
PART V. CONCLUSION

The chemistry detailed in Parts II-IV originated on paper with three structures that appeared promising as chiral auxiliaries. Specific uses for the title compounds became evident as their chemistry was explored.

Part II found a new use for the ubiquitous \( \alpha \)-methyldimethylamine. In comparison with the vast number of asymmetric reducing agents reported in the literature, the system described here gave a competitive result for the reduction of a secondary alkyl ketone. The low temperature asymmetric reductions in Part II and the thermal Michael addition in Part III attest to the value of following reactions as a function of time in order to detect subtle features.

The Michael addition of lithium amide 42 in Part III gives sufficient induction such that reagent-controlled diastereoselection might be possible. Asymmetric carbon-nitrogen bond forming reactions are rare; and the selectivity obtained with methyl crotonate encourages the testing of more substrates with this reagent, and the exploration of conditions for the reductive removal of the auxiliary.

The pyridinediol ligands in Part IV led to novel structural chemistry with molybdenum, and suggested an alkyl hydroperoxide dependent change in the mechanism of epoxidation with titanium. Other metals and other systems should be amenable to these diols.
PART VI. EXPERIMENTAL

General

All reactions were performed under a nitrogen atmosphere in oven dried glassware unless otherwise stated. Cold baths were prepared as follows: 
-100°C to -55°C = Multi-Cool MC-4-130 (FTS Systems, Inc.), -78°C = dry ice/acetone, -20°C = dry ice/carbon tetrachloride, -5°C = Stir Kool SK 12 (Thermoelectronics Unlimited, Inc.), 0°C = ice/water. Tetrahydrofuran was dried by distillation from the sodium benzophenone ketyl. Dichloromethane, dimethylformamide, and pyridine were dried over 3A molecular sieves. Methyl crotonate was distilled and dried over 4A molecular sieves. Bromoform was distilled immediately before use as an IR solvent. Organolithiums were titrated according to Ronald’s procedure. 117

"Flash Chromatography" was performed according to Still’s procedure using 230–400 mesh Silica Gel 60 (EM Reagents). 118 Thin layer chromatography was performed on Silica Gel 60 F–254 0.25 mm pre-coated TLC plates (EM Reagents) and visualized by UV and phosphomolybdic acid. HPLC was conducted with a Perkin-Elmer Series 2 Liquid Chromatograph with a LC-65T UV detector set between 254 and 280 nm.

IR spectra were recorded on a Perkin-Elmer 597 Infrared Spectrophotometer. NMR spectra were recorded on a Bruker WM-250 250 MHz instrument unless otherwise designated as follows: 270 MHz = Bruker WM-270, 300 MHz = Varian XL-300. Optical rotations were measured with a Perkin-Elmer 241 Polarimeter. Elemental analyses were performed by Robertson Laboratory, Inc.
Experimental Section for Part II.

(S,S)-threo-\(_2\)N,N'\(_2\)-Bis(\(\alpha\)-methylbenzyl)sulfamide (3)  
(R,R)-threo-\(_2\)N,N'\(_2\)-Bis(\(\alpha\)-methylbenzyl)sulfamide (3)  
Asymmetric Reduction of \(n\)-Butyl 2-Naphthyl Ketone in the Presence of Secondary Amines  
Asymmetric Reduction of \(n\)-Butyl 2-Naphthyl Ketone as a Function of Time  
Competitive Asymmetric Reduction of Ethyl 2-Naphthyl Ketone and \(n\)-Nonyl 2-Naphthyl Ketone  
Asymmetric Reduction of \(n\)-Butyl 2-Naphthyl Ketone at -20°C  
Asymmetric Reduction of Acetophenone  
Asymmetric Reduction of 9-Anthryl Trifluoromethyl Ketone  
Asymmetric Reduction of 2-Octanone  
Asymmetric Reduction of Cyclohexyl Methyl Ketone  
Asymmetric Reduction of 1-Adamantyl Methyl Ketone  
Asymmetric Reduction of \(n\)-Butyl Cyclohexyl Ketone  
Asymmetric Reduction of \(n\)-Butyl tert-Butyl Ketone
(S,S)-threo-N,N’-Bis(α-methylbenzyl)sulfamide (3)

An oven dried, nitrogen purged, 2-L three-necked flask equipped with a mechanical stirrer and 250 mL addition funnel was cooled in a -78°C bath and charged with 360 mL of dry dichloromethane, 139 mL (101 g, 1.00 mol) of triethylamine (distilled from CaH₂), and 129 mL (121 g, 1.00 mol) of (S)-(-)-α-methylbenzylamine (Hexcel, distilled from CaH₂, [α]D²⁰ -40.5° (neat)). Subsequently, 40.2 mL (67.5 g, 0.500 mol) of sulfuryl chloride (freshly distilled) in 155 mL of dry dichloromethane were added dropwise with rapid stirring over 2 h causing white solids to precipitate. The reaction mixture was stirred at ca. -78°C for 15 min and then allowed to warm to ca. 5°C. Addition of 250 mL of water produced two clear phases: the aqueous phase was washed with dichloromethane (100 mL); and the combined organic phases were washed with water (3 x 250 mL), dried (Na₂SO₄), and filtered through a 1.5 cm pad of Florisil. Concentration afforded 148.3 g of white solid. Two recrystallizations from ether–dichloromethane (3:1)/hexane (equal volume) yielded 135.8 g (89%) of white crystalline solid: mp 98-99°C; [α]D²⁰ -80.1° (c 2.18, ethanol); IR (mull) 3315, 1320 (νSO₂ as), 1150 (νSO₂ s), 975 (νNSN a), 700 cm⁻¹; ¹H NMR (CDCl₃) 7.26-7.12 (m, 10H), 4.48-4.36 (m, 4H), 1.47 (d, J=7.2 Hz, 6H); ¹³C NMR (CDCl₃) 142.65, 128.60, 127.51, 126.07, 50.75, 20.64. Anal. Calcd for C₁₆H₂₀N₂O₂S: C, 63.13; H, 6.62; N, 9.20; S, 10.53. Found: C, 63.30; H, 6.79; N, 9.18; S, 10.80.

(R,R)-threo-N,N’-Bis(α-methylbenzyl)sulfamide (3)

A similar procedure employing (R)-(+)–α-methylbenzylamine on a 97 mmol scale yielded 25.5 g (87%) of white crystalline solid: mp 97.5-98°C; [α]D²⁰ +83.1° (c 1.33, ethanol); IR (mull) 3310, 1320, 1150, 980, 700 cm⁻¹; ¹H NMR (CDCl₃) 7.26-7.12 (m, 10H), 4.42-4.38 (m, 4H), 1.46 (d, J=6.3 Hz, 6H). Anal. Calcd for C₁₆H₂₀N₂O₂S: C, 63.13; H, 6.62; N, 9.20; S, 10.53. Found: C, 63.38; H, 6.66; N, 9.10; S, 10.50.
Asymmetric Reduction of n-Butyl 2-Naphthyl Ketone in the Presence of Secondary Amines

To 1.00 equiv (0.70-1.34 mmol) of powdered LiAlH₄ (transferred under nitrogen) stirred in dry tetrahydrofuran (0.16 M) at ca. 0°C was added via cannula over ca. 1 min. A solution of 1.01 equiv of the amine (see below, distilled and dried over molecular sieves) in dry tetrahydrofuran (0.34 M) causing gentle gas evolution. The ice bath was removed and the reaction mixture was stirred for 20 min. The ice bath was replaced and a solution of 1.01 equiv of (S,S)-3 in dry tetrahydrofuran (0.34 M) was added via cannula over ca. 5 min causing gas evolution. The ice bath was removed and the reaction mixture was stirred for 1.2 h. The resulting cloudy solution was cooled to the reaction temperature (see below) and treated via cannula over ca. 2 min with a solution 0.33 equiv of n-butyl 2-naphthyl ketone in dry tetrahydrofuran (0.11 M) precooled to the reaction temperature.

After the indicated period, a 0.5 mL aliquot was removed by syringe and quickly injected into a stirred mixture of 0.5 mL of 3.6 M H₂SO₄ and 3 mL of ether. The organic phase was separated, dried (MgSO₄), passed through a short plug of silica gel with ether, and analyzed by HPLC (Regis Pirkle Type 1-A, 25 cm x 4.6 mm I.D., two columns in series; 2% isopropanol in hexane, 3 mL/min; retention times: ketone, 4.38 min; S-alcohol, 11.64 min; R-alcohol, 13.24 min). With the exception of the morpholine reaction (which showed minor impurities), only the starting material and product peaks were observed by HPLC. [A solution of 27.6 mg (0.130 mmol) of ketone and 25.2 mg (0.118 mmol) of racemic alcohol gave these peaks with relative areas of 62.54, 18.42, and 18.13 at 276 nm. The conversion = \{(\text{area}_R\text{-alcohol})+(\text{area}_S\text{-alcohol})\}/\{(\text{area}_R\text{-alcohol})+(\text{area}_S\text{-alcohol})+[(\text{area ketone})\times(0.130/62.54)\times(18.42+18.13)/0.118]\}.]

(over)
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<thead>
<tr>
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<td>18 h</td>
<td>94%</td>
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<tr>
<td>pyrrolidine</td>
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<td>89% (R)</td>
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Asymmetric Reduction of n-Butyl 2-Naphthyl Ketone as a Function of Time

To 36.3 mg (0.957 mmol) of powdered LiAlH$_4$ stirred in 6.1 mL of dry tetrahydrofuran at ca. 0°C was added via cannula over ca. 4 min a solution of 291 mg (0.957 mmol) of (R,R)-3 in 2.9 mL of dry tetrahydrofuran causing vigorous gas evolution. The ice bath was removed and the translucent cloudy grey solution was stirred for 15 min. A solution of 123.4 μL (116 mg, 0.957 mmol) of dry N-benzylmethylamine in 2.9 mL of dry tetrahydrofuran was then added via cannula over ca. 1 min causing slow gas evolution. The resulting cloudy grey solution was stirred at room temperature for 1 h, cooled on a -100°C bath, and treated via cannula over ca. 2 min with a solution of 50.8 mg (0.239 mmol) of n-butyl 2-naphthyl ketone in 1.6 mL of dry tetrahydrofuran precooled to ca. -100°C. The reaction mixture was warmed to -78°C at 5 h, to -55°C at 22 h, and to -24°C between 48 h and 63 h. Aliquots were taken at the indicated times (as above). Only starting material and product peaks were observed by HPLC:

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<tr>
<td>2.1 h</td>
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<tr>
<td>63 h</td>
<td>85%</td>
<td>88% (S)</td>
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</table>
Competitive Asymmetric Reduction of Ethyl 2-Naphthyl Ketone and n-Nonyl 2-Naphthyl Ketone

To 1.03 mmol of asymmetric reducing agent prepared as above from (R,R)-3 and cooled on a -78°C bath was added via cannula over ca. 2 min a precoolled solution of 23.8 mg (0.129 mmol) of ethyl 2-naphthyl ketone\textsuperscript{119} in 2.0 mL of dry tetrahydrofuran. After 1.3 h at ca. -78°C, a precoolled solution of 36.4 mg (0.129 mmol) of n-nonyl 2-naphthyl ketone\textsuperscript{119} in 2.5 mL of dry tetrahydrofuran was added via cannula over ca. 2 min. The reaction mixture was warmed to -55°C at 21 h after the first addition. Aliquots were taken at the indicated times (as above) and analyzed by HPLC (Regis Pirkle Type 1-A, 25 cm x 4.6 mm I.D., two columns in series; 2% isopropanol in hexane, 3 mL/min; retention times: nonyl ketone, 4.18 min; ethyl ketone, 5.42 min; (S)-nonyl alcohol, 11.00 min; (R)-nonyl alcohol, 12.52 min; (S)-ethyl alcohol, 14.69 min; (R)-ethyl alcohol, 16.21 min).\textsuperscript{120,122} Only starting material and product peaks were observed by HPLC:

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<th>Nonyl Substrate</th>
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<td></td>
<td>conversion</td>
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<td>1 h</td>
<td>58%</td>
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<tr>
<td>2 h</td>
<td>62%</td>
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<tr>
<td>24 h</td>
<td>75%</td>
<td>68% (S)</td>
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<tr>
<td>45 h</td>
<td>86%</td>
<td>66% (S)</td>
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Asymmetric Reduction of n-Butyl 2-Naphthyl Ketone at -20°C

To 123.4 mg (3.25 mmol) of powdered LiAlH\textsubscript{4} stirred in 20 mL of dry tetrahydrofuran at ca. 0°C was added via cannula over ca. 12 min a solution of 0.990 g (3.25 mmol) of (S,S)-3 in 9 mL of dry tetrahydrofuran causing gas evolution. The ice bath was removed and the cloudy grey solution was stirred for 15 min. A solution of 420 μL (394 mg, 3.25 mmol) of dry N-benzylmethylamine in 9 mL of dry tetrahydrofuran was then added via cannula over ca. 2 min causing mild gas evolution. The resulting cloudy grey solution was stirred at room temperature for 1 h, cooled on a -20°C bath, and treated via cannula over ca. 2 min with a solution of 173 mg
(0.815 mmol) of \( n \)-butyl 2-naphthyl ketone in 5.4 mL of dry tetrahydrofuran precooled to ca. \(-20^\circ\text{C} \). The reaction mixture was stirred at ca. \(-20^\circ\text{C} \) for 1 h and quenched by adding via cannula over ca. 10 min to a stirred ice-cold mixture of 10 mL of ether and 10 mL of 3.6 M \( \text{H}_2\text{SO}_4 \). The resulting cloudy grey aqueous phase was separated and extracted with ether (3 x 15 mL). The clear organic phase was combined with the ether extracts and washed with brine (2 x 15 mL), dried (MgSO\(_4\)), and concentrated to a clear oil. HPLC at this point indicated 87% ee (\( \text{R} \)) and 82% conversion (calculated as above). Trituration in ca. 40 mL of hexane precipitated (\( \text{S}, \text{S} \))-3 (0.939 g = 95% recovery, mp 98–99°C, homogeneous by TLC).

Concentration of the filtrate and flash chromatography (15% ethyl acetate in hexane) yielded 139.8 mg (80%) of white crystalline solid: mp 65.5–66°C, \([\alpha]_D^{20}\) +24.9° (c 1.34, ethanol); IR (mull) 3280, 3060, 862, 830, 750 cm\(^{-1}\), \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.88–7.77 (m, 4H), 7.53–7.46 (m, 3H), 4.85 (td, J=3.4, 6.4 Hz, 1H), 1.92–1.77 (m, 3H), 1.45–1.23 (m, 4H), 0.89 (t, J=7.6 Hz, 3H).

Anal. Calcd for \( \text{C}_{15}\text{H}_{18} \): C, 84.07; H, 8.47. Found: C, 84.12; H, 8.48. HPLC (as above) indicated 87% ee (\( \text{R} \)). Starting material, 31.0 mg (18%), was also isolated from the chromatography.

**Asymmetric Reduction of Acetophenone**

Acetophenone, 105 \( \mu \)L (108 mg, 0.90 mmol, distilled and stored over 4A molecular sieves), was reduced with 3.61 mmol of reagent for 1 h at ca. \(-20^\circ\text{C} \) as above. Flash chromatography (35% ether in pentane) yielded 54.9 mg (50%) of clear oil: \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.37–7.24 (m, 5H), 4.88 (br q, J=6.8 Hz, 1H), 2.02 (br s, 1H), 1.50 (d, J=6.8 Hz, 3H). HPLC of the corresponding acetate (Regis Pirkle Type 1-A, 25 cm x 4.6 mm I.D., two columns in series; 0.25% isopropanol in hexane, 1 mL/min; retention times of racemate 15.42 min (\( \text{R} \)) and 16.32 min (\( \text{S} \))\(^{99} \)) indicated 81% ee (\( \text{R} \)).
Asymmetric Reduction of 9-Anthryl Trifluoromethyl Ketone

9-Anthryl trifluoromethyl ketone, 274 mg (1.00 mmol), was reduced as above with 3.99 mmol of reagent for 18 h at ca. -20°C (the reaction flask was sealed and transferred to a freezer after 1.3 h). Sulfamide precipitation included some of the alcohol product according to TLC, so the precipitate was recombined with the crude product. Flash chromatography (25% ethyl acetate in hexane) yielded 266 mg (97%) of pale yellow solid: mp 117.5-132°C, $^1$H NMR (CDCl$_3$, 270 MHz) δ 8.95 (br s, 1H), 8.55 (s, 1H), 8.15 (br s, 1H), 8.03 (d, J=9.2 Hz, 2H), 7.61-7.46 (m, 4H), 6.67 (qd, J=4.2, 8.8 Hz, 1H), 2.95 (d, J=4.2 Hz, 1H). Anal. Calcd for C$_{16}$H$_{13}$OF$_3$: C, 69.56; H, 4.01; F, 20.63. Found: C, 69.51; H, 4.09; F, 20.39. HPLC (Regis Pirkle Type 1-A, 25 cm x 4.6 mm I.D., two columns in series; 10% isopropanol in hexane, 3 mL/min; retention times of racemate 7.76 min (R) and 9.21 min (S) $^{52}$) indicated 55% ee (S).

Asymmetric Reduction of 2-Octanone

2-Octanone, 172 µL (141 mg, 1.10 mmol, distilled and stored over 4Å molecular sieves), was reduced with 4.41 mmol of reagent for 1 h at ca. -20°C as above. Flash chromatography (30% ether in pentane) yielded 81.4 mg (57%) of clear oil: [α]$^{21}_D$ -2.92° (c 3.77, ethanol) [lit.$^{123,124}$ [α]$^{21}_D$ +10.1° (S)]; $^1$H NMR (CDCl$_3$) δ 3.79 (m, 1H), 1.49-1.34 (m, 11H), 1.19 (d, J=6.9 Hz, 3H), 0.89 (t, J=7.3 Hz, 3H).

Asymmetric Reduction of Cyclohexyl Methyl Ketone

Cyclohexyl methyl ketone, 110 µL (101 mg, 0.80 mmol, distilled and stored over 4Å molecular sieves), was reduced with 3.20 mmol of reagent for 1 h at ca. -20°C as above. Flash chromatography (25% ethyl acetate in hexane) yielded 73 mg (71%) of clear oil: [α]$^{20}_D$ -4° (c 4, ether)$^{124}$; $^1$H NMR (CDCl$_3$) δ 3.54 (quint, J=6.0 Hz, 1H), 1.90-1.60 (m, 6H), 1.33-0.88 (m, 9H). Mosher ester (from (+)-MTPA-Cl) methoxide quartets appeared at 3.560 and 3.535 ppm: 71% ee favoring the upfield signal.
Asymmetric Reduction of 1-Adamantyl Methyl Ketone

1-Adamantyl methyl ketone, 130 mg (0.73 mmol), was reduced with 2.92 mmol of reagent for 18 h at ca. -20°C as above (the reaction flask was sealed and transferred to a freezer after 1.5 h). Flash chromatography (25% ethyl acetate in hexane) yielded 112 mg (85%) of white solid: mp 64-70°C; $^1$H NMR (CDCl$_3$) δ 3.29 (q, J=7.2 Hz, 1H), 2.01 (m, 3H), 1.78-1.45 (m, 12H), 1.36 (br s, 1H), 1.11 (d, J=7.2 Hz, 3H). Mosher ester (from (+)-MTPA-Cl) methoxide peaks appeared at 3.58 and 3.54 ppm: 48% ee favoring the upfield signal. 125

Asymmetric Reduction of $n$-Butyl Cyclohexyl Ketone

$n$-Butyl cyclohexyl ketone, 119 204 µL (183 mg, 1.09 mmol, distilled and stored over 4Å molecular sieves), was reduced with 4.36 mmol of reagent for 18 h at ca. -20°C as above (the reaction flask was sealed and transferred to a freezer after 1.5 h). Flash chromatography (15% ethyl acetate in hexane) yielded 180 mg (97%) of clear oil: [$\alpha$]$^D_{30}$ +1.11° (neat) [lit. 124, 126 [$\alpha$]$^D_{30}$ +12.9° (neat) (R)]; $^1$H NMR (CDCl$_3$) δ 3.35 (m, 1H), 1.85-1.57 (m, 13H), 0.92 (t, J=7.4 Hz, 3H).

Asymmetric Reduction of $n$-Butyl tert-Butyl Ketone

$n$-Butyl tert-butyl ketone, 119 159 µL (131 mg, 0.92 mmol, distilled and stored over 4Å molecular sieves), was reduced with 3.68 mmol of reagent for 21 h at ca. -20°C as above (the reaction flask was sealed and transferred to a freezer after 15 min). Flash chromatography (10% ethyl acetate in hexane) yielded 132 mg (99%) of clear oil: [$\alpha$]$^D_{25}$ +0.55° (neat) [lit. 124, 127 [$\alpha$]$^D_{25}$ +40.24° (neat) (R)]; $^1$H NMR (CDCl$_3$) δ 3.19 (dd, J=5.6, 10 Hz, 1H), 1.59-1.45 (m, 2H), 1.45-1.23 (m, 5H), 0.93 (t, J=5.6 Hz, 3H), 0.90 (s, 9H).
Experimental Section for Part III. \textsuperscript{128}

(\pm)-2,2'-Bis(bromomethyl)-1,1'-binaphthyl (35) \hspace{1cm} page 78

(\pm)-3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine 2,2,2-
trifluoroacetamide (37) \hspace{1cm} page 78

(\pm)-3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine (4) \hspace{1cm} page 79

(\textit{S})-(\pm)-3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine (4) \hspace{1cm} page 79

Methyl \textit{\textbeta}-(3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]-4-azepinyl)butanoate (40) by Thermal Michael Addition \hspace{1cm} page 80

Methyl \textit{\textbeta}-(3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]-4-azepinyl)butanoate (41) via Lithium Amide and Excess Methyl Crotonate \hspace{1cm} page 81

Methyl \textit{\textbeta}-(3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]-4-azepinyl)butanoate (41) via Excess Lithium Amide (Two Equivalents) \hspace{1cm} page 82

Methyl \textit{\textbeta}-(3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]-4-azepinyl)butanoate (41) via Excess Lithium Amide (Four Equivalents) \hspace{1cm} page 82

Methyl \textit{\textbeta}-(3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]-4-azepinyl)-
butanoate (41) via (\textit{S})-Lithium Amide \hspace{1cm} page 83

4-(1-Hydroxy-3-butanyl)-3,5-dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine \hspace{1cm} page 84

4-(1-Triphenylmethoxy-3-butanyl)-3,5-dihydro-4H-dinaphth-
[2,1-c:1',2'-e]azepine (43) \hspace{1cm} page 84

(\textit{S})-1-Triphenylmethoxy-3-butanol \hspace{1cm} page 85

(\textit{S})-1-Triphenylmethoxy-3-butyl p-toluenesulfonate (45) \hspace{1cm} page 85

4-(1-Triphenylmethoxy-3-butanyl)-3,5-dihydro-4H-dinaphth-
[2,1-c:1',2'-e]azepine (44) from Tosylate (45) \hspace{1cm} page 86

77
(±)-2,2'-Bis(bromomethyl)-1,1'-binaphthyl (35) \(^{129}\)

A stirred mixture of 8.06 g (28.5 mmol) of (±)-2,2'-dimethyl-1,1'-binaphthyl, \(^{129,130}\) 10.64 g (59.8 mmol) of N-bromosuccinimide (suspended), and 30 mg (0.15 mmol) of azobisisobutyronitrile in 18.6 mL of carbon tetra-
chloride was heated to reflux. The reaction mixture became deep orange
with foaming. Additional azobisisobutyronitrile, 30 mg (0.15 mmol) each,
was added at 50, 80, and 115 min after the initial heating. At 155 min,
the cloudy yellow–gold reaction mixture was cooled and filtered through a 7
\(\text{cm}^2\) bed of silica gel with the aid of carbon tetrachloride. The resulting
pale yellow solution was concentrated \textit{in vacuo} to 13.79 g of viscous yellow
oil. Crystallization from benzene/hexane yielded 8.04 g (64\%) of very pale
yellow crystals: mp 150–153°C \textit{litr.}^{129} 148–149°C\textdegree; IR (mull) 1214 (\(\nu_{\text{CH}}\)
\text{wagging}), 824, 758, 570, 506 \text{cm}^{-1}; ^1\text{H NMR (CDCl}_3\text{)} \delta 8.02 (d, \text{J}=9.1 \text{Hz}, 2\text{H}),
7.94 (d, \text{J}=7.6 \text{Hz}, 2\text{H}), 7.75 (d, \text{J}=7.6 \text{Hz}, 2\text{H}), 7.50 (t, \text{J}=7.6 \text{Hz}, 2\text{H}),
7.27 (t, \text{J}=7.6 \text{Hz}, 2\text{H}), 7.08 (d, \text{J}=9.1 \text{Hz}, 2\text{H}), 4.26 (s, 4\text{H}).

(±)-3,5-Dihydro-4\(\text{H}\)-dinaphth[2,1-c:1’,2’-e]azepine 2,2,2-trifluoroacetamide
(37)

To a stirred room temperature suspension of 0.545 g (13.6 mmol) of a
60\% oil dispersion of sodium hydride in 50 mL of dry dimethylformamide was
added 0.770 g (6.82 mmol) of 2,2,2-trifluoroacetamide causing gentle
foaming for ca. 1 min. After 15 min, 3.00 g (6.82 mmol) of (±)-35 was
added causing vigorous gas evolution. Gas evolution gradually diminished
over the next 10 min as the solution cleared and turned yellow–green.
After stirring 2.5 h at room temperature, the reaction mixture was treated
with 50 mL of saturated NaCl (aq), and extracted with ether (2 x 50 mL).
The combined ether extracts were washed with saturated NaCl (2 x 50 mL),
dried (Na\(_2\)SO\(_4\)), and concentrated to give 2.98 g of yellow oil. Flash
chromatography (8\% ethyl acetate in hexane) yielding 1.57 g (59\%) of white
solid which was used for further transformations: ^1\text{H NMR (CDCl}_3\text{)} \delta 7.97 (t,
\text{J}=9.8 \text{Hz}, 4\text{H}), 7.62–7.43 (m, 6\text{H}), 7.33–7.24 (m, 2\text{H}), 5.31 (d, \text{J}=13.6 \text{Hz},
1\text{H}), 4.84 (d, \text{J}=13.6 \text{Hz}, 1\text{H}), 4.02 (d, \text{J}=14.0 \text{Hz}, 1\text{H}), 3.71 (d, \text{J}=14.0 \text{Hz},
1\text{H}).
A small sample was recrystallized from hexane: mp 163-165°C; IR (mull) 1690, 1200, 1140 (νCF), 825, 751 cm⁻¹. Anal. calcd for C₂₄H₁₆NO₃: C, 73.65; H, 4.12; N, 3.58; F, 14.56. Found: C, 73.91; H, 4.25; N, 3.37; F, 14.64.

(±)-3,5-Dihydro-4H-dinaph[2,1-c:1′,2′-e]azepine (4)

A solution of 0.873 g (2.23 mmol) of (±)-37 in 60 mL of methanol was treated with a solution of 0.516 g (4.87 mmol) of Na₂CO₃ in 10 mL of water. The resulting colorless solution with white precipitate was stirred at room temperature for 17 h before removing the methanol in vacuo, adding 50 mL of 5% NaOH (aq), and extracting with ether (2 x 60 mL). The combined ether extracts were washed with 5% NaOH (3 x 40 mL), dried (Na₂SO₄), and concentrated to afford 0.650 g (99%) of white solidified foam: mp 147-149°C; IR (mull) 3335, 1098, 820, 778, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 8.02-7.94 (m, 4H), 7.58 (d, J=8.3 Hz, 2H), 7.50-7.43 (m, 4H), 7.31-7.23 (m, 2H), 3.85 (d, J=11.7 Hz, 2H), 3.53 (d, J=11.7 Hz, 2H), 2.12 (broad s, 1H); ¹³C NMR (CDCl₃, 67.9 MHz) 134.80, 134.63, 132.84, 131.17, 128.69, 128.08, 127.12, 126.84, 125.55, 125.16, 48.40.

(S)-(+)–3,5-Dihydro-4H-dinaph[2,1-c:1′,2′-e]azepine (4)

A solution of 2.09 g (7.09 mmol) of (±)-4 in 235 mL of methanol was added slowly with gentle mixing to a solution of 2.67 g (7.09 mmol) of (-)-dibenzoyl-L-tartaric acid monohydrate (Aldrich) in 400 mL of methanol at room temperature. White needles began to form upon standing 1 h. After 24 h, the mixture was cooled to 0°C for 30 h, and then to -20°C for 15 h. Filtration yielded 2.12 g of pale yellow needles: mp 170-175°C (d).

A 0.992 g sample of this material was slurried in 70 mL of ether and treated with 50 mL of 5% NaOH (aq) with stirring giving two cloudy phases. The ether phase was separated, and the aqueous phase was extracted with ether (2 x 50 mL). The combined ether phases were washed with 5% NaOH (2 x 40 mL) and water (2 x 30 mL), dried (Na₂SO₄), and concentrated to give 0.444 g (45% = 90% of theory, based on (±)-4) of white solidified foam; mp
73–84°C; [α]_D^{20} +620° (c 0.78, CHCl₃) [lit.¹¹ [α]_D^{20} +574.8° (c 0.7, CHCl₃)];
IR (mull) 1090, 1030, 819, 770, 755 cm⁻¹; ^1H NMR (CDCl₃) δ 7.99–7.94 (m, 4H), 7.58 (d, J=8.7 Hz, 2H), 7.50–7.44 (m, 4H), 7.30–7.24 (m, 2H), 3.86 (d, J=12.1 Hz, 2H), 3.52 (d, J=12.1 Hz, 2H), 1.82 (broad s, 1H).

A small sample of free base was derivatized with 1-naphthoyl chloride
(pyridine, ca. 95°C, 45 min) and analyzed by chiral stationary phase HPLC
(Regis Pirkle Type 1-A, 25 cm x 4.6 mm I.D., two columns in series; 10%
isopropanol in hexane, 2.6 mL/min, retention times of racemate: 27.6 and
33.0 min) indicating 100% ee favoring the first eluted enantiomer.

Methyl β-[3,5-Dihydro-4H-dinaphth[2,1-c:1’,2’-e]-4-azepinyl]butanoate (40)
by Thermal Michael Addition

A solution of 0.150 g (0.508 mmol) of (+)-4 in 5.4 mL (51 mmol) of dry
methyl crotonate was heated at reflux for 21 h. The resulting clear orange
solution was cooled and concentrated in vacuo (rotory evaporator followed
by 0.5 mm overnight) to 0.199 g of brown oil. Flash chromatography (50%
ethyl acetate in hexane) yielded 0.137 g (68%) of very pale yellow oil: IR
(neat film) 1733, 1200, 1143, 819, 754, 735, 503 cm⁻¹; ^1H NMR (CDCl₃, 300
MHz) δ 7.94 (dd, J=4.0, 7.7 Hz, 4H), 7.58 (d, J=8.4 Hz, 2H), 7.47–7.40 (m,
4H), 7.27–7.22 (m, 2H), 3.82–3.64 (m, 5H), 3.52–3.32 (m, 3H), 2.70–2.60 (m,
1H), 2.40–2.29 (m, 1H), 1.20 (d, J=6.2 Hz, 1.0H), 1.13 (d, J=7.0 Hz, 2.0H);
¹³C NMR (CDCl₃, 75.4 MHz) δ 172.80, 172.72, 134.79, 134.73, 134.27, 134.16,
132.95, 131.22, 128.55, 128.19, 127.87, 127.41, 125.65, 125.32, 56.86,
56.74, 56.56, 56.45, 51.94, 51.52, 40.38, 40.26, 18.30, 18.19; HPLC (Regis
Pirkle Type 1-A, 25 cm x 10 mm I.D.; 5% isopropanol in hexane, 1 mL/min,
retention times 41.13 and 44.02 min) 3.48:1 favoring the first eluted
diastereomer.

Aliquots, 0.5 mL, were syringed from an identical reaction, rapidly
cooled in an ice bath, passed through a plug of silica gel with 50% ethyl
acetate in hexane, and analyzed by HPLC as above:
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<th>diastereomer ratio</th>
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<tr>
<td>264</td>
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</table>

Methyl β-[3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]-4-azepinyl]butanoate (41) via Lithium Amide and Excess Methyl Crotonate

To 5 mL of dry tetrahydrofuran on a -78°C bath was added 0.146 mL (0.339 mmol) of n-butyllithium (2.32 M in hexane). The resulting solution was added dropwise via cannula over 3 min to a solution of 0.100 g (0.339 mmol) of (+)-4 in 5 mL of dry tetrahydrofuran stirred on a -78°C bath. The resulting yellow-green solution was stirred 25 min at -78°C before adding dropwise via cannula over 3 min to a solution of 0.359 mL (0.339 g, 3.39 mmol) of dry methyl crotonate in 10 mL of dry tetrahydrofuran stirred on a -78°C bath. The resulting light brown solution was stirred 30 min at -78°C before quenching with a solution of 18.1 mg (0.339 mmol) of NH₄Cl in 5 mL of water and warming to room temperature. The majority of tetrahydrofuran was removed in vacuo before extracting with dichloromethane (2 x 25 mL). The combined organic extracts were dried (Na₂SO₄), and concentrated in vacuo (0.3 mm overnight) to 0.112 g of brown oil. Flash chromatography (50% ethyl acetate in hexane) yielded 20.7 mg (15%) of yellow oil: $^1$H NMR (CDCl₃, 300 MHz) δ 7.95-7.93 (m, 4H), 7.58 (d, J=8.3 Hz, 2H), 7.48-7.40 (m, 4H), 7.27-7.21 (m, 2H), 3.81-3.66 (m, 5H), 3.46-3.32 (m, 3H), 2.68-2.61 (m, 1H), 2.41-2.31 (m, 1H), 1.20 (d, J=6.2 Hz, 2.6H), 1.13 (d, J=6.6 Hz, 0.4H); HPLC (as above) 7.7:1 favoring the second eluted diastereomer.
Methyl β-[3,5-dihydro-4H-dinaphth[2,1-c:1',2'-e]-4-azepinyl]butanoate (41) via Excess Lithium Amide (Two Equivalents)

To 4 mL of dry tetrahydrofuran in a -78°C bath was added 0.146 mL (0.339 mmol) of n-butyllithium (2.32 M in hexane). The resulting solution was added dropwise via cannula over 2.5 min to a solution of 0.100 g (0.339 mmol) of (+)-4 in 4 mL of dry tetrahydrofuran rapidly stirred in a -78°C bath. The resulting dark green solution was stirred 25 min at -78°C before treatment with a solution of 18 μL (16.9 mg, 0.169 mmol) of dry methyl crotonate in 3 mL of dry tetrahydrofuran precooling in a -78°C bath dropwise via cannula over 2 min. The resulting light brown solution was stirred 30 min at -78°C before quenching with a solution of 18.1 mg (0.339 mmol) of NH₄Cl in 5 mL of water and warming to room temperature. The majority of tetrahydrofuran was removed in vacuo before extracting with dichloromethane (2 x 20 mL). The combined organic extracts were dried (Na₂SO₄), and concentrated in vacuo (1.9 mm overnight) to 0.106 g of orange oil. Flash chromatography (50% ethyl acetate in hexane) yielded 27.2 mg (41%) of light yellow oil: ¹H NMR (CDCl₃) δ 7.96-7.91 (m, 4H), 7.58 (d, J=8.4 Hz, 2H), 7.48-7.39 (m, 4H), 7.27-7.21 (m, 2H), 3.80 (d, J=12.3 Hz, 2H), 3.66 (s, 3H), 3.42 (d, J=12.3 Hz, 2H), 3.40-3.30 (m, 1H), 2.66 (dd, J=5.3, 14.4 Hz, 1H), 2.37 (dd, J=8.7, 14.4 Hz, 1H), 1.20 (d, J=6.6 Hz, 3H); HPLC (as above) 83:1 favoring the second eluted diastereomer.

Methyl β-[3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]-4-azepinyl]butanoate (41) via Excess Lithium Amide (Four Equivalents)

To 5 mL of dry tetrahydrofuran in a -78°C bath was added 0.219 mL (0.508 mmol) of n-butyllithium (2.32 M in hexane). The resulting solution was added dropwise via cannula over 3 min to a solution of 0.150 g (0.508 mmol) of (+)-4 in 5 mL of dry tetrahydrofuran rapidly stirred in a -78°C bath. The resulting dark green solution was stirred 25 min at -78°C before treatment with a solution of 13.5 μL (12.7 mg, 0.127 mmol) of dry methyl crotonate in 2.3 mL of dry tetrahydrofuran precooling in a -78°C bath dropwise via cannula over 1.3 min. The resulting brown solution was stirred 30 min at -78°C before quenching with a solution of 27.2 mg (0.508
mmol) of NH₄Cl in 7 mL of water and warming to room temperature. The majority of tetrahydrofuran was removed in vacuo before extracting with dichloromethane (2 x 30 mL). The combined organic extracts were dried (Na₂SO₄), and concentrated in vacuo (1 mm overnight) to 0.169 g of orange oil. Flash chromatography (50% ethyl acetate in hexane) yielded 44.2 mg (88%) of yellow oil: ¹H NMR (CDCl₃) δ 7.95–7.92 (m, 4H), 7.58 (d, J=8.3 Hz, 2H), 7.47–7.40 (m, 4H), 7.27–7.21 (m, 2H), 3.80 (d, J=12.3 Hz, 2H), 3.66 (s, 3H), 3.42 (d, J=12.3 Hz, 2H), 3.40–3.30 (m, 1H), 2.66 (dd, J=5.3, 14.4 Hz, 1H), 2.37 (dd, J=8.7, 14.4 Hz, 1H), 1.20 (d, J=6.6 Hz, 3H); HPLC (as above) 94:1 favoring the second eluted diastereomer.

Methyl β-[3,5-Dihydro-4H-dinaphth[2,1-c:1',2'-e]-4-azepinyl]butanoate (41) via (S)-Lithium Amide

To 5 mL of dry tetrahydrofuran in a -78°C bath was added 0.219 mL (0.508 mmol) of n-butyllithium (2.32 M in hexane). The resulting solution was added dropwise via cannula over 4 min to a solution of 0.150 g (0.508 mmol) of (S)-4 in 5 mL of dry tetrahydrofuran rapidly stirred in a -78°C bath. The resulting dark red-brown solution was stirred 25 min at -78°C before treatment with a solution of 13.5 µL (12.7 mg, 0.127 mmol) of dry methyl crotonate in 2.3 mL of dry tetrahydrofuran precooled in a -78°C bath dropwise via cannula over 2 min. The resulting orange solution was stirred 30 min at -78°C before quenching with a solution of 27.2 mg (0.508 mmol) of NH₄Cl in 7 mL of water and warming to room temperature. The majority of tetrahydrofuran was removed in vacuo before extracting with dichloromethane (2 x 35 mL). The combined organic extracts were dried (Na₂SO₄), and concentrated in vacuo (ca. 1 mm overnight) to 0.173 g of white solidified foam. Flash chromatography (50% ethyl acetate in hexane) yielded 0.08 mg (81%) of clear oil: [α]²⁵⁺D +267° (c 2.46, CHCl₃); ¹H NMR (CDCl₃) δ 7.95–7.91 (m, 4H), 7.58 (d, J=8.4 Hz, 2H), 7.48–7.40 (m, 4H), 7.27–7.21 (m, 2H), 3.79 (d, J=12.3 Hz, 2H), 3.66 (s, 3H), 3.42 (d, J=12.3 Hz, 2H), 3.40–3.30 (m, 1H), 2.65 (dd, J=5.4, 14.5 Hz, 1H), 2.37 (dd, J=8.7, 14.5 Hz, 1H), 1.20 (d, J=6.6 Hz, 3H); ¹³C NMR (CDCl₃, 75.4 MHz) δ 172.82, 134.85, 134.16, 132.99, 131.30, 128.60, 128.21, 127.86, 127.44, 125.69, 125.37, 56.55, 51.99, 51.58, 40.40, 18.31; HPLC (as above) 61:1 favoring the second eluted
4-(1-Hydroxy-3-butanyl)-3,5-dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine

To a solution of 27.7 mg (70.0 μmol) of the thermal Michael adduct in 7 mL of dry tetrahydrofuran stirred in a 0°C bath was added 5.3 mg (0.140 mmol) of powdered lithium aluminum hydride. The resulting mixture was stirred 30 min at 0°C before the dropwise addition of 3 mL of water saturated ether. The resulting mixture was stirred 30 min at room temperature, treated with 2 g of Celite, stirred an additional 1 h, filtered (Celite), and concentrated to give 40.9 mg of pale yellow oil. Flash chromatography (3% triethylamine and 20% ethanol in hexane) yielded 22.1 mg (86%) of clear oil: $^1$H NMR (CDCl$_3$, 300 MHz) δ 7.97-7.93 (m, 4H), 7.61 (d, J=8.4 Hz, 2H), 7.49-7.38 (m, 4H), 7.29-7.22 (m, 2H), 3.93-3.80 (m, 4H), 3.49 (d, J=12.0 Hz, 2H), 3.40-3.26 (m, 1.4H, diastereomeric carbonyl protons), 3.17-3.07 (m, 0.6H, diastereomeric carbonyl protons), 2.06-1.88 (m, 1H), 1.62-1.52 (m, 1H), 1.09 (d, J=7.0 Hz, 1.1H, diastereomeric methyl protons), 0.98 (d, J=7.0 Hz, 1.9H, diastereomeric methyl protons).

4-(1-Triphenylmethoxy-3-butanyl)-3,5-dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine (43)

A solution of 11.0 mg (29.9 μmol) of 4-(1-hydroxy-3-butanyl)-3,5-dihydro-4H-dinaphth[2,1-c:1',2'-e]azepine in 5 mL of dry dichloromethane was treated with 2.0 mg (16 μmol) of 4-dimethylaminopyridine, 0.1 mL of triethylamine, and 12.5 mg (44.9 μmol) of chlorotriphenylmethane. The resulting clear solution was stirred at room temperature and treated with 20.9 mg (75.0 μmol) additional chlorotriphenylmethane at 5 h and 21 h. After 53 h, the reaction mixture was flash chromatographed (25% ethyl acetate in hexane) yielding 13.5 mg (74%) of clear oil: $^1$H NMR (CDCl$_3$) δ 7.96-7.89 (m, 4H), 7.57-7.43 (m, 12H), 7.32-7.19 (m, 11H), 3.79-3.70 (m, 2H), 3.39-3.33 (m, 2H), 3.29-3.21 (m, 1H), 3.19-2.94 (m, 2H), 2.18-1.86 (m, 1H), 1.74-1.55 (m, 1H), 1.03 (d, J=6.4 Hz, 1.0H, diastereomeric methyl protons), 0.96 (d, J=6.4 Hz, 2.0H, diastereomeric methyl protons); HPLC
(Regis Pirkle Type 1-A, 25 cm x 10 mm I.D.; 6% isopropanol in hexane, 2 mL/min, retention times 32.18 and 35.00 min) 1.8:1 favoring the second eluted diastereomer.

(S)-1-Triphenylmethoxy-3-butanol

A solution of 0.446 g (4.95 mmol) of (S)-(+)−1,3-butanediol (Aldrich) in 20 mL of dry dichloromethane was treated with 2 g of 3A molecular sieves, 1.2 mL of triethylamine, and 24.2 mg (0.198 mmol) of 4-dimethylaminopyridine and stirred 30 min at room temperature. Chlorotriphenylmethane, 1.517 g (5.44 mmol), was then added. After stirring 13 h at room temperature, the reaction mixture was filtered (Celite), diluted with 80 mL of dichloromethane, washed with water (3 x 30 mL), dried (Na₂SO₄), and concentrated to give 2.02 g of light brown oil. Flash chromatography (30% ethyl acetate in hexane) yielded 1.536 g (93%) of oil with faint yellow tint: $\left[\alpha\right]_{D}^{25}$ -17.8° (c 4.63, CHCl₃); IR (neat film) 3420 (broad), 1173, 763, 748, 709, 702, 635 cm⁻¹; ¹H NMR (CDCl₃) δ 7.47–7.42 (m, 6H), 7.35–7.21 (m, 9H), 4.07–3.92 (m, 1H), 3.41–3.33 (m, 1H), 3.26–3.17 (m, 1H), 2.85 (d, J=2.8 Hz, 1H), 1.88–1.64 (m, 2H), 1.16 (d, J=6.2 Hz, 3H).

(S)-1-Triphenylmethoxy-3-butyl p-toluenesulfonate (45)

A solution of 0.285 g (0.857 mmol) of (S)-1-triphenylmethoxy-3-butanol in 4.5 mL of dry pyridine was cooled in an ice bath and treated with 0.327 g (1.71 mmol) of p-toluenesulfonyl chloride. The reaction mixture was allowed to slowly warm to room temperature, and after 16 h, 5.2 mg (43 µmol) of 4-dimethylaminopyridine was added. After a total of 43 h, the reaction mixture was cooled in an ice bath (producing a precipitate), and treated with 10 mL of water dropwise over several minutes (causing homogeneity and then an oil). The resulting mixture was diluted with 30 mL of water and extracted with chloroform (3 x 25 mL). The combined organic extracts were washed with water (2 x 20 mL), dried (Na₂SO₄), and concentrated to give 0.399 mg of yellow oil. Flash chromatography (20% ethyl acetate in hexane) yielded 0.312 g (75%) of white solid: mp
116–121°C; $[\alpha]_D^{25} +2.0^\circ$ (c 1.03, CHCl$_3$); IR (mull) 1189, 1176, 1075, 916, 896, 821, 751, 708, 700 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.72 (d, J=8.4 Hz, 2H), 7.35–7.23 (m, 17H), 4.78 (sextet, J=6.3, 1H), 3.10–2.93 (m, 2H), 2.42 (s, 3H), 2.07–1.88 (m, 1H), 1.75–1.62 (m, 1H), 1.23 (d, J=6.3 Hz, 3H). Anal. calcd. for C$_{30}$H$_{30}$O$_4$S: C, 74.04; H, 6.21; S, 6.59. Found: C, 73.86; H, 6.27; S, 6.77.

4-(1-Triphenylmethoxy-3-butanyl)-3,5-dihydro-4H-dinaphth[2,1-e;1',2'-e]-azepine (44) from Tosylate 45

A solution of 50.0 mg (0.169 mmol) of (S)-4 and 41.2 mg (0.085 mmol) of (S)-45 in 0.5 mL of dry dimethylformamide was heated in an 86°C oil bath for 2 h. The resulting light yellow solution was diluted with 15 mL of ether, washed with 5% NaHCO$_3$ (2 x 5 mL) and water (2 x 5 mL), dried (Na$_2$SO$_4$), and concentrated to a yellow oil. Flash chromatography (25% ethyl acetate in hexane) yielded 23.4 mg (45%) of clear oil: $[\alpha]_D^{25} +173^\circ$ (c 2.21, CHCl$_3$); $^1$H NMR (CDCl$_3$) $\delta$ 7.94–7.91 (m, 4H), 7.54 (d, J=8.3 Hz, 2H), 7.49–7.41 (m, 10H), 7.34–7.18 (m, 11H), 3.75 (d, J=12.3 Hz, 2H), 3.36 (d, J=12.3 Hz, 2H), 3.30–3.21 (m, 1H), 3.12–2.97 (m, 2H), 2.04–1.90 (m, 1H), 1.75–1.60 (m, 1H), 1.02 (d, J=6.5 Hz, 3H); HPLC (as above) 17:1 favoring the first eluted diastereomer.

A parallel reaction employing (±)-4 in place of (S)-4 gave a 1.0:1 ratio of diastereomers by HPLC (as above).
Experimental Section for Part IV.

(+)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol-N-oxide (49) and meso-α,α'-Di-tert-butyl-2,6-pyridinedimethanol-N-oxide (50) by Reduction of 49

meso-α,α'-Di-tert-butyl-2,6-pyridinedimethanol (51) by Reduction of 50

(+)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol (5) from 2,6-Dibromopyridine

(+)-threo-α,α'-Di-iso-propyl-2,6-pyridinedimethanol (52)

α,α',α',α'-Tetraethyl-2,6-pyridinedimethanol (53)

threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol diacetate (54), Resolution by HPLC

(+)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol (5) from (+)-54

(+)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol (5) by Classical Resolution

(-)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) (55), Solution Molecular Weight, and Crystallography

(+)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) (55)

[meso-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) (56)

(+)-[threo-2,6-Bis(2-methyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) (57)

Reaction of (+)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]-dioxomolybdenum(VI) with H₂O₂ (Single Phase)

Attempted Epoxidation of 2-Methyl-2-tetradecene with (+)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) and H₂O₂ (Single Phase)

Reaction of (+)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]-dioxomolybdenum(VI) with H₂O₂ (Two Phases)

Epoxidation of 2-Methyl-2-tetradecene with Molybdenum(VI) and H₂O₂ (continued)
Epoxidation of 2-Methyl-2-tetradecene with (−)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) and H₂O₂ (Two Phases)

Epoxidation of (E)-α-Phenylcinnamyl Alcohol with (−)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) and TBHP

Reaction of (±)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol with Titanium(IV) Isopropoxide

Epoxidations of (E)-α-Phenylcinnamyl Alcohol with Titanium(IV) - (±)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol and TBHP

Epoxidations of (E)-α-Phenylcinnamyl Alcohol with Titanium(IV) - (±)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol and Trityl Hydroperoxide

Epoxidation of (E)-1-Cyclohexyl-2-butene-1-ol with Titanium(IV) - (±)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol and TBHP

Epoxidation of (E)-1-Cyclohexyl-2-butene-1-ol with Titanium(IV) - (±)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol and Trityl Hydroperoxide

Epoxidations of (E)-1-Cyclohexyl-2-butene-1-ol with Titanium(IV) - (±)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol and Alkyl Hydroperoxides

Epoxidations of (E)-1-Cyclohexyl-2-butene-1-ol with Titanium(IV) - meso-α,α'-Di-tert-butyl-2,6-pyridinedimethanol and Alkyl Hydroperoxides

Epoxidation of (E)-1-Cyclohexyl-2-butene-1-ol with Titanium(IV) - α,α,α',α'-Tetraethyl-2,6-pyridinedimethanol and TBHP

Epoxidation of (E)-1-Cyclohexyl-2-butene-1-ol with Titanium(IV)-α,α,α',α'-Tetraethyl-2,6-pyridinedimethanol and Trityl Hydroperoxide

88
(±)-three-α,α'-Di-tert-butyl-2,6-pyridinedimethanol-N-oxide (49) and meso-α,α'-Di-tert-butyl-2,6-pyridinedimethanol-N-oxide (50)

To a solution of 5.24 mL (4.38 g, 31.0 mmol) of 2,2,6,6-tetramethylpiperidine (dried over 3A molecular sieves) in 2.9 mL of dry tetrahydrofurane stirred on a -78°C bath was added 12.9 mL (31.0 mmol) of n-butyl-lithium (2.4 M in hexane) over 1.5 min. The resulting cloudy yellow solution was stirred 5 min at -78°C and 1 h at room temperature before being added over 20 min to a solution of 1.18 g (12.4 mmol) of pyridine-N-oxide (dried azeotropically with four portions of dry dichloromethane at 0.6 mm Hg and subsequently handled under nitrogen) and 5.4 mL (4.3 g, 50 mmol) of pivalaldehyde (distilled, dried over 3A molecular sieves) in 100 mL of dry tetrahydrofurane stirred on a -78°C bath. The resulting clear pale orange solution was stirred 1.7 h at -78°C before quenching with 31 mL (62 mmol) of 2 N HCl (aq) and warming to room temperature. The majority of tetrahydrofurane was removed in vacuo and the resulting mixture was extracted with ether (3 x 40 mL). The combined ether extracts were dried (Na₂SO₄) and concentrated to 3.48 g of yellow oil which was separated into two partially purified samples by flash chromatography (65% ethyl acetate in hexane).

The higher Rf material (0.864 g of off white solid) was recrystallized from ether yielding 0.517g (16%) of 49 as a white crystalline solid: mp 207-207.5°C; IR (mull) 3410, 3200 (broad), 1216 (νNO), 1067, 1016, 844, 780 cm⁻¹; ¹H NMR (CDCl₃) δ 7.33-7.17 (m, 3H), 6.25 (broad d, J=9.4 Hz, 2H), 4.68 (d, J=9.4 Hz, 2H), 1.03 (s, 18H). Anal. Calcd for C₁₅H₂₅NO₃: C, 67.38; H, 9.43; N, 5.24. Found: C, 67.37; H, 9.64; N, 5.30.

The lower Rf material (0.592 g of white solid) was flash chromatographed (80% ethyl acetate in hexane) yielding 0.284 g (9%) of 50 as a white crystalline solid: mp 141-147°C; IR (mull) 3460, 3320 (broad), 3140 (broad), 1205 (νNO), 1071, 1016, 840, 775 cm⁻¹; ¹H NMR (CDCl₃) δ 7.35-7.18 (m, 3H), 6.43 (broad d, J=8.7 Hz, 2H), 4.68 (d, J=8.7 Hz, 2H), 1.02 (s, 18H).

Fractions from the two columns which contained a mixture of 49 and 50 were combined and concentrated to 0.342 g (10%).
(±)-three-α,α'-Di-tert-butyl-2,6-pyridinedimethanol (5) by Reduction of 49

A dry 25 x 200 mm pyrex test tube with side arm and stir bar was flushed with nitrogen through the side arm while charging with 0.300 g (1.12 mmol) of (±)-49 and 2.94g (11.2 mmol) of triphenylphosphine. The tube was septum sealed and evacuated and refilled with nitrogen three times before the lower third of the tube was then submerged in a 220±5°C silicone oil bath for 1 h with stirring. The resulting light brown melt was cooled, dissolved in 75 mL of ether, and extracted with 2N HCl (4 x 30 mL, 0.24 mol). The combined acid extracts were stirred on an ice bath and treated portionwise with 12 g (0.3 mol) of NaOH pellets. After all of the NaOH dissolved, the resulting mixture was extracted with ether (3 x 110 mL). The combined ether extracts were dried (Na₂SO₄), and concentrated to 0.331 g of white solid. Flash chromatography (35% ethyl acetate in hexane) yielded 0.251 g (89%) of white crystalline solid: mp 136-137°C; IR (mull) 3400, 3290 (broad), 1596, 1577, 1081, 1050, 1018, 834, 775 cm⁻¹; ¹H NMR (CDCl₃) δ 7.61 (t, J=7.8 Hz, 1H), 7.13 (d, J=7.8 Hz, 2H), 4.37 (d, J=7.5 Hz, 2H), 3.73 (d, J=7.5 Hz, 2H), 0.92 (s, 18H). Anal. Calcd for C₁₅H₂₅NO₂: C, 71.67; H, 10.03; N, 5.57. Found: C, 71.82; H, 10.23; N, 5.64.

Chiral stationary phase HPLC (Regis Pirkle Type 1-A, 25 cm x 4.6 mm I.D.; 2% isopropanol in hexane, 3 mL/min) displayed two peaks of equal area at 9.56 and 9.85 min.

meso-α,α'-Di-tert-butyl-2,6-pyridinedimethanol (51) by Reduction of 50

The above procedure for the reduction of 49 was followed for 50 on a 0.315 mmol scale. Flash chromatography (42% ethyl acetate and 1.5% triethylamine in hexane) yielded 67.2 mg (85%) of clear oil which solidified on standing: mp 61-73°C; IR (mull) 3450, 3380 (broad), 1595, 1576, 1100, 1050, 1015, 830, 771 cm⁻¹; ¹H NMR (CDCl₃) δ 7.61 (t, J=7.9 Hz, 1H), 7.13 (d, J=7.9 Hz, 2H), 4.39 (d, J=7.5 Hz, 2H), 3.78 (d, J=7.5 Hz, 2H), 0.93 (s, 18H).

Chiral stationary phase HPLC (Regis Pirkle Type 1-A, 25 cm x 4.6 mm I.D.; 2% isopropanol in hexane, 3 mL/min) displayed a single peak at 17.29 min.
(±)-threo-α,α′-Di-tert-butyl-2,6-pyridinedimethanol (5) from 2,6-Dibromopyridine

To a slurry of 10.00 g (42.2 mmol) of 2,6-dibromopyridine in 156 mL of dry tetrahydrofuran stirred on a -78°C bath was added 17.1 mL (42.2 mmol) of n-butyllithium (2.47 M in hexane) over 4 min. The resulting dark green solution was stirred 35 min at ca. -78°C before adding a solution of 4.58 mL (3.64 g, 42.2 mmol) of pivalaldehyde (distilled, dried over 3A molecular sieves) in 20 mL of dry tetrahydrofuran over 2.5 min. The resulting dark solution was stirred 35 min at ca. -78°C before adding 17.1 mL (42.2 mmol) of n-butyllithium solution over 2 min. The resulting dark green solution was stirred 40 min at ca. -78°C before adding a solution of 5.96 mL (4.73 g, 54.9 mmol) of dry pivalaldehyde in 25 mL of dry tetrahydrofuran over 7 min. The resulting dark solution was stirred 1 h at ca. -78°C before the portionwise addition of 80 mL of water followed by warming to room temperature.

The majority of tetrahydrofuran was removed in vacuo and the resulting mixture was extracted with ether (4 x 110 mL). The combined orange ether extracts were dried (Na₂SO₄) and concentrated to 11.39 g of pale brown oil. Flash chromatography (35–40% ethyl acetate in hexane) in three portions gave 4.93 g of tan solid which was recrystallized from ether/hexane yielding 3.67 g (35%) of off white solid: mp 120–134°C; IR (mull) 3400, 3280 (broad), 1594, 1573, 1080, 1049, 1015, 830, 774 cm⁻¹; ¹H NMR (CDCl₃) δ 7.61 (t, J=8.2 Hz, 1H), 7.14 (d, J=8.2 Hz, 2H), 4.37 (d, J=7.5 Hz, 2H), 3.75 (d, J=7.5 Hz, 2H), 0.92 (s, 18H).

(±)-threo-α,α′-Di-iso-propyl-2,6-pyridinedimethanol (52)

To a slurry of 2.59 g (10.9 mmol) of 2,6-dibromopyridine in 40 mL of dry tetrahydrofuran stirred on a -78°C bath was added 3.50 mL (10.9 mmol) of n-butyllithium (3.12 M in hexane) over 2 min. The resulting dark green solution was stirred 35 min at ca. -78°C before adding a solution of 0.99 mL (0.787 g, 10.9 mmol) of isobutyraldehyde (distilled, dried over 4A molecular sieves) in 5 mL of dry tetrahydrofuran over 3 min. The resulting pale brown solution was stirred 40 min at ca. -78°C before adding 3.50 mL
(10.9 mmol) of n-butyllithium solution over 1 min. The resulting solution was stirred 1 h at ca. -78°C before adding a solution of 1.29 mL (1.02 g, 14.2 mmol) of dry isobutyraldehyde in 5 mL of dry tetrahydrofuran over 2.5 min. The resulting solution was stirred 45 min at ca. -78°C before the portionwise addition 20 mL of water and warming to room temperature.

The majority of tetrahydrofuran was removed in vacuo and the resulting mixture was extracted with ether (4 x 30 mL). The combined ether extracts were dried (Na₂SO₄) and concentrated to 2.52 g of yellow oil. Flash chromatography (50% ethyl acetate in hexane) yielded 0.517 g (21%) of clear oil which was used for further transformations: ¹H NMR (CDCl₃) δ 7.66 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H), 4.44 (dd, J = 5, 6 Hz, 2H, α), 3.61 (d, J = 6.0 Hz, 2H, hydroxyl), 2.11–1.98 (m, 2H), 0.97 (d, J = 6.0 Hz, 6H), 0.82 (d, J = 6.0 Hz, 6H).

Chiral stationary phase HPLC (Regis Pirkle Type 1–A, 25 cm x 10 mm I.D.; 3% isopropanol in hexane, 3 mL/min) displayed two peaks of equal area at 28.0 and 28.6 min.

A small portion of the oil which had solidified on standing was recrystallized from ether/hexane producing a white crystalline solid: mp 72–76°C; IR (mull) 3380, 3070 (broad), 1601, 1577, 1054, 1037, 816, 760 cm⁻¹. Anal. Calcd for C₁₃H₂₁NO₂: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.63; H, 9.62; N, 6.27.

α,α,α',α'–Tetraethyl-2,6-pyridinedimethanol (53)

To a slurry of 3.00 g (12.7 mmol) of 2,6-dibromopyridine in 47 mL of dry tetrahydrofuran stirred on a -78°C bath was added 5.63 mL (12.7 mmol) of n-butyllithium (2.25 M in hexane) over 1 min. The resulting green solution was stirred 35 min at ca. -78°C before adding a ca. -78°C solution of 1.34 mL (1.09 g, 12.7 mmol) of 2-pentanone (distilled, dried over 4A molecular sieves) in 5 mL of dry tetrahydrofuran via cannula over 2 min. The resulting bluish-green solution was stirred 35 min at ca. -78°C before adding 5.63 mL (12.7 mmol) of n-butyllithium solution over 1 min. The resulting green solution was stirred 40 min at ca. -78°C before adding a precooled solution of 1.74 mL (1.42 g, 16.5 mmol) of dry 2-pentanone in 7 mL dry tetrahydrofuran over 3 min. The resulting solution was stirred 1 h
at ca. –78°C before the portionwise addition 24 mL of water and warming to room temperature.

The majority of tetrahydrofuran was removed in vacuo and the resulting mixture was extracted with ether (3 x 50 mL). The combined ether extracts were dried (Na₂SO₄) and concentrated to 2.81 g of pale orange oil. Flash chromatography (30% ethyl acetate in hexane) gave 2.01 g of oil which was chromatographed a second time (10% ethanol in hexane) yielding 1.18 g (37%) of pale yellow oil: IR (neat film) 3420 (broad), 1580, 1168, 973, 820 cm⁻¹; ¹H NMR (CDCl₃) δ 7.73 (t, J=7.9 Hz, 1H), 7.23 (d, J=7.9 Hz, 2H), 4.20 (s, 2H), 1.88 (q, J=7.1 Hz, 8H), 0.68 (t, J=7.1 Hz, 12H).

**3α,α′-Di-tert-butyl-2,6-pyridinedimethanol diacetate (54), Resolution by HPLC**

A mixture of 0.150 g (0.597 mmol) of (+)-5 and 14.6 mg (0.119 mmol) of 4-dimethylaminopyridine was treated with 20 mL of triethylamine and 10 mL of acetic anhydride. The resulting solution was stirred 1.3 h at room temperature before concentration in vacuo (rotory evaporator followed by high vacuum overnight) to an oil. Flash chromatography (25% ethyl acetate in hexane) yielded 0.192 g (96%) of white crystalline solid: mp 123-124°C; IR (mull) 1740, 1730, 1594, 1578, 1253, 1237, 1025, 833, 770 cm⁻¹; ¹H NMR (CDCl₃) δ 7.57 (t, J=7.6 Hz, 1H), 7.14 (d, J=7.6 Hz, 2H), 5.51 (s, 2H), 2.11 (s, 6H), 0.97 (s, 18H). Anal. Calcd for C₁₉H₂₉NO₄: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.97; H, 8.83; N, 4.08.

Chiral stationary phase HPLC (Regis Pirkle Type 1-A, 25 cm x 10 mm I.D.; 1% isopropanol in hexane, 3 mL/min) of 98 mg of (+)-54 (dissolved in 25% chloroform and 1% isopropanol in hexane; 24 injections of 40 μL each at 8 min intervals, retention times 15.4 and 17.1 min) yielded 40.0 mg (41% = 82% of theory) of the first eluted enantiomer: mp 40.5-42.5°C, [α]D²⁵ +92° (c 0.71, ethanol); 100% ee by HPLC (Regis Pirkle Type 1-A, 25 cm x 10 mm I.D.; 1% isopropanol in hexane, 3 mL/min); and 40.7 mg (42% = 83% of theory) of the second eluted enantiomer: mp 71.5-72.5°C; [α]D²⁵ -87° (c 0.90, ethanol); 98% ee by HPLC.
(+)-{three}-α,α'-Di-tert-butyl-2,6-pyridinedimethanol (5) from (+)-54

A 40.0 mg (0.119 mmol) sample of (+)-54 was dissolved in 20 mL of potassium carbonate saturated dry methanol and stirred 50 min at room temperature. The resulting solution was concentrated, diluted with 5 mL of water, and extracted with ether (3 x 10 mL). The combined ether extracts were dried (Na$_2$SO$_4$), and concentrated to 32.9 mg of pale yellow solid. Flash chromatography (35% ethyl acetate in hexane) yielded 28.7 mg (96%) of white solid: 100% ee, second enantiomer to elute by chiral stationary phase HPLC (Regis Pirkle Type 1-A, 25 cm x 10 mm I.D.; 2% isopropanol in hexane, 2 mL/min).

(+)-{three}-α,α'-Di-tert-butyl-2,6-pyridinedimethanol (5) by Classical Resolution

A mixture of 1.964 g (7.81 mmol) of (±)-5 and 2.940 g (7.81 mmol) of (-)-dibenzoyl-L-tartaric acid monohydrate was dissolved in a minimum amount of ether at room temperature (in air). The solution was diluted with an equal volume of hexane and concentrated slowly with a stream of nitrogen producing a fluffy white precipitate which was refrigerated overnight before filtering. The mother liquor was concentrated to 3.97 g of white solid (19% de favoring the first eluted enantiomer as analyzed below) and recrystallized three times from ether/hexane (as above) giving 0.610 g of white solid (82% de, second enantiomer). This material was combined with the initial precipitate (0.797 g, 97% de, second enantiomer) and recrystallized three more times giving 1.092 g of white solid (99.6% de, second enantiomer).

This material was dissolved in 60 mL of ether, washed with 5% NaOH (3 x 5 mL) and water (2 x 10 mL), dried (Na$_2$SO$_4$), and concentrated to 0.502 g of clear oil which solidified under high vacuum. Flash chromatography (35% ethyl acetate in hexane) yielded 0.409 g (21% = 42% of theory, based on (±)-5) of white crystalline solid: mp 87.5-88.5°C; [α]$_D^{25}$ +42.5° (c 1.30, ethanol); IR (mull) 3430, 3220, 1596, 1575, 1071, 1010, 832, 778 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.62 (t, J=7.5 Hz, 1H), 7.13 (d, J=7.5 Hz, 2H), 4.37 (d, J=7.1 Hz, 2H), 3.73 (d, J=7.1 Hz, 2H), 0.92 (s, 18H).
The diastereomeric excesses were analyzed by dissolving 2.3 mg of salt in 2.0 mL ether, washing with 5% NaOH (3 x 0.5 mL) and water (0.5 mL), drying (Na₂SO₄), and chiral stationary phase HPLC (Regis Pirkle Type 1-A, 25 cm x 10 mm I.D.; 2% isopropanol in hexane, 2 mL/min, retention times 34.48 and 35.97 min).

(-)[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) (55), Solution Molecular Weight, and Crystallography

A solution of 0.100 g (0.398 mmol) of (+)-5 in 5.2 mL of dry dichloromethane was treated with 0.126 g (0.386 mmol) of MoO₂(acac)₂ (Alfa, purified by filtering in dichloromethane and drying in vacuo). The initial slightly cloudy greenish-yellow solution decolored gradually to a pale yellow tint while stirring at room temperature for 23 h. Volatiles were removed in vacuo (rotary evaporator followed by 2 mm overnight) giving 0.146 g of very pale tan solid. Filtration in dichloromethane and recrystallization from dichloromethane/ether yielded 0.128 g (88%) of white crystalline air stable solid: mp 256-263°C (d); [α]D²⁵ -38.0° (c 1.02, CH₂Cl₂); IR (KBr) 1600, 1575, 1067, 929, 916, 650, 497 cm⁻¹; IR (CHBr₃) νMoO 943, 918 cm⁻¹; ¹H NMR (CDCl₃) δ 8.09 (t, J=7.5 Hz, 2H), 7.56 (d, J=7.5 Hz, 2H), 5.69 (s, 2H), 1.07 (s, 18H). Anal. Calcd for C₁₅H₂₃NO₄Mo: C, 47.75; H, 6.15; N, 3.71. Found: C, 47.79; H, 6.27; N, 3.64.

Solution Molecular Weight. A Signer apparatus¹⁰³ was charged in air with 49.1 mg of (-)-55 (transferred in ca. 1 mL of dichloromethane into the "unknown" bulb) and 60.8 mg (0.175 mmol) of tetrabutylin (transferred in ca. 4 mL of dichloromethane into the "reference" bulb). The system was freeze-thaw degassed (three cycles); and the evacuated apparatus was laid in a room temperature draft free cabinet. The volumes of the unknown and reference solutions were measured daily. The calculated figure (last column) asymptotically approaches the molecularity of the unknown:
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Crystallography. Crystals of (−)-55 suitable for crystallography were grown by slow evaporation of a dichloromethane solution at room temperature and washed with ether/dichloromethane. X-ray data were collected on an Enraf-Nonius CAD4F-11 diffractometer using Mo Kα radiation. Details of the data collection, reduction, and refinement procedures have been described elsewhere. A total of 6155 reflections (+h, +k, +l), as well as Friedel pairs (−h, −k, ±l), were collected in the range 3° ≤ 2θ ≤ 50° with the 5269 having F_o > 4σ(F_o) being used in the structure refinement which was by full-matrix least-squares techniques (382 variables) using SHELX-76. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions (C-H = 0.95 Å) and were constrained to ride on their respective carbon atoms.

The absolute configuration was assigned by first assuming the R, R-configuration. Six final cycles of least-squares refinement converged at R_1 = 0.0448 and R_2 = 0.0493. Anomalous dispersion due to Mo was included in the calculation. The alternate hand of the structure was then refined to convergence from the same starting point, again with six cycles of least-squares refinement, giving a final R_1 = 0.0466 and R_2 = 0.0515. Thus
Table XII. Final Positional and Thermal Parameters for (-)-55a (top) and (-)-55b (bottom)

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<td>-0.0841</td>
<td>0.0203</td>
<td>0.0610</td>
<td>0.0610</td>
<td>0.0931</td>
<td>-0.0078</td>
<td>0.0106</td>
<td>-0.0127</td>
<td>-0.0127</td>
</tr>
</tbody>
</table>

Numbers in parentheses are errors in the least significant digits.

The anisotropic temperature factors are of the form

\[ F_{ij} = 
\begin{pmatrix}
U_{11} & U_{12} & U_{13} \\
U_{12} & U_{22} & U_{23} \\
U_{13} & U_{23} & U_{33}
\end{pmatrix}
\]
the original assignment of configuration, depicted in Figure 4, was shown to be correct.

Crystal data are: \( a = 6.881 (3) \text{ Å}, b = 12.679 (2) \text{ Å}, c = 20.176 (4) \text{ Å}, \beta = 92.03 (3)^\circ, V = 1759.1 \text{ Å}^3, \) space group = \( P2_1 \), \( Z = 4 \), mol. wt. = 377.3 g, \( \rho(\text{calcd}) = 1.425 \text{ gcm}^{-3}, \mu = 7.2 \text{ cm}^{-1} \). A semi-empirical absorption correction was applied. Table XII shows the final positional and thermal parameters. Figure 4 shows the geometry of (−)−55a and (−)−55b along with the atomic numbering scheme. Table X shows selected bond distances and angles.

\((\pm)-[\text{threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato}dioxomolybdenum(VI)](55)\)

A solution of 0.385 g (1.53 mmol) of (±)-5 in 20 mL of dry dichloromethane was treated with 0.487 g (1.49 mmol) of \( \text{MoO}_2(\text{acac})_2 \) (Alfa, purified by filtering in dichloromethane and drying in vacuo). The initial clear bright yellow solution faded to a pale yellow while stirring at room temperature for 28 h. Volatiles were removed in vacuo (rotory evaporator followed by 0.4 mm) giving 0.625 g of tan solid. Two recrystallizations (dichloromethane/ether; dichloromethane/hexane) yielded 0.361 g (64%) of white crystalline air stable solid: mp 236–254°C (d); IR (KBr) 1599, 1578, 1067, 934, 857, 663, 496 cm\(^{-1}\); IR (CHBr\(_3\)) \( \nu_{\text{MoO}} \) 943, 918 cm\(^{-1}\); \( ^1\text{H NMR} \) (CDCl\(_3\)) \& 8.10 (t, \( J=7.5 \text{ Hz}, 1\text{H}\)), 7.57 (d, \( J=7.5 \text{ Hz}, 2\text{H}\)), 5.70 (s, 2H), 1.07 (s, 18H). Anal. Calcd for \( \text{C}_{15}\text{H}_{23}\text{NO}_4\text{Mo} \): C, 47.75; H, 6.15; N, 3.71. Found: C, 47.79; H, 6.19; N, 3.69.

\([\text{meso-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato}dioxomolybdenum(VI)](56)\)

A solution of 40.0 mg (0.159 mmol) of 51 in 5 mL of dry dichloromethane was treated with 51.9 mg (0.159 mmol) of \( \text{MoO}_2(\text{acac})_2 \) (Alfa, purified by filtering in dichloromethane and drying in vacuo). The initial yellow solution decolored gradually while stirring at room temperature for 13 h. Filtration and concentration in vacuo gave 62.1 mg of off white solid. Recrystallization from dichloromethane/ether yielded 49.6 mg (83%) of white
air stable needles: mp 194.5-195.5°C; IR (KBr) 1600, 1576, 1075, 940, 914, 665, 610, 503 cm\(^{-1}\); IR (CHBr\(_3\)) \(\nu\)\(_{\text{MoO}}\) 943, 917 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \& 8.08 (t, J=7.5 Hz, 1H), 7.50 (d, J=7.5 Hz, 2H), 5.62 (s, 2H), 1.09 (s, 18H).
Anal. Calcd for C\(_{15}\)H\(_{23}\)NO\(_4\)Mo: C, 47.75; H, 6.15; N, 3.71. Found: C, 47.51; H, 6.01; N, 3.46.

\((\pm)-[\text{three}-2,6-\text{Bis}(2\text{-methyl-1-oxypopyl})\text{pyridinato}]\text{dioxomolybdenum(VI)}\) (57)

A solution of 40.0 mg (0.179 mmol) of (\(\pm\))-52 in 5 mL of dry dichloromethane was treated with 58.4 mg (0.179 mmol) of MoO\(_2\)(acac)\(_2\) (Alfa). The initial slightly cloudy greenish-yellow solution gradually became pale blue while stirring at room temperature for 25 h. Filtration and concentration in vacuo (rotary evaporator followed by 0.1 mm overnight) gave 66.2 mg of pale tan solid. Recrystallization from dichloromethane/ether yielded 40.0 mg (64\%) of pale blue needles: mp 227-230°C (d); IR (KBr) 1600, 1578, 1040, 934, 868, 688, 664, 499 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \& 8.14 (t, J=8.3 Hz, 1H), 7.43 (d, J=8.3 Hz, 2H), 5.90 (d, J=3.5 Hz, 2H), 2.37-2.25 (m, 2H), 1.20 (d, J=7.2 Hz, 6H), 0.86 (d, J=7.2 Hz, 6H).

A small sample was filtered in dichloromethane and recrystallized from dichloromethane/ether producing fine white needles: IR (CHBr\(_3\)) \(\nu\)\(_{\text{MoO}}\) 943, 919 cm\(^{-1}\).

Reaction of \((\pm)-[\text{three}-2,6-\text{Bis}(2,2\text{-dimethyl-1-oxypopyl})\text{pyridinato}]\text{dioxomolybdenum(VI)}\) with H\(_2\)O\(_2\) (Single Phase)

A solution of 50 mg (0.13 mmol) of (\(\pm\))-55 in 18 mL of dry tetrahydrofuran was treated with 8 drops (ca. 5 mmol) of 90\% hydrogen peroxide, and the resulting clear solution was stirred at room temperature. Over 38 h, the solution became bright yellow, and TLC (75\% ethyl acetate in hexane) showed the disappearance of the starting complex and the appearance of a new, more polar, N,N,N',N'-tetramethyl-1,4-phenylenediamine spray active spot. The solvent was removed in vacuo (rotary evaporator, followed by 0.4 mm) giving 62.9 mg of yellow solid: IR (KBr) 3420-3100 (broad),

99
1061, 969, 896, 691, 671, 565, 502 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.02 (t, \(J=7.9\) Hz, 1H), 7.76 (d, \(J=7.9\) Hz, 1H), 7.59 (d, \(J=7.8\) Hz, 1H), 5.94 (s, 1H), 5.80 (s, 1H), 1.80 (br s, ca. 12H), 1.21 (s, 9H), 1.19 (s, 9H).

**Attempted Epoxidation of 2-Methyl-2-tetradecene with (±)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) and H\(_2\)O\(_2\) (Single Phase)**

A solution of 20 mg (53 \(\mu\)mol) of (±)-55 and 145 \(\mu\)L (112 mg, 0.53 mmol) of 2-methyl-2-tetradecene in 10 mL of dry tetrahydrofuran was treated with 8 drops (ca. 5 \(\mu\)mol) of 90\% hydrogen peroxide, and the resulting clear solution was stirred at room temperature. Over 66 h, the solution became bright yellow, but no epoxidation occurred according to TLC (15\% ethyl acetate in hexane).

**Reaction of (±)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) with H\(_2\)O\(_2\) (Two Phases)**

A solution of 25 mg (66 \(\mu\)mol) of (±)-55 in 3 mL of dichloromethane was treated with 3 mL (29 mmol) of 30\% hydrogen peroxide and the resulting clear two phase system was rapidly stirred at room temperature. After 5.5 h, the organic phase was pale yellow and the phases were separated. The aqueous phase was extracted with dichloromethane, and the combined organic phases were washed with water, dried (\(\text{Na}_2\text{SO}_4\)), and concentrated in vacuo to 25 mg of light yellow solid. The \(^1\)H NMR (CDCl\(_3\)) showed resonances corresponding to (±)-55, (±)-5, and the product from the single phase reaction above with a molar ratio of 66 : 6 : 28.

**Epoxidation of 2-Methyl-2-tetradecene with Molybdenum(VI) and H\(_2\)O\(_2\)**

Test tubes equipped with a stir bar and septum were charged in air with the Mo species (see below) and 1.1 mL of dichloromethane. Complex (±)-55 dissolved, but \((\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot4\text{H}_2\text{O}\) did not. Hydrogen peroxide, 0.54
mL (5.3 mmol) of 30% aqueous solution, was added producing two homogeneous phases (see descriptions below). 2-Methyl-2-tetradecene, 145 µL (112 mg, 0.53 mmol), and the additive (see below) were then added, and the reaction mixtures were rapidly stirred at room temperature. Aliquots, 1 drop, were taken from the organic phase at the indicated times, diluted with 12 drops of ether, and analyzed by gc (10% carbowax; 70°C for 2 min, 16°C/min ramp, and 240°C maximum temperature). Peaks with retention times corresponding to the starting olefin (7.11 min), dodecyl aldehyde (8.52 min), and 2-methyl-2-tetradecene oxide (9.27 min) were obtained with the relative peak areas shown below:

<table>
<thead>
<tr>
<th>No species</th>
<th>additive</th>
<th>color of phases</th>
<th>gc peak areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>(±)-55, 20 mg (53 µmol)</td>
<td>---</td>
<td>org: clear initially, became yellow 1-4 h, faded to clear 6-20 h</td>
<td>21 : 2.2 : 77</td>
</tr>
<tr>
<td>(NH₄)₆Mo₇O₂₄·4H₂O, 9.4 mg (7.6 µmol)</td>
<td>---</td>
<td>org: clear, aq: yellow</td>
<td>99.4 : 0.2 : 0.5</td>
</tr>
<tr>
<td>(±)-5, 13.3 mg (53 µmol)</td>
<td></td>
<td>org: clear, aq: yellow</td>
<td>53 : 0.3 : 47</td>
</tr>
</tbody>
</table>

Epoxidation of 2-Methyl-2-tetradecene with (−)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) and H₂O₂ (Two Phases)

A 16 mm test tube equipped with a stir bar and septum was charged in air with 20 mg (53 µmol) of (−)-55, 1.1 mL of dichloromethane, and 0.54 mL (5.3 mmol) of 30% H₂O₂ (aq) producing two clear phases. After stirring 5 min, 145 µL (112 mg, 0.53 mmol) of 2-methyl-2-tetradecene were added, and the reaction mixture was rapidly stirred at room temperature. After 1.6 h, the organic phase was pale yellow and a trace of epoxide was visible by TLC (15% ethyl acetate in hexane, co-spot with authentic epoxide). After 14.5
h, the organic phase was clear, the aqueous phase was yellow, and TLC showed ca. 50% conversion. After 42 h, the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 1 mL), and the combined organic phases were washed with water (3 x 1 mL), dried (Na$_2$SO$_4$), and concentrated to 126 mg of pale yellow oil. Flash chromatography (7% ethyl acetate in hexane) yielded 89.6 mg (75%) of clear oil: [$\alpha$]$_D^{25}$ +0.54° (c 3.15, ethanol); $^1$H NMR (CDCl$_3$) δ 2.73 (t, J=5.3 Hz, 1H), 1.58-1.43 (m, 2H), 1.43-1.24 (m, 24H), 0.89 (t, J=6.4 Hz, 3H). Shift study: $^1$H NMR (CDCl$_3$), 0.20 equiv Eu(hfc)$_3$, epoxymethyl protons shifted to 2.53, 2.49, 2.30, and 2.25 ppm, <5% ee.

Epoxidation of (E)-α-Phenylcinnamyl Alcohol with (-)-[threo-2,6-Bis(2,2-dimethyl-1-oxypropyl)pyridinato]dioxomolybdenum(VI) and TBHP

To a solution of 20.0 mg (0.053 mmol) of (-)-55 in 5 mL of dry dichloromethane was added 11.1 mg (0.053 mmol) of (E)-α-phenylcinnamyl alcohol, and 40.0 µL (0.159 mmol) of TBHP (3.98 M in toluene). The resulting clear solution was stirred at room temperature for 111 h and then quenched by addition via cannula over ca. 2 min to an aqueous solution of 10% tartaric acid and 5% FeSO$_4$ (5 mL) rapidly stirred at room temperature. After stirring ca. 3 min, the resulting mixture was extracted with ether (3 x 10 mL). The combined organic extracts were dried (Na$_2$SO$_4$), and concentrated to 38.4 mg of white solid. Flash chromatography (two columns: 40% ethyl acetate in hexane followed by 6% ethyl acetate in dichloromethane) yielded 8.1 mg (68%) of white solid which co-spotted with authentic epoxide by TLC (10% ethyl acetate in dichloromethane): $^1$H NMR (CDCl$_3$) δ 7.28-7.02 (m, 10H), 4.53 (s, 1H), 4.05 (d, J=7.2 Hz, 2H), 2.00 (t, J=7.2 Hz, 1H); chiral bound phase HPLC (Regis Pirkle Type 1-A, 25 cm x 10 mm I.D.; 3% isopropanol in hexane, 5 mL/min, retention times 21.47 min (2-R) and 24.23 min (2-S)) indicated 1% ee (2-R).
Reaction of (+)-threo-α,α'-Di-tert-buty1-2,6-pyridinedimethanol with Titanium(IV) Isopropoxide

A solution of 33.8 mg (0.134 mmol) of (+)-5 in 2.0 mL of dry chloroform-d (stored over 3A molecular sieves) was treated with 40.0 μL (38.2 mg, 0.134 mmol) of titanium(IV) isopropoxide at room temperature. The NMR of the resulting clear solution was obtained 7-9 min after mixing: \(^1H\) NMR δ 7.75 (t, J=7.6 Hz, 1H), 7.34 (d, J=7.6 Hz, 2H), 5.30 (s, 2H), 4.82 (sept, J=6.1 Hz, 2H), 3.99 (sept, J=6.1 Hz, 2H), 1.30 (d, J=6.1 Hz, 6H), 1.20 (d, J=6.1 Hz, 6H), 1.19 (d, J=6.1 Hz, 12H), 0.96 (s, 18H).

Epoxidations of (E)-α-Phenylcinnamyl Alcohol with Titanium(IV) – (+)-threo-α,α'-Di-tert-buty1-2,6-pyridinedimethanol and TBHP

To a solution of (+)-5 (see below) in 6.8 mL of dry dichloromethane was added 27.2 μL (26.0 mg, 0.091 mmol) of titanium(IV) isopropoxide. The resulting clear solution was stirred at room temperature for 20 min before the addition of 19.2 mg (0.091 mmol) of (E)-α-phenylcinnamyl alcohol. The resulting clear solution was stirred at room temperature for 5 min, transferred to a -5ºC bath, and stirred 15 min before the addition of 69.0 μL (0.274 mmol) of TBHP (3.98 M in toluene). After the indicated time (below), the reaction was quenched by addition via cannula over ca. 2 min to an aqueous solution of 10% tartaric acid and 5% FeSO₄ (6.8 mL) rapidly stirred at room temperature. After stirring 3 min, the resulting mixture was extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (10 mL), dried (Na₂SO₄), concentrated to a clear oil, and purified by flash chromatography (5-15% ethyl acetate in dichloromethane). Each of the products co-spotted by TLC (10% ethyl acetate in dichloromethane), and overlapped in the \(^1H\) NMR (as above) with authentic epoxide. Enantiomeric excesses were determined by chiral bound phase HPLC (as above):
<table>
<thead>
<tr>
<th>(+)-5</th>
<th>reaction time</th>
<th>isolated yield</th>
<th>enantiomeric excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.7 mg (0.114 mmol)</td>
<td>2.6 h</td>
<td>19.3 mg (93%)</td>
<td>41% (2-S)</td>
</tr>
<tr>
<td>34.4 mg (0.137 mmol)</td>
<td>3.5 h</td>
<td>15.5 mg (75%)</td>
<td>40% (2-S)</td>
</tr>
<tr>
<td>45.5 mg (0.183 mmol)</td>
<td>4.5 h</td>
<td>20.6 mg (100%)</td>
<td>41% (2-S)</td>
</tr>
</tbody>
</table>

Epoxidations of (E)-α-Phenylcinnamyl Alcohol with Titanium(IV) - (+)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol and Trityl Hydroperoxide

To a solution of 34.4 mg (0.137 mmol) of (+)-5 in dry dichloromethane (see below) was added 27.2 μL (26.0 mg, 0.091 mmol) of titanium(IV) isopropoxide. The resulting clear solution was stirred at room temperature for 20 min before the addition of 19.2 mg (0.091 mmol) of (E)-α-phenylcinnamyl alcohol. The resulting clear solution was stirred at room temperature for 5 min, transferred to a -5°C bath, and stirred 15 min before the portionwise addition of 75.7 mg (0.274 mmol) of trityl hydroperoxide. (The most concentrated reaction became slightly cloudy after ca. half of the trityl hydroperoxide was added.) After the indicated time (below), the reaction was quenched by addition via cannula over ca. 2 min to an aqueous solution of 10% tartaric acid and 5% FeSO₄ (6.8-10 mL) rapidly stirred at room temperature. After stirring 3 min, the resulting mixture was extracted with ether (3 x 10 mL). (For the least concentrated reaction, the dichloromethane phase was separated before extracting the aqueous phase with ether.) The combined organic fractions were washed with water (10 mL), dried (Na₂SO₄), concentrated to an oil, and purified by flash chromatography (5-15% ethyl acetate in dichloromethane). Each of the products co-spotted by TLC (10% ethyl acetate in dichloromethane), and overlapped in the ¹H NMR (as above) with authentic epoxide. Enantiomeric excesses were determined by chiral bound phase HPLC (as above):

<table>
<thead>
<tr>
<th>dichloromethane</th>
<th>reaction time</th>
<th>isolated yield</th>
<th>enantiomeric excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>34 mL</td>
<td>26 h</td>
<td>17.8 mg (86%)</td>
<td>64% (2-R)</td>
</tr>
<tr>
<td>6.8 mL</td>
<td>13.5 h</td>
<td>18.6 mg (90%)</td>
<td>64% (2-R)</td>
</tr>
<tr>
<td>1.4 mL</td>
<td>4.5 h</td>
<td>17.8 mg (86%)</td>
<td>52% (2-R)</td>
</tr>
</tbody>
</table>
Epoxidation of (E)-1-Cyclohexyl-2-butene-1-ol with Titanium(IV) — (+)-threo-α,α’-Di-tert-butyl-2,6-pyridinedimethanol and TBHP

To a solution of 38.0 mg (0.151 mmol) of (+)-5 in 7.5 mL of dry dichloromethane was added 30.0 μL (28.7 mg, 0.101 mmol) of titanium(IV) isopropoxide. The resulting clear solution was stirred at room temperature for 20 min before the addition of 17.0 μL (15.5 mg, 0.101 mmol) of (E)-1-cyclohexyl-2-butene-1-ol. The resulting clear solution was stirred at room temperature for 5 min, transferred to a -5°C bath, and stirred 15 min before the addition of 17.7 μL (0.071 mmol) of TBHP (3.98 M in toluene). After 23 h, the reaction was quenched by addition via cannula over ca. 2 min to an aqueous solution of 10% tartaric acid and 5% FeSO₄ (7.5 mL) rapidly stirred at room temperature. After stirring 3 min, the resulting mixture was extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (10 mL), and dried (Na₂SO₄).

Gas chromatography (20 m carbowax capillary column; 70°C for 2 min, 16°C/min ramp, and 220°C maximum temperature) gave peaks with retention times corresponding to the starting olefin (7.41 min), known epoxides (9.04 min), and 5 (13.44 min) with relative peak areas of 16.82, 29.04, and 54.14 respectively. [A solution of 19.6 mg (0.127 mmol) of (E)-1-cyclohexyl-2-butene-1-ol and 13.8 mg (0.055 mmol) of (+)-5 gave relative peak areas of 81.76 and 18.24, respectively.]

The crude solution was then concentrated to an oil, dissolved in 10 mL of ether, washed with 2 N HCl (3 x 5 mL) and water (2 x 5 mL), dried (Na₂SO₄), concentrated to a clear oil, and acetylated according to the general procedure below. Gas chromatography of the worked-up acetylation (20 m carbowax capillary column; 70°C for 2 min, 16°C/min ramp, and 220°C maximum temperature) gave peaks with retention times corresponding to known erythro- (8.77 min) and threo- (9.55 min) epoxyacetates with a peak area ratio of 54:46. Flash chromatography (10% ethylacetate in hexane) gave 5.4 mg (corresponding to 27% recovered starting olefin) of (E)-1-cyclohexyl-2-butene-1-ol acetate: [α]D²³ +10° (c 0.32, ethanol); ¹H NMR (C₆D₆) δ 5.74 (dq, J=6.1, 15 Hz, 1H), 5.43 (ddq, J=1, 7.9, 15 Hz, 1H), 5.30 (dd, J=7.6, 7.9 Hz, 1H), 1.85–1.47 (m, 5H), 1.79 (s, 3H), 1.56 (dd, J=1, 6.1 Hz, 3H), 1.27–0.85 (m, 6H). Shift study: ¹H NMR (C₆D₆), 0.13 equiv Eu(hfc)₃, acetate protons shifted to 2.77 and 2.73 ppm, 69% ee favoring the downfield
peak.

Acetylation. The alcohol (5-30 mg) was treated with 2 mL of dry pyridine and 1 mL of acetic anhydride, sealed, and stirred at room temperature. After 4-13 h, the reaction mixture was cooled on a ice bath, treated with 1 mL of water, and allowed to stir at room temperature. After 10-24 h, the reaction mixture was diluted with 20 mL of ether, washed with aqueous CuSO₄ (5 x 4 mL or until the extract no longer turned dark blue) followed by water (2 x 4 mL), dried (Na₂SO₄), and concentrated in vacuo.

Epoxidation of (E)-1-Cyclohexyl-2-buten-1-ol with Titanium(IV) - (+)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol and Trityl Hydroperoxide

The above procedure was followed using 22.3 mg (0.081 mmol) of trityl hydroperoxide with a 46 h reaction time. The crude gc showed the starting olefin, epoxides, and 5 with relative peak areas of 18.83, 28.49, and 52.68 respectively. Flash chromatography (25-50% ether in hexane) of the worked-up reaction mixture gave the unreacted starting olefin, and a mixture of the epoxyalcohols and 5. The recovered starting material was acetylated as above giving 5.9 mg (corresponding to 30% recovered starting olefin) of acetate which was analyzed by a shift study as above indicating 76% ee (R). The mixture of epoxyalcohols and 5 was dissolved in 15 mL of ether, washed with 2N HCl (3 x 6 mL) and water (5 mL), dried (Na₂SO₄), concentrated, acetylated as above, and analyzed as above indicating an erythro/threo ratio of 68:32.

Epoxidations of (E)-1-Cyclohexyl-2-buten-1-ol with Titanium(IV) - (+)-threo-α,α'-Di-tert-butyl-2,6-pyridinedimethanol and Alkyl Hydroperoxides

To a solution of 38.0 mg (0.151 mmol) of (±)-5 in 7.5 mL of dry dichloromethane was added 30.0 µL (28.7 mg, 0.101 mmol) of titanium(IV) isopropoxypoxide. The resulting clear solution was stirred at room temperature for 20 min before the addition of 17.0 µL (15.5 mg, 0.101 mmol) of
(E)-1-cyclohexyl-2-butene-1-ol. The resulting clear solution was stirred at room temperature for 5 min, transferred to a -5°C bath, and stirred 15 min before the addition of the oxidant (see below). After the indicated time (below), the reaction was quenched by addition via cannula over ca. 2 min to an aqueous solution of 10% tartaric acid and 5% FeSO₄ (7.5 mL) rapidly stirred at room temperature. After stirring 3 min, the resulting mixture was extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (10 mL), dried (Na₂SO₄), and concentrated to an oil. The trityl hydroperoxide reaction mixture was flash chromatographed (50% ether in hexane) giving a mixture of the epoxyalcohols with 5. Both product mixtures were then washed with aqueous HCl, acetylated, and analyzed by gc as above:

<table>
<thead>
<tr>
<th>oxidant</th>
<th>reaction time</th>
<th>erythro/threo</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.2 μL (0.060 mmol) of TBHP (3.98 M in toluene)</td>
<td>23 h</td>
<td>50:50</td>
</tr>
<tr>
<td>19.5 mg (0.071 mmol) of trityl hydroperoxide</td>
<td>39 h</td>
<td>77:23</td>
</tr>
</tbody>
</table>

Epoxidations of (E)-1-Cyclohexyl-2-butene-1-ol with Titanium(IV) - meso-α,α'-Di-tert-butyl-2,6-pyridinedimethanol and Alkyl Hydroperoxides

To a solution of 38.0 mg (0.151 mmol) of 51 in 7.5 mL of dry dichloromethane was added 30.0 μL (28.7 mg, 0.101 mmol) of titanium(IV) isopropoxide. The resulting clear solution was stirred at room temperature for 20 min before the addition of 17.0 μL (15.5 mg, 0.101 mmol) of (E)-1-cyclohexyl-2-butene-1-ol. The resulting clear solution was stirred at room temperature for 5 min, transferred to a -5°C bath, and stirred 15 min before the addition of the oxidant (see below). After the indicated time (below), the reaction was judged >95% complete by TLC (10% ethyl acetate in dichloromethane) and quenched by addition via cannula over ca. 2 min to an aqueous solution of 10% tartaric acid and 5% FeSO₄ (7.5 mL) rapidly stirred at room temperature. After stirring 3 min, the resulting mixture was extracted with ether (3 x 10 mL). The combined organic extracts were washed with water (10 mL), dried (Na₂SO₄), concentrated to an
oil, and purified by flash chromatography (50% ether in hexane). The erythro/threo ratio was determined by acetylation and gas chromatography as described above:

<table>
<thead>
<tr>
<th>oxidant</th>
<th>reaction time</th>
<th>erythro/threo</th>
</tr>
</thead>
<tbody>
<tr>
<td>76 µL (0.302 mmol) of TBHP</td>
<td>21 h</td>
<td>74:26</td>
</tr>
<tr>
<td>(3.98 M in toluene)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83.5 mg (0.302 mmol) of</td>
<td>18 h</td>
<td>66:34</td>
</tr>
<tr>
<td>trityl hydroperoxide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Epoxidation of (E)-1-Cyclohexyl-2-butene-1-ol with Titanium(IV) – α,α,α’,α’-Tetraethyl-2,6-pyridinedimethanol and TBHP**

To a solution of 75.0 mg (0.298 mmol) of 53 in 14.8 mL of dry dichloromethane was added 59.2 µL (56.5 mg, 0.199 mmol) of titanium(IV) isopropoxide. The resulting clear solution was stirred at room temperature for 1.8 h before the addition of 33.5 µL (30.7 mg, 0.199 mmol) of (E)-1-cyclohexyl-2-butene-1-ol. The resulting clear solution was stirred at room temperature for 5 min, transferred to a -5°C bath, and stirred 40 min before the dropwise addition of 150 µL (0.597 mmol) of TBHP (3.98 M in toluene). After 5.5 h, the reaction was judged >95% complete by TLC (10% ethyl acetate in dichloromethane) and quenched by addition via cannula over ca. 2 min to an aqueous solution of 10% tartaric acid and 5% FeSO₄ (15 mL) rapidly stirred at room temperature. After stirring 3 min, the resulting mixture was extracted with ether (3 x 20 mL). The combined organic extracts were washed with water (10 mL), dried (Na₂SO₄), and concentrated to an oil. Flash chromatography (50% ether in hexane) gave a mixture of the epoxyalcohols with 53 which was acetylated as above. The tertiary diol, 53, did not acetylate and was removed by the CuSO₄ (aq) washings. An erythro/threo ratio of 80:20 was determined by gas chromatography as described above.
Epoxidation of (E)-1-Cyclohexyl-2-butene-1-ol with
Titanium(IV)-α,α,α′,α′-Tetraethyl-2,6-pyridinedimethanol and Trityl
Hydroperoxide

To a solution of 36.1 mg (0.144 mmol) of 53 in 7.1 mL of dry
dichloromethane was added 28.5 μL (27.2 mg, 0.096 mmol) of titanium(IV)
isopropoxide. The resulting clear solution was stirred at room temperature
for 2.3 h before the addition of 16.1 μL (14.8 mg, 0.096 mmol) of
(E)-1-cyclohexyl-2-butene-1-ol. The resulting clear solution was stirred
at room temperature for 5 min, transferred to a -5°C bath, and stirred 15
min before the portionwise addition of 79.4 mg (0.287 mmol) of trityl
hydroperoxide. After 39 h, the reaction was judged >90% complete by TLC
(10% ethyl acetate in dichloromethane) and quenched by addition via cannula
over ca. 2 min to an aqueous solution of 10% tartaric acid and 5% FeSO₄ (7
mL) rapidly stirred at room temperature. After stirring 3 min, the
resulting mixture was extracted with ether (3 x 10 mL). The combined
organic extracts were washed with water (10 mL), dried (Na₂SO₄), and
concentrated to an oil. Flash chromatography (50% ether in hexane) gave a
mixture of the epoxyalcohols with 53 which was acetylated as above. The
tertiary diol, 53, did not acetylate and was removed by the CuSO₄ (aq)
washings. An erythro/threo ratio of 69:31 was determined by gas
chromatography as described above.
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121. These amines were prepared from the corresponding primary amines by formylation (excess ethyl formate, reflux) followed by reduction (1.5 LiAlH₄, THF, reflux).
122. The relative molar absorbance at 276 nm of the 2-naphthyl ketones vs. the corresponding 2-naphthyl carbinols for the ethyl and n-nonyl substrates was assumed to be the same as found for the n-butyl substrate in calculating the conversion.
125. Absolute configuration assigned according to Mosher's model. Dale, J.


128. The synthesis of (+)-4, recrystallization of the corresponding dibenzoyl tartrate salt, and preliminary Michael reactions (not described here) were performed by Gregory C. Fu under the author's direction.


131. X-ray data collection and subsequent reduction and refinement were performed by Dr. J. C. Dewan.


133. Using 5 as an internal standard, the amount of recovered starting material = (16.82/54.14)x(0.127/81.76)x(18.24/0.055)x150% = 24%.


135. Using 5 as an internal standard, the amount of recovered starting material = (18.83/52.68)x(0.127/81.76)x(18.24/0.055)x150% = 28%.