New Catalytic Enantioselective Functionalizations of Alcohols through Silylation and Tosylation

a dissertation

by

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ABSTRACT

Chapter 1 A survey of silicon-based reactions and potential for Lewis base catalysis.

Chapter 2 An efficient site- and enantioselective catalytic silylation of triols is disclosed. The protocol is applied to total syntheses of cleroindicins D, F and C.

Chapter 3 Catalytic kinetic resolution of β-hydroxyketones is disclosed. A readily available amino acid-based catalyst promotes the kinetic resolution with high efficiency.

Chapter 4 A presentation of catalytic enantioselective tosylation of syn-1,2-diols.
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Chapter 1 A Survey of Silicon-based Reactions and Potential for Lewis Base Catalysis

1.1 Basic Concepts of Lewis Base Activation of Silicon

Silicon is a truly exceptional element as it serves as a reactive site for an almost infinite number of transformations pertinent to synthetic chemistry.\(^1\) Importantly, the relationship of valency at silicon and its chemical reactivity represents the key to understanding and readily allowing us to design novel reactions. Silicon is a group 14 element and not a transition metal. It is generally accepted that the empty 3d orbitals on silicon are too diffuse to engage in meaningful bonding.\(^2\) The ability of silicon to expand its coordination sphere is due to the ability of silicon 3p orbitals to engage in electron-rich three-center four-electron (3c-4e) bonding.\(^3\)

Silicon normally bonds with only four other atoms, which completes the electronic requirements for an outer-shell octet. In SiL\(_4\) compounds, the molecules have a tetrahedral geometry, and therefore the central silicon atom displays sp\(^3\) hybridization (I, Figure 1). Expansion to a trigonal bipyramidal, pentacoordinate silicon complex SiL\(_5\) (II) requires a p orbital to engage in hypervalent three-center four-electron (3c-4e) bonding, and the central silicon atom employs sp\(^2\) hybridization. Further expansion of the coordination sphere to an octahedral, hexacoordinate complex SiL\(_6\) (III), requires a second p orbital to engage in hypervalent 3c-4e bonding, and the silicon atom to be formally sp hybridized. Consequently, the result of such valency expansion and electron

---


redistribution is that the Lewis acidity at silicon is increased and the nucleophilicity of ligands around silicon is also increased. It should be noted that complex III is not acting as Lewis acid since any further expansion of this valence shell is unusual.4

**Figure 1.1** Valency and Electron Density at Silicon in Organosilicon Compounds

![Diagram of valency and electron density at silicon]

Figure 1.2 shows the molecular orbitals of 3c-4e hybrids. The highest occupied molecular orbital (HOMO)5 of this hybrid (ψ2) is the nonbonding orbital with a node at the central silicon atom and localizes the electron density at the peripheral atoms. Therefore, it is clear that how enhancement of both electrophilicity of the central silicon atom and nucleophilicity of the ligands around silicon can be generated.

**Figure 1.2** Molecular Orbitals of 3c-4e hybrids

![Diagram of molecular orbitals]

---


Calculation on SiF$_5^-$ demonstrates such phenomenon. The tetra-substituted silicon in SiF$_4$ is tetrahedral, with Si–F bond lengths of 1.56 Å, a charge of $-0.392$ on each F, and a charge of $+1.568$ on central Si (Figure 3). The facile addition of a fifth ligand (F') leads to a rehybridization of the silicon atom, where the equatorial ligands are elongated to 1.62 Å with a charge of $-0.571$, and the axial ligands are elongated to 1.66 Å with a charge of $-0.539$. More importantly, the overall positive charge on silicon is increased from $+1.568$ to $+1.792$.

**Figure 1.3 Calculations of SiF$_4$ in Comparison of SiF$_5^-$**

- Charge at F = $-0.392$
- Charge at F (equatorial) = $-0.571$
- Charge at F (axial) = $-0.539$
- Charge at Si = $+1.568$
- Charge at Si = $+1.792$

Si–F bond length = 1.56 Å
Si–F bond length (equatorial) = 1.62 Å
Si–F bond length (axial) = 1.66 Å

Chemistry involving Lewis base activation of silicon has been reviewed recently. In this survey, a overview of well-developed Lewis base catalyzed reactions will be given as examples. Meanwhile, reactions involving silicon-based or mediated reactions that have not been successfully catalyzed will also be discussed.

---


1.2 Lewis Base Activation of Silicon for Nucleophilic Addition

*Activation of Si–C bond for Nucleophilic Addition*

The asymmetric addition of allylmetal reagents to aldehydes has evolved into a powerful and selective tactic in modern organic synthesis. Lewis base activation of allyltrichlorosilane for addition to aldehydes is a well studied area. The mechanism of such reaction was first proposed by Sakurai and Kobayashi. As illustrated in Scheme 1.1, coordination of a chiral Lewis base (LB) with allyltrichlorosilane renders the silicon center Lewis acidic enough to activate the aldehyde. Allylation takes place through a closed chair transition state (intermediate IV in Scheme 1.1), which results in a diastereospecific allylation. Turnover of the Lewis base is possible by dissociation from the trichlorosilyl ether product and re-coordination of allyltrichlorosilane. If a chiral Lewis base catalyst is incorporated, enantioselectivity of the allylation reaction is determined by the effectiveness of the chirality transfer from the chiral Lewis base to the newly formed stereogenic centers.

---

The choice of Lewis base is critical to turnover. Bassindale introduced the interesting concept of ‘silaphilicity’.\(^\text{11}\) It is the relative affinity of certain entities to silicon species. As shown in Scheme 1.2, by measuring the average \(^{29}\text{Si}\) resonance of the reaction mixture, a relative equilibrium constant \(K\) was assigned to each reaction, as well as a scale of silaphilicity of each Lewis base. Fluoride is known as the strongest silaphilic group due to the exceedingly strong Si–F bond. However, because of the strength of Si–F bond, fluoride-product dissociation is less likely to happen, thus catalytic turnover is an issue.\(^\text{12}\) On the other hand, the weakly silaphilic pyridine or triethylamine cannot efficiently activate silicon to afford any reactivity.

---

**Scheme 1.1** Mechanism of Lewis Base-catalyzed Allylation with Allyltrichlorosilane

\[
\begin{align*}
\text{R}^1\text{H} + \text{R}^2\text{R}^3\text{SiCl}_3 & \xrightarrow{\text{Lewis Base Catalyst}} \text{R}^1\text{R}^2\text{R}^3\text{OH} \\

\text{IV} & \quad \text{Scheme 1.1}
\end{align*}
\]

---

**Scheme 1.2** Silaphilicity of Different Lewis Bases

\[
\begin{align*}
\begin{array}{c}
\text{F}^- > \\
\text{NMe}_2 > \\
\text{Me}_2\text{N}^- > \\
\text{Ph}^+ > \\
\end{array}
\end{align*}
\]

---


According to the considerations discussed above, a variety of Lewis base catalysts have been developed for enantioselective allylation of aldehydes. Iseki and co-workers reported a chiral monodentate phosphoramide for allylation of aromatic aldehydes (eq. 1.1).\(^\text{13}\) In the presence of 10 mol % phosphoramide catalyst 1.1, homoallylic alcohol 1.2 can be obtained with 88% ee in 83% yield. The reaction proceeds with low efficiency; long reaction time (7 days) is needed to obtain maximum yield.

\[
\text{PhCHO} + \text{SiCl}_3\overset{10 \text{ mol} \% \text{1.1}}{\longrightarrow} \overset{\text{THF, } -78 \degree \text{C, 7 days}}{\longrightarrow} \text{Ph} \text{OH} \quad (\text{eq. 1.1})
\]

Denmark and co-workers have done systematic mechanistic studies of phosphoramide-catalyzed allylation of aldehydes.\(^\text{14}\) They developed bidentate phosphoramide 1.5 (eq. 1.2) for allylation of aromatic and alkenyl aldehydes. With 5 mol % catalyst 1.5, the reaction takes 8 to 10 hours to deliver product 1.2 with 87% ee. Crotylation of this catalytic system is shown to be highly diastereodivergent with 98% de for most of the cases.

\[
\text{PhCHO} + \overset{5 \text{ mol} \% \text{1.5}}{\longrightarrow} \overset{\text{CH}_2\text{Cl}_2, (i\text{-Pr})_2\text{EtN}}{\longrightarrow} \overset{-78 \degree \text{C, 8 to 10 h}}{\longrightarrow} \text{Ph} \text{OH} \quad (\text{eq. 1.2})
\]

\[
\begin{align*}
1.2 & \quad R^1=R^2=\text{H}, 87\% \text{ ee, 85}\% \\
1.3 & \quad R^1=\text{Me}, R^2=\text{H}, 86\% \text{ ee, 98}\% \text{ de, 82}\% \\
1.4 & \quad R^1=\text{H}, R^2=\text{Me}, 94\% \text{ ee, 98}\% \text{ de, 89}\% 
\end{align*}
\]


N-oxide, especially pyridine N-oxide has been used extensively for catalyzing enantioselective allylation. Scheme 1.3 lists the some of the recently successful catalysts for allylation of aldehydes, including pyridine-based tri-N-oxide 1.6,\(^{15}\) bis-N-oxides 1.7\(^{16}\) and 1.8,\(^{17}\) mono-N-oxides 1.9,\(^{18}\) 1.10,\(^{19}\) 1.11,\(^{20}\) 1.12\(^{21}\) as well as proline N-oxide 1.13.\(^{22}\)

**Scheme 1.36.** N-Oxide Catalyzed Asymmetric Allylation of Aldehydes with Allyltrichlorosilane

1.6 Kwong
74% ee, 89%

1.7 Nakajima
88% ee, 85%

1.8 Hayashi
84% ee, 95%

1.9 Kocovsky
96% ee, 75%

1.10 Kocovsky
87% ee, 60%

1.11 Kocovsky
96% ee, 90%

1.12 Benaglia
73% ee, 40%

1.13 Snapper & Hoveyda
87% ee, 82%

---


**Activation of Si–O bond for Nucleophilic Addition**

Other than the allylation reaction, aldol reactions have also been successfully catalyzed by Lewis bases. Si–O bond is activated for nucleophilic addition in these reactions. Denmark and co-workers reported a catalytic enantioselective aldol reaction of cyclohexanone derivative 1.14 to benzaldehyde.\(^{23}\) Reaction was catalyzed by a monodentate phosphoramide 1.16; anti-aldol product 1.15 was obtained with 93% ee and 95% yield. The formation of anti-aldol product from an \(E\)-configured enolate 1.14 is indicative of a chair-like transition state model \(V\).\(^{24}\) The relative stereoinduction could be viewed in terms of a ternary assembly wherein aldehyde, Lewis base, and enolate are arranged in a hexacoordinate constellation about the silicon atom.

_Scheme 1.4_ Catalytic Enantioselective Aldol Additions of Cyclohexanone Enolate

![Scheme 1.4](image)

**Silicon-based Reactions with Potential to be Catalyzed by Lewis Base**

As shown in the brief overview above, Si–C and Si–O bonds can be efficiently activated by Lewis bases. This strategy might be applicable to a broader range of reactions, for example, rearrangements. When 1,5-dienes are substituted with a hydroxy group at the C3 position, they undergo a rearrangement to first give enols that are

---


subsequently converted to the corresponding δ,ε-unsaturated carbonyl compounds. This reaction is referred to as Oxy-Cope rearrangement.\textsuperscript{25} When the C3 hydroxy group is converted to its alkoxide, the rate of the reaction is accelerated by the factors of $10^{10} - 10^{17}$ and rearrangement usually occurs below room temperature.\textsuperscript{26} The reaction goes through a highly ordered chairlike transition VI (Scheme 1.5).

**Scheme 1.5 Anionic-oxy Cope Rearrangement**

\[
\begin{array}{c}
\text{O}
\end{array}
\]

Silyl ethers of vinyl allyl alcohols have also been used in oxy-cope rearrangement.\textsuperscript{27} These reactions proceed at 140–180 °C. The concept of Lewis base activation of Si–O bond might be applicable here. As shown in Scheme 1.6, if a Lewis base can coordinate to the silyl ether and activate it, which makes the ligands around the silicon more electron rich (closer to the anionic transition state VI), the oxy-Cope reaction might be accelerated and catalyzed. Incorporating a chiral Lewis base, the oxy-Cope might be promoted in an enantioselective fashion.

**Scheme 1.6 Anionic-oxy Cope Rearrangement**

\[
\begin{array}{c}
\text{R}_3\text{SiO}
\end{array}
]\n


\textsuperscript{27} Schneider, C.; Rehfeuter, M. Synlett 1996, 212–214.
The [3,3]-sigmatropic rearrangement of silyl ketene acetals to $\gamma,\delta$-unsaturated carboxylic acids is referred to as the Claisen-Ireland rearrangement.\textsuperscript{28} It has been found that with forming a carbanion on substrate \textbf{1.17} (Scheme 1.7), the reaction temperature can be lowered for the Claisen rearrangement.\textsuperscript{29} With sodium hydride in the reaction, a carbanion was formed $\alpha$ to the $p$-Ts group. This significantly lowered the reaction temperature to $20 \degree C$. Without sodium hydride, the same transformation has to be carried out at $100 \degree C$. High diastereoselectivity indicates that the Claisen rearrangement proceeds with a chair-like closed transition state.

\begin{figure} 
\centering 
\includegraphics[width=\textwidth]{Scheme1.png} 
\caption{Carbanion-accelerated Claisen Rearrangement} 
\end{figure}

The Ireland-Claisen rearrangement incorporating a silyl ketene acetal might also be catalyzed by Lewis base. When a Lewis base activates the silyl ketene acetal (Scheme 1.8), the silyl ether oxygen should be more electron rich. As show above in Scheme 1.7, the carbanion at the same position should accelerate the reaction. In a similar situation, Ireland-Claisen rearrangement catalyzed by Lewis base might be feasible.

\textsuperscript{28} The reaction was first reported by R. E. Ireland. For reference, see: Ireland, R. E.; Mueller, R. H. \textit{J. Am. Chem. Soc.} \textbf{1972}, \textit{94}, 5897–5898.
1.3 Silicon-Based Lewis Acid Mediated Reactions

Aldol Reaction and Passerini Reaction as Examples

The weakly Lewis acidic species, silicon tetrachloride (SiCl₄), can be activated by Lewis basic ligands, leading to formation of a stronger Lewis acid. The concept of Lewis based activation of Lewis acid introduced by Denmark has been applied to catalytic enantioselective aldol and other reactions.

In the aldol reaction discussed above in Scheme 1.4, the trichlorosilyl enol ether nucleophile is activated by Lewis base. In contrast, with the Lewis base activation of Lewis acid strategy, the aldehyde electrophile is activated in the aldol reaction (Scheme 1.9).³⁰ In the presence of 1.1 equivalents of SiCl₄ and 5 mol % bidentate catalyst 1.20 in 15 minutes, high enantioselectivities were observed for the addition of silyl ketene acetal to aromatic aldehyde to afford 1.21 and aliphatic aldehyde to afford 1.22 in good yields.

Scheme 1.9 Aldol Reaction using Lewis Base Activation of Lewis Acid Strategy

As shown in complex VIII (Scheme 1.9), the Lewis basic bidentate phosphoramide 1.20 coordinates to SiCl₄, followed by dissociation of chloride anion. The process generates a stronger Lewis acidic complex. Subsequent coordination of the Lewis basic carbonyl oxygen of aldehyde at the hypervalent silicon-based chiral Lewis acid finally leads to intermediate VIII.

The aldol reaction is highly stereoconvergent; (E)- or (Z)-configured silyl ketene acetal affords the identical product 1.23 (eq. 1.2) with exceptional diastereoselectivity (98% de). This finding indicates that the reaction proceeds with an open transition state. The scope of the aldol reaction has been extended to silyl enol ether as well as vinylogous aldol reaction.

Denmark and co-workers also reported a catalytic enantioselective Passerini-type reaction.\textsuperscript{35} Isocyanides such as 1.24 are also potential nucleophiles for addition to carbonyls. Benzaldehyde was converted into α-hydroxy amide 1.25 with >98% ee in 96% yield after hydrolysis.

**Scheme 1.10 Catalytic Enantioselective Passerini-type Reaction**

The concept of Lewis base activation of Lewis acids introduced by Denmark is a significant enhancement of catalytic asymmetric addition to carbonyls. In these reactions, the actual catalyst is a hypervalent silicon-based Lewis acid, which interacts with the electrophilic reactant, thereby lowering its lowest unoccupied molecular orbital (LUMO);\textsuperscript{5} the nucleophilic reactant in turn is activated neither by this catalyst nor by the chiral additive.

**Reactions with Potential to be Mediated by Silicon-based Lewis Acids**

Isocyanides undergo a four-component reaction in the presence of an anime, aldehyde or ketone and a nucleophile to provide a single condensation product is referred

\textsuperscript{35} Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* 2003, 125, 7825–7827.
to as Ugi multicomponent reaction.\textsuperscript{36} The mechanism of the reaction is shown in Scheme 1.11. Condensation between an aldehyde and an amine affords an imine intermediate. Isocyanide addition followed by nucleophilic attack by water delivers the $\alpha$-amino amide product.

The catalytic enantioselective Passerini reaction developed by Denmark and co-workers involves activation of an aldehyde by a chiral Lewis acidic hypervalent silicon complex (Scheme 1.10). If the similar concept is applicable to activation of imine intermediates (Scheme 1.11),\textsuperscript{37} then catalytic enantioselective Ugi multicomponent reaction might be possible.

**Scheme 1.11 Ugi Multicomponent Reaction**

![](https://example.com/scheme_1.11.png)

Takasu, Ihara and co-workers reported a novel enantioselective enol silylation process.\textsuperscript{38} Cyclohexanone 1.24 was desymmetrized by forming an silyl enol ether with 42\% ee at $-100$ °C. The mechanism of the reaction is believed to involve the pentavalent intermediate IX (Scheme 1.10). Generation of IX is likely to occur by an associative displacement of the triflate moiety at silicon by amine 1.28, followed by coordination of the Lewis basic carbonyl of 1.26. Then the intramolecular proton abstraction by silyl amine nitrogen enables differentiation of the enantiotopic protons. This methodology


replies on the super-stoichiometric amount of a modified chiral silicon reagent since the chiral amine is protonated and, thus, consumed in the course of the reaction.

Scheme 1.12 Enantioselective Enol Silylation

This methodology might be improved by incorporating a more Lewis acidic silicon species, such as SiCl₄. Choice of a chiral promoter for the reaction is critical; involving a stronger promoter such as phosphoramidate, imidazole or N-oxide instead of secondary amine would further increase the Lewis acidity of activated hypervalent silicon. A general base might also be needed to deprotonate the chiral promoter after intramolecular deprotonation, so the chiral promoter is not consumed in the course of reaction. These factors might be helpful for making this enantioselective enol silylation process into a catalytic protocol with better enantioselectivity.

1.4 Lewis Base Activation of Silicon by Strain Release Strategy

Research groups led by Myers and Denmark independently discovered that enol silacyclobutanes could undergo aldol-like reaction with benzaldehyde while no reaction was observed with the corresponding acyclic enol silanes (Scheme 1.13)
Scheme 1.13 Aldol Reaction of Cyclic and Acyclic Enol Silanes

This phenomenon responsible for this unusual reactivity was termed “strain-release Lewis acidity” by Denmark. As illustrated in Scheme 1.14, When a tetravalent silicon is incorporated into a small (4 or 5-membered) ring, the endocyclic bond angle (79° or 90°) is much smaller than the preferred angle of a tetrahedral configuration (109°) and adds significant strain to the system. In a pentavalent silicon, the two endocyclic bonds can possess the axial and equatorial positions of a trigonal bipyramidal, which has a preferred angle of 90°. Thus, silicon constrained in a small ring has a higher tendency to expand its valance and thus possesses higher Lewis acidity.

Enantioselective Strain-released Allylation

With this concept, Leighton and co-workers have developed practical allylations of aldehydes as well as imines. They examined a variety of chiral allylating reagents

incorporated to small rings. Allylsilane 1.29 derived from pseudoephedrine is a highly efficient and enantioselective reagent for allylation of various aldehydes (eq. 1.3).\textsuperscript{42} Later, Leighton and co-workers significantly improved the allylation reaction by using a modified chiral allylsilane 1.30. Excellent enantioselectivities were obtained for a wide range of aldehydes (96-98% ee, eq 1.4).\textsuperscript{43}

\[
\text{RCHO} + \text{PhMe} \xrightarrow{-10 \, ^\circ\text{C}, 2 \, \text{h}} \text{RCH}(_2\text{CHMe}_2)\text{OH}
\]

Houk and co-workers carried out computational mechanistic study and located the transition states of the allylation reaction.\textsuperscript{44} The model (Figure 1.4) based on the transition states suggests the components important for the stereoselectivity of the chiral allylsilane reagents: 1) attack of aldehyde oxygen on an apical position of the Lewis acidic silicon center (anti to a N); 2) an antiperiplanar arrangement of an oxygen lone-pair and the Si–Cl bond in the chair transition state; 3) location of the chlorine with the lone pair anti to the lone-pair of apical nitrogen.

\textsuperscript{44} Zhang, X.; Houk, K. N.; Leighton, J. L. \textit{Angew. Chem., Int. Ed.} \textbf{2005}, \textit{44}, 938-941.
Reactions with Potential to be Catalyzed by Strain Release Strategy

Silicon-tethered cycloadditions are useful synthetic tools to access polycyclic structures. As shown in Scheme 1.15, silicon-tethered Diels-Alder reaction proceeds with good diastereoselectivity and yield. However, the reaction needs high temperature (190 °C) and long reaction time (20 h).

Scheme 1.15 Silicon-tethered Intramolecular Diels-Alder Reaction

To improve the reaction, silicon-tethered substrates could be modified into more reactive silacyclobutane, such as 1.32 (Scheme 1.16). The silicon in substrate 1.32 is highly Lewis acidic, thus, is likely to be activated by silaphilic Lewis base to formation a hypervalent silicon complex for strain release. In the activated hypervalent silicon intermediate, the diene dienophile might be brought closer toward each other (from tetrahedral to trigonal bipyrimidal, angles might change from 109° to 90°), thus the intramolecular Diels-Alder reaction might be facilitated and catalyzed by a Lewis base. Incorporating substrate 1.33 into a 5-membered ring with chiral backbone might increase the reactivity as well as bring in enantioselectivity. Ideally, with appropriate substrate with Lewis acidic silicon as well as incorporating an effective chiral Lewis base, the silicon-tethered Diels-Alder reaction might be catalyzed in an enantioselective fashion.

**Scheme 1.16** Possible Improvement of Silicon-tethered Intramolecular DA Reaction

In principle, silicon-tethered [5+2] cycloaddition (eq. 1.5)\(^{47}\) as well as 1,3-dipolar cycloaddition (eq. 1.6)\(^{48}\) might also be catalyzed by Lewis base by strain release strategy if the silicon tether is incorporated into a small ring.

1.5 Conclusion and Outlook

In conclusion, some recent significant developments of reaction involving hypervalent silicon intermediate have been briefly discussed. The concept of Lewis base activation of silicon might be applicable to a broader range of silicon-based or mediated reactions that have not been catalyzed before. With the focus on organocatalysis and continuing interest in reactions involving silicon, organosilicon chemistry will continue to have a significant influence on organic synthesis.


Chapter 2 Catalytic Enantioselective Silylation of Acyclic and Cyclic Triols: Application to Total Syntheses of Cleroindicins D, F and C

2.1 Introduction and Background

*Enantioselective Silylation Reaction*

The importance of the silicon–oxygen linkage to temporarily protect a hydroxy group is reflected in its extensive use in the synthesis of complex molecules.\(^{49}\) Silyl ethers are easily introduced with a variety of reagents, have the virtue of being quite stable to a variety of organic reactions, and are readily removed under specific conditions that do not attack other functional groups.\(^{50}\) Thus, development of chiral reagents to undergo or, more importantly, chiral catalysts to promote enantioselective silylation can greatly increase the efficiency with which optically enriched organic molecules are prepared.

*Reagent Controlled Enantioselective Silylation Reaction*

There are a few examples of reagent controlled enantioselective silylation reactions. In the classical formation of a silyl ether, a chlorosilane is treated with an alcohol in the presence of a nucleophilic catalyst and stoichiometric amount of base.\(^{51}\) Ishikawa and co-workers employed chiral guanidine 2.6 as a superbase reagent to activate silyl chlorides for enantioselective silylation of secondary alcohols such as 2.1 and 2.3, and at that time unprecedented, obtained enantioselectivity (Scheme 2.1).\(^{52}\)

---


Stoichiometric quantity of guanidine 2.6 was used for these reactions. With TBSCI, the enantioselectivity was poor ($k_{rel} = 2$). With bulkier TIPSCI, moderate selectivity was obtained ($k_{rel} = 5$ and 6 for substrate 2.1 and 2.3, respectively). Long reaction time was required for the chiral guanidine promoted silylation (6 to 10 days). Although this silylation reaction requires stoichiometric chiral reagents, long reaction time and only achieved moderate enantioselectivity, it still represents the first asymmetric silylation and proves that chiral Lewis base activation of silicon for asymmetric silylation of alcohols is feasible.

**Scheme 2.1** Chiral Guanidine as Superbase for Enantioselective Silylation of Alcohol

with TBSCI:

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, 23 \, ^\circ\text{C}, 10 \, \text{d} \\
&
\begin{align*}
(\pm)-2.1 &
\quad 2 \, \text{equiv.} \\
(\pm)-2.2 &
\quad 78\%, 31\% \text{ ee} \\
(\pm)-2.3 &
\quad 18\% \text{ ee} \\
\end{align*}
\end{align*}
\]

with TIPSCI:

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, 23 \, ^\circ\text{C}, 6 \, \text{d} \\
&
\begin{align*}
(\pm)-2.1 &
\quad 2 \, \text{equiv.} \\
(\pm)-2.3 &
\quad 2 \, \text{equiv.} \\
(\pm)-2.4 &
\quad 79\%, 58\% \text{ ee} \\
(\pm)-2.5 &
\quad 15\%, 70\% \text{ ee} \\
\end{align*}
\end{align*}
\]

Wiskur and co-workers recently reported an enantioselective tandem Mukayama aldol reaction, consisting of a carbon-carbon bond-forming process and a silylation protection step in which the enantioselectivity results exclusively from the silylation step.\textsuperscript{53} The addition of a TMS silyl ketene acetal 2.7 to benzaldehyde 2.8 promoted by a Lewis basic chiral ammonium salt (CD-\text{Me}^+\text{OAc}^- a methylated cinchona alkaloid paired

with acetate, 2.11, Scheme 2.2) afforded aldol product alcohol 2.9 with 68% ee and TMS ether 2.10 with 8% ee, both are enantioenriched in the opposite enantiomer. The proposed mechanism is shown in Scheme 2.2. The acetate of ammonium salt 2.11 activates the silyl ketene acetal 2.7 for nucleophilic attack on the aldehyde to afford the racemic alkoxide. Racemic alkoxide pair with chiral cinchonidine cation to form diastereomeric salts 2.12 and 2.13. The enantioselectivity arises from the different reactivities of the diastereomeric salts with the silyl source, thus it is a kinetic resolution of the second silylation step. Silyl source could be TMSOAc or silyl ketene acetal 2.7, the authors hypothesized it’s the silyl ketene acetal 2.7 because it presents in higher concentration. The mechanism of the reaction is still not clear and the enantioselectivity of the silylation step is poor ($k_{rel}=2$).

Scheme 2.2 Enantioselective Silylation in Mukaiyama Aldol Reaction

Alternatively, a less established approach of forming an oxygen-silicon bond is

\[ \text{CD-Me}^\ominus \text{OAc} \rightarrow \text{TMSOAc} \]

transition metal-catalyzed dehydrogenation, with hydrogen gas as the only byproduct generated by this transformation.\textsuperscript{55} Oestreicher and co-workers devised a novel concept based on an unprecedented diastereoselective transition metal-catalyzed dehydrogenative silicon-oxygen coupling of silicon-stereogenic silane and racemic alcohol (Scheme 2.3).\textsuperscript{56} Racemic secondary alcohol 2.14 with a pendant donor can be resolved using enantioenriched silane 2.15 (96% ee) with a $k_{rel}$ value around 10. The donor ligand (pyridine) of the substrate 2.14 is critical to the selectivity. In the proposed transition state model 1 (Scheme 2.3), the bi-dentate substrate 2.14 chelates to copper, chiral silane 2.15 undergoes preferential concerted $\sigma$-bond metathesis with one of the enantiomeric Cu(I)-alkoxide complex to afford enantioenriched product 2.16.

\textbf{Scheme 2.3} Kinetic Resolution of Secondary Alcohol by Dehydrogenative Coupling with Silicon-Stereogenic Silane (Copper System)

Later, the same research group found that use of rhodium and N-heterocyclic carbene 2.17 (Scheme 2.4) instead of CuCl and phosphine ligand, the selective of the dehydrogenative coupling increased significantly ($k_{rel} > 50$ for rhodium system \textit{v.s.} $k_{rel} = 10$ for copper system).\textsuperscript{57} The limitation of this methodology is the strict requirement of substrate structure. Two-point binding of substrates emerged as a pivotal feature for selectivity, which required pre-installation of pendant nitrogen-containing donor (N-


containing ligands shows in Scheme 2.4) on substrates.

**Scheme 2.4** Kinetic Resolution of Secondary Alcohol by Dehydrogenative Coupling with Silicon-Stereogenic Silane (Rhodium System)

$$\text{(±)-2.14} + \text{[SiR]} \text{2.15} \xrightarrow{5 \text{ mol} \% \text{ Rh}[(\text{cod})_2] \text{OTf}} \text{2.16} \xrightarrow{10 \text{ mol} \% \text{ HCl}} \text{(S)-2.14} + \text{(R)-2.14}$$

All the substrates possessing these N-containing donor ligands:

**Catalytic Enantioselective Silylation Reaction**

Chiral catalyst that can promote important transformations to obtain organic molecules with high enantiomeric purity is critical to modern chemical synthesis. A chiral catalyst for enantioselective silylation can increase the efficiency of synthesis. The example shown in Scheme 2.5 illustrates this point. Silyl ether 2.24 is a valuable building block used to prepare several biologically active entities in the optically active form (for example, neocarzinostatins, prostaglandins, thromboxane and nucleosides). Several procedures are known for the preparation of optically enriched 2.24. One of the most widely utilized routes is the five-step procedure (through 2.20 and 2.21) reported by Paquette and co-workers, which involves a 10-day deacylation reaction to obtain β-hydroxyketone 2.21. Later, Myers and co-workers noted that “aspects of this protocol were found to be inconvenient for rapid and large-scale material throughput” and 2.24 was produced with eroded optical purity. To overcome the recemization problem, Myers

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and co-workers developed a seven–step sequence to synthesize enantiomerically pure 2.24, including four steps of protecting group manipulation.⁶⁰

**Scheme 2.5 Enantioselective Silylation Could Increase the Efficiency of Chemical Synthesis**

A chiral catalyst that directly converts achiral diol 2.18 to optically enriched silyl ether 2.23 would present a two-step sequence to optically enriched 2.24. Thus, by shortening the synthesis route, waste production can be minimized and time efficiency is enhanced. In contrast to enzymatic or biomimetic enantioselective acylation reactions, there is no example of enantioselective silylation in biological systems.

Hoveyda, Snapper and co-workers recently identified an amino acid-based small organic molecule 2.25 (Scheme 2.6) as catalyst for enantioselective silylation of meso diols.⁶¹ As illustrated in Scheme 2.6, a variety of meso diols can be catalytically desymmetrized with good enantioselectivity and yield, including cyclic meso 1,2-diols with different ring sizes (Scheme 2.6, 2.26–2.29) and acyclic meso 1,2-diol (2.30). Moreover, desymmetrization of selected meso 1,3-diols was also accomplished with the

---


same strategy (Scheme 2.6, 2.31 and 2.23).

Scheme 2.6 First Example of Catalytic Enantioselective Silylation

![Scheme 2.6](image)

The proposed transition state model II is shown in Scheme 2.6. Catalyst 2.25 is formed of two parts: N-methyl imidazole moiety and amino acid-based chiral backbone. N-methyl imidazole is a proven silaphilic activator of chlorosilanes. On the basis of principles presented by Guttmann and developed by Denmark, by serving as a donor ligand to the Si center, the imidazole moiety promotes redistribution of electron density and enhancement of Si electrophilicity. Substrate-catalyst association by H-bonding, secondary amine and amide sites of the catalyst 2.25 serving as H-bond acceptors from

---

the diol substrates, results in silylation of one enantiotopic alcohol.\textsuperscript{65} A shortcoming of this methodology is that it requires relatively high catalyst loading. Routinely used catalyst loadings are 20-30 mol %, leaving room for improvement. However, this deficiency is tempered by the practical advantage that the chiral catalyst is easily recovered in quantitative yield after a mild aqueous wash. The recovered catalyst can be re-used with the initial efficiency and enantioselectivity.

Later, Hoveyda, Snapper and co-workers extended this catalytic enantioselective silylation from desymmetrization of \textit{meso} diols to kinetic resolution of unsymmetrically substituted 1,2-diols.\textsuperscript{66} Kinetic resolution of chiral 1,2-diols is more complex than that of desymmetrization of \textit{meso} diols. An effective kinetic resolution, must involve preferable with one enantiomer of the substrate (rate of a$\rightarrow$b $\gg$ ent-a$\rightarrow$ent-b; Scheme 2.7). This class of transformation, however, demands an additional and critical attribute: the silylation must proceed with high site selectivity (rate of a$\rightarrow$b $\gg$ a$\rightarrow$ent-c).

Scheme 2.8 demonstrates the representative substrates of kinetic resolution of chiral 1,2-diols catalyzed by small organic molecule \textsuperscript{2.25}. Primary/secondary diol \textit{rac-}

2.32 and primary/tertiary diol rac-2.33 can be catalytically resolved with remarkable selectivity \( (k_{rel} > 50) \).\(^{67}\) (S)-2.32 and (R)-2.33 can be recovered as a single enantiomer, primary hydroxy groups are silylated over secondary and tertiary hydroxy groups exclusively in the reaction. Silylation of compound rac-2.34 demonstrates the highly discriminating nature of the catalyst 2.25 that it is able to differentiate small steric variations (methyl group versus ethyl group in a vicinal diol). Kinetic resolution of rac-2.34 proceeds with good site selectivity (97:3 favoring methyl vicinal alcohol) and good enantioselectivity \( (k_{rel} = 29) \). Compound (2S,3R)-2.33 was obtained with 98% ee. Syn 1,2-diols such as 2.34 are not available through Sharpless asymmetric dihydroxylation.\(^{68}\)

**Scheme 2.8** Representative Substrates of Enantio- and Site-Selective Silylation of Chiral Racemic 1,2-Diols

The proposed transition state model III (Scheme 2.8) is similar to that of enantioselective silylation of meso diols (II in Scheme 2.6). The only difference is that for kinetic resolution, chiral 1,2-diols associate with catalyst through H-bonding, putting the hydroxy group with the smaller \( R_S \) group close to the bulky activated hypervalent


silicon moiety, which accounts for the high site selectivity.

The recent findings by Hovayda, Snapper and co-workers have rapidly advanced the area of catalytic enantioselective silylation. The reactions are operational simple. A variety of 1,2-diols and selected 1,3-diols are effective substrates for the methodology. Expanding the substrate scope of enantioselective silylation to more complex system such as polyols and introducing more effective catalysts (<5 mol % catalyst loading and shorter reaction time) will make this methodology truly practical.

**Synthetic Utility and Synthesis of Chiral Triols**

Polyoxygenated molecules are entities commonly found in biologically active agents. Chiral polyols, especially 1,2,3-triols are useful building block for asymmetric synthesis. Two examples shown in Scheme 2.9 demonstrate the synthetic utility of chiral triols. In an enantioselective totally synthesis of aquayamicin, compound 2.36 (Scheme 2.9) was needed as a key intermediate of AB ring that contains many oxygen functionalities. In order to obtain 2.36 with high enantiomeric purity, Suzuki and co-workers synthesized *meso* bis acetate 2.35. Enzymatic hydrolysis of 2.35 selectively took off one of the two enantiotopic acetates to afford chiral 1,2,3-triol mono acetate 2.36 as a single enantiomer in 94% yield. All-secondary 1,2,3-triol 2.38 was used in asymmetric synthesis of (−)-palitantin. To obtain compound 2.38 with good enantioselectivity, racemic acetate 2.37 was subjected to enzymatic kinetic resolution. The acetate group of one enantiomer was selectively cleaved to yield acetonide protected all-secondary triol

---

2.38 with good enantioselectivity.

Outside of the enzymatic world, there are only two examples of desymmetrization of triols through catalytic asymmetric protocols to date. Miller and co-workers developed a ‘kinase mimic’ strategy for catalytic asymmetric phosphorylation of benzyl protected myo-inositol 2.39 (Scheme 2.10).\textsuperscript{72} π-Methyl histidine-containing peptide catalysts were shown to act as minimal kinase mimics for phosphorylation reaction. Peptide 2.31 was identified as a highly site- and enantioselective catalyst through random screening algorithm. Myo-inositol derivative 2.39 was selectively phosphorylated with catalyst 2.42 to afford phosphate 2.40 with >98% ee in 65% yield. Later, the same research group discovered that peptide 2.43 with a β-turn secondary structure (induced by incorporation of proline) efficiently catalyzed the same reaction but affords the opposite enantiomer of the product. Phosphate ent-2.29 was obtained with >98% ee and 56% yield.\textsuperscript{73}


Scheme 2.10 'Kinase Mimic' Peptide-Catalyzed Phosphorylation of myo-Inositol Derivative

In summary, polyoxygenated molecules are important chiral building blocks for chemical synthesis. Catalytic asymmetric protocols that deliver chiral triols or polyols are

Kang and co-workers have developed copper-catalyzed benzylation reactions of acyclic 1,2,3-triols. Alkyl or aryl substituted triols (Scheme 2.11) can be desymmetrized using CuCl₂ with either BOX type ligand 2.44 or pyridyl imine ligand 2.45 with enantioselectivities up to 95%.

Scheme 2.11 Copper-Catalyzed Enantioselective Benzoylation of Acyclic 1,2,3-Triols

In summary, polyoxygenated molecules are important chiral building blocks for chemical synthesis. Catalytic asymmetric protocols that deliver chiral triols or polyols are

rare and still present its great challenge in catalysis.

2.2 Catalytic Enantioselective Silylation of Acyclic and Cyclic Triols

*Initial Inspiration and Retrosynthetic Analysis of Cleroindicin D*

Catalyst that promotes site-selective modification of poly-functional molecules can be of significant utility in selective chemical synthesis. Of particular importance are chiral catalysts that initiate site- and enantioselective functionalization of polyoxygenated molecules–entities commonly found in biologically active agents. Our interests in developing methods for catalytic enantioselective silylation of triols (eq. 2.1) were inspired in part by a retrosynthesis of cleroidicin D (Scheme 2.12).

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{R} \\
\text{R} & \quad \text{SiCl} \\
\text{R} & \quad \text{OH}
\end{align*}
\]

(eq. 2.1)

Cleroindicin D was isolated from *clerodendrum indicum*, a plant used in China to treat malaria and rheumatism. The structure of cleroidicin D was first assigned as *trans* diol (2.46, Figure 2.1). A racemic synthesis of cleroidicin D revised the stereochemistry of the nature product to *cis* diol (2.47), which is critical to our synthesis.

---

A retrosynthesis of cleroindicin D is shown in Scheme 2.12. We envisioned that intramolecular conjugative cyclization of enone 2.48 would afford the target hydrobenzofuran. Enantiomerically enriched enone 2.48 would be prepared by a selective β-elimination of β-hydroxy kenone 2.49, which in turn, could be accessed by site- and enantioselective silylation of tetraol 2.50.

**Scheme 2.12 A Retrosynthesis of Cleroindicin D**

On the basis of previously proposed mechanistic models, enantioselective conversion of 2.50 to silyl ether 2.49 might involve the association of a catalyst (e.g. 2.25) with either a 1,2-diol or 1,3-diol moiety through H-bonding.

**Possible Modes of Interaction between 1,2,3-triols and Catalyst**

In our laboratories, we have reported enantioselective silylation of diols. Compared to that of 1,2-diols, enantioselective silylation of 1,2,3-triols is more complex.
Whereas enantioselective silylations of cyclic as well as acyclic 1,2-diols have been largely proven to be highly selective (>80% ee), the related transformation of 1,3-diols can proceed with inferior selectivity. The examples in Scheme 2.13 are illustrative. Cyclic and acyclic 1,2-diols are all selectively silylated to afford highly enantioenriched products 2.27, 2.30, 2.33. Whereas the silylation reactions of the corresponding cyclic 1,3-diol, acyclic 1,3-diol and primary acyclic 1,3-diol are much less selective, silyl ether of 1,3-diols 2.54, 2.55 and 2.56 are obtained with low enantiomeric purity. Thus the complication regarding enantioselective silylation reaction of 1,2,3-triols (such as 2.51, 2.52 and 2.53 in Scheme 2.13) is whether the 1,2-diol (high selectivity) or the 1,3-diol (potential inferior selectivity) moieties more dominantly associate with the catalyst through H-bonding.

Scheme 2.13 Possible Modes of Interaction between Substrates and Catalyst

---

2.27
TBSO
\[
\begin{array}{c}
\text{OH} \\
\text{H}
\end{array}
\]
92% ee, -28 °C

2.30
TBSO
\[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]
90% ee, -28 °C

2.33
TBSO
\[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]
\[
\begin{array}{c}
\text{Bu}
\end{array}
\]
k_{rel} > 50, -78 °C

2.54
TBSO
\[
\begin{array}{c}
\text{OH} \\
\text{H}
\end{array}
\]
25% ee, -40 °C

2.55
TBSO
\[
\begin{array}{c}
\text{Me} \\
\text{Me}
\end{array}
\]
13% ee, -78 °C

2.56
TBDPSO
\[
\begin{array}{c}
\text{Ph}
\end{array}
\]
30% ee, -78 °C

___

78 Jason Rodrigo, Boston College, unpublished results.
Catalytic Enantioselective Silylation of Acyclic 1,2,3-Triols

Acyclic 1,2,3-triols were the class of substrates that was first tested. Substrates were synthesized in few steps from commercially available material. Trizma hydrochloride 2.57 (Scheme 2.14) is protected as acetonide 2.58. Oxidative cleavage with sodium periodate under acidic condition delivers ketone 2.59. Alkylation of the ketone 2.59 followed by deprotection of the acetonide affords the final 1,2,3-triols.

Acyclic 1,2,3-triols were subjected to catalytic enantioselective silylation conditions, 30 mol % catalyst 2.25, 1.5 equivalents of TBSCl and (i-Pr)₂EtN were used. The results of desymmetrization of 1,2,3-triols are summarized in Table 2.1. As shown in entries 1–3, triols with large alkyl substituents are silylated with high enantioselectivity (93% ee to >98% ee) to afford the desired mono silyl ether products 2.60–2.62 in 78–85% yield after purification. The reactions of the corresponding aryl-substituted triols (entries 4–6, Table 2.1) are equally efficient and enantioselective. Silylation of the triol that bears a less sterically demanding allyl group substituent (entry 7, Table 2.1) proceeds with equal efficiency with a lower enantioselectivity (89% ee).

Scheme 2.14 Synthesis of Acyclic 1,2,3-Triols

---

Table 2.1 Catalytic Enantioselective Silylation Reactions of Acyclic Triols[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Temp. [°C]</th>
<th>t (h)</th>
<th>Yield [%][b]</th>
<th>e.r. [%][c]</th>
<th>ee [%][c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBSO$_2$H$_2$R$_2$OH</td>
<td>-30</td>
<td>96</td>
<td>78</td>
<td>96.5:3.5</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>TBSO$_2$H$_2$Cy$_2$OH</td>
<td>-30</td>
<td>96</td>
<td>85</td>
<td>97:3</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>TBSO$_2$H$_2$iPr$_2$OH</td>
<td>-30</td>
<td>96</td>
<td>81</td>
<td>&gt;99:1</td>
<td>&gt;98</td>
</tr>
<tr>
<td>4</td>
<td>TBSO$_2$H$_2$Ph$_2$OH</td>
<td>-50</td>
<td>120</td>
<td>70</td>
<td>&gt;99:1</td>
<td>&gt;98</td>
</tr>
<tr>
<td>5</td>
<td>TBSO$_2$H$_2$pOMePh$_2$OH</td>
<td>-50</td>
<td>120</td>
<td>68</td>
<td>97.5:2.5</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>TBSO$_2$H$_2$pFPh$_2$OH</td>
<td>-50</td>
<td>120</td>
<td>75</td>
<td>98:2</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>TBSO$_2$H$_2$OH$_2$OH</td>
<td>-30</td>
<td>96</td>
<td>62</td>
<td>94.5:5.5</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>TBSO$_2$Me$_2$OH$_2$OH</td>
<td>-50</td>
<td>120</td>
<td>57</td>
<td>75:25</td>
<td>50</td>
</tr>
</tbody>
</table>

[a] Conditions: 1.0 M in THF, 1.5 equiv TBSCI, 1.5 equiv DIPEA; >98% primary silyl ether observed in all cases. [b] Yield of isolated product after purification. [c] Enantiomeric ratios and ee values determined by chiral GLC or HPLC analysis (see Supporting Information for details).

The results in entries 1–7 in Table 2.1 show that enantioselective silylation reactions of acyclic 1,2,3-triols proceed with high level of selectivity. These findings, as well as the previous observation regarding reactions of 1,2 and 1,3-diols (see Scheme
suggest that the silylation acyclic 1,2,3-triols proceed predominantly via complex established through H-bonding between the chiral catalyst and two adjacent alcohols of the substrate.

**Figure 2.2** Proposed Model for Enantioselective Silylation of 1,2,3-Triols

The sense of enantiodifferentiation in the transformation of acyclic 1,2,3-triols is likely controlled by the complexation between the catalyst and the substrate in a manner that leads to minimal unfavorable steric repulsion (IV in Figure 2.2). Large substituent, R_L, is positioned away from amino acid-based structure of the catalyst, while smaller hydroxy methylene unit is pointing towards the catalyst. This suggested scenario is also consistent with the level of enantioselectivity in entries 1–7 in Table 2.1. Higher selectivities are obtained with more sizable large alkyl or aryl groups (e.g. entries 1–6 in Table 1). Silylation of the substrate bearing a less steric demanding allyl group results in lower enantioselectivity (entry 7 in Table 2.1). To further test this working model, a triol with a methyl substituent was made and subjected to silylation condition. Lower selectivity was obtained (50% ee, entry 8 in Table 2.1), more importantly, it’s the opposite sense of enantioselectivity. The reversal of selectivity is likely because of the smaller size of a methyl substituent versus a hydroxy methylene unit. In this case, smaller methyl group is positioned towards catalyst chiral backbone while the hydroxy methylene
unit is away from the catalyst (V, Figure 2.2). The level of enantioselectivity is low (50% ee) because of the diminished steric difference between methyl and hydroxy methylene groups.

**Catalytic Enantioselective Silylation of Cyclic 1,2,3-Triols**

The less selective reactions of triols that contain a linear alkyl substituent at the central carbinol site (e.g. 2.66 in entry 7, Table 2.1) did not bode well for the projected plan for total synthesis of cleroindicin D (Scheme 2.12). Cyclic 1,2,3-triols with a linear alkyl substituent at the central carbinol site were further tested. *Meso* triol substrates were synthesized using the directed dihydroxylation method.\(^8^0\) Bromination followed by elimination of ketone 2.68 delivers enone 2.69.\(^8^1\) Allylic alcohol 2.70 is synthesized using the standard Lush reduction conditions. The allylic alcohol directed dihydroxylation using stoichiometric osmium tetraoxide and TMEDA as the chelating reagent affords the desired *meso*-triol 2.71 with >10:1 diastereomeric ratio, favoring all the hydroxy groups *syn* to one another.

**Scheme 2.15 Synthesis of *meso* Cyclic 1,2,3-Triols**


Cyclic triols bearing a central tertiary hydroxy group are sterically more hindered. So smaller TESCl was used instead of TBSCl for this type of substrates to achieve maximum efficiency. Silylation reactions were carried with 20 mol % catalyst loading, at –78 °C for 2 days. As summarized in Table 2.2, desired monosilylated cyclic triols 2.72–2.74 are isolated in 60–85% yield with >98% ee, regardless of the size of central alkyl group and the ring size of the substrates (entries 1–3). It is noteworthy that, in this single silylation step, three stereogenic centers are established including a synthetically challenging tertiary alcohol center with exceptional level of enantioselectivity. These silyl-protected triols obtained by this protocol cannot be selectively prepared by asymmetric dihydroxylation or stoichiometric dehydroxylations (including the directed variants). Enantioselective silylation reactions using TBSCl afford low conversion even at elevated temperature. Kolb, H.; VanNieuwenhze, M.; Sharpless, K. Chem. Rev. 1994, 94, 2483–2547.

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82 Enantioselective silylation reactions using TBSCl afford low conversion even at elevated temperature.
Table 2.2 Catalytic Enantioselective Silylation of Cyclic Triols.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield [%][b]</th>
<th>e.r.[%][c]</th>
<th>ee [%][c]</th>
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<td>60</td>
<td>&gt;99:1</td>
<td>&gt;98</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>85</td>
<td>&gt;99:1</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>84</td>
<td>&gt;99:1</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

[a] Conditions: 0.5 M in THF, 1.25 equiv TESCl, 1.5 equiv DIPEA; >98% primary silyl ether in all cases. [b-c] See Table 1.

The exceptional enantiopurity obtained of the six-membered ring triol product 2.74 is in contrast to the inferior level of enantioselectivity with which the corresponding silylation of cyclohexane-1,3-diol proceeds (38% ee with TBSCl, Scheme 2.13). This again suggests that it is more likely that two adjacent alcohols are involved in interacting with catalyst’s chiral backbone through H-bonding. The sense of the enantioselectivity comes from the exo mode of substrate-catalyst association, as depicted in VI (Figure 2.3).
Catalytic Enantioselective Silylation of All-Secondary 1,2,3-Triols

Enantioselective silylations of all-secondary triols present an additional challenge for the chiral catalyst. The external hydroxy groups and the internal hydroxy group of the meso all-secondary triols reside in a less differentiable environment and they are with diminished steric difference. In order to efficiently desymmetrize this type of substrate, chiral catalyst should be able to silylate the external hydroxy groups over the internal one (rate of $a \rightarrow b \gg a \rightarrow c$; Scheme 2.16). The central hydroxy group silylated product $c$ is still a meso compound. The chiral catalyst should be able to silylate the two external hydroxy groups selectively (rate of $a \rightarrow b \gg a \rightarrow \text{ent-b}$).

Scheme 2.16 Challenges for Enantioselective Silylation of All Secondary Triols
Enantioselective silylations of all secondary triols, summarized in Table 2.3, uniformly proceed with exceptional selectivity (from 96% to >98% ee), regardless of the substrate ring size. The outcomes of these transformations (sense and level of enantioselectivity) are consistent with the mechanistic proposal outlined above in Figure 2.3. The transformation illustrated in entry 3 of Table 2.3 requires 100 mol % of the chiral catalyst and a relatively elevated temperature (0 ºC) because of the low solubility of the cyclohexyl triol.84 Notably, processes shown in Table 2.3 proceed with exceptional site selectivity: less than 2% of the product derived from the silylation of the central secondary alcohol is observed. These silyl-protected triols are valuable building blocks for asymmetric synthesis,71 and again are not available from asymmetric or directed hydroxylation.68,80

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84 In the presence of 30 mol % catalyst 2.14 (0 ºC) and after 72 h of reaction time, silyl ether 2.65 is isolated in 32% yield and 97% ee.
Table 2.3 Catalytic Enantioselective Silylation of All-Secondary Triols.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Mol % 1</th>
<th>Temp. [°C]</th>
<th>t [h]</th>
<th>Yield [%][b]</th>
<th>e.r.[c]</th>
<th>ee[%][c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBSO</td>
<td>30</td>
<td>-30</td>
<td>96</td>
<td>70</td>
<td>98:2</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>TBSO</td>
<td>100</td>
<td>0</td>
<td>24</td>
<td>51</td>
<td>&gt;99:1</td>
<td>&gt;98</td>
</tr>
<tr>
<td>3</td>
<td>TBSO</td>
<td>30</td>
<td>-30</td>
<td>120</td>
<td>65</td>
<td>&gt;99:1</td>
<td>&gt;98</td>
</tr>
<tr>
<td>4</td>
<td>TBSO</td>
<td>30</td>
<td>-50</td>
<td>120</td>
<td>72</td>
<td>&gt;99:1</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

[a] Conditions: 1 M in THF, 1.5 equiv TESCl, 1.5 equiv DIPEA; >98% secondary silyl ether in all cases.
[b-c] See Table 4.1.

Enhancement of Enantioselectivity by the Third Hydroxy Group

As illustrated in the sections above, a variety of triols can be catalytically silylated with exceptional selectivity (Table 2.1, 2.2 and 2.3). The enantioselectivity of silylation of triols is significantly higher than that of the corresponding diols. Silylation of cycloheptane-1,2-diol affords the silyl ether product 2.28 (Scheme 2.17) with 93% ee at 40 °C. In comparison, the silyl ether of cycloheptane-1,2,3-triol 2.26 is obtained as a single enantiomer (>98% ee) at −30 °C. Six-membered ring diol and triol also show the same enantioselectivity difference (92% ee of 2.27 versus >98% ee of 2.26) even the silylation of cyclohexane-1,2,3-triol is performed at relatively elevated temperature.
It is very likely that there is a so-called ‘correction’ mechanism in the catalytic processes that helps ‘polish’ the enantioselectivity of mono silylated product.\(^\text{85}\) The detail is depicted in Scheme 2.18. The initial desymmetrization step controlled by chiral catalyst \(2.25\) might afford both enantiomers of the mono silyl ether (\(2.76\) and \(\text{ent}-2.76\) in Scheme 2.18). The dihydroxy unit of the minor enantiomer \(\text{ent}-2.76\) still has the right geometry to interact with the chiral catalyst, which could be further silylated to form the \(\text{bis}\)-silyl ether \(2.79\). Both the initial desymmetrization step and the secondary kinetic resolution step are controlled by catalyst \(2.25\). So the net result of the reaction is that mono-silyl ether \(2.76\) is obtained as a single enantiomer while \(\text{bis}\)-TBS ether is also isolated. It should be noted that, in contrast, silylation reactions of 1,2-diols, <2% \(\text{bis}\)-silyl ether product is obtained in all case.

\(\text{Scheme 2.17} \) Comparison of Enantioselectivity of Diols and the Corresponding Triols

\[
\begin{array}{ccc}
\text{TBSO} & \text{OH} & \text{TBSO} \\
2.28 & 2.27 & 2.76 \\
-40 °C & -28 °C & 0 °C \\
93% ee & 92% ee & >98% ee
\end{array}
\]

\(\text{Scheme 2.18} \) ‘Correction’ Mechanism of Enantioselective Silylation of Triols

---

Examples in Scheme 2.19 show that various amount of bis silyl ether by-product is generated from the silylation reaction, while the ‘polished’ desired mono silyl ether product is obtain as a single enantiomer.

**Scheme 2.19** 'Polished' mono Silyl Ether of Triols

\[
\begin{align*}
&\text{2.62} \quad >98\% \text{ ee, } 81\% \\
&\text{2.77} \quad >98\% \text{ ee, } 65\% \\
&\text{2.78} \quad >98\% \text{ ee, } 72\% \\
&\text{2.74} \quad >98\% \text{ ee, } 84\%
\end{align*}
\]

8% bis
18% bis
12% bis
5% bis

### 2.3 Application to Total Synthesis of Cleroindicins D, F and C

A variety of acyclic and cyclic 1,2,3-triols can be enantioselectively silylated with catalyst 2.25. The results of cyclic triols bearing a central tertiary group (Table 2.2) bode especially well with the target nature product cleroindicin D. The retrosynthesis is shown in Scheme 2.12.

**Scheme 2.12** A Retrosynthesis of Cleroindicin D

The synthesis begins with a two-step sequence involving commercially available *para*-substituted phenol 2.80 (Scheme 2.20); prettection of the primary alcohol and subsequent conversion into cyclic dienone 2.82 through oxidative dearomatization\(^8\)

\[^{86}\text{Felpin, F. }\text{Tetrahedron Lett.} \text{ 2007, 48, 409–412.}\]
proceed in 69% overall yield. Directed epoxidation of the two electrophilic alkenes in 2.82 proceeds with exceptional diastereoselectivity,\(^{87}\) affording bis-epoxide 2.83 in 92% yield after silica gel chromatography. X–ray crystal structure analysis\(^{88}\) further confirms that the tertiary alcohol and two epoxides of 2.83 are exclusively syn. Site selective reduction of the two electronically activated C–O bonds in 2.83 using Adam’s catalyst under hydrogen atmosphere\(^{89}\) yields the labile bis β-hydroxy ketone 2.84.\(^{90}\) Conversion of 2.84 into the dimethylacetal proceeds with concomitant removal of the primary silyl ether to deliver the meso tetraol 2.85 in 40% overall yield.

Scheme 2.20 Synthesis towards the meso Tetraol Intermediate

Enantioselective silylation of meso tetraol 2.85 is the key step of total synthesis. Tetraol 2.85 is a challenging substrate. Multiple H-bonding, as well as multiple Lewis basic sites of the substrate 2.85 necessitate a higher degree of precision of the catalyst 2.14 to effectively desymmetrize it. Enantioselective silylation of 2.85 in the presence of

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\(^{87}\) McKillop, A.; Taylor, R.; Watson, R.; Lewis, N. Synlett 1992, 1005–1006. For a review of hydroxyl-directed epoxidations, see:


\(^{90}\) Other reduction condition, such as SmI\(_2\) or Zn/Cu give various by-products with a maximum 20% optimized yield.
20 mol % catalyst 2.25 and 2.25 equivalents of TESCl led to the formation of 2.86 (Scheme 2.21) in >98% ee and 83% yield. The primary alcohol is protected first then one of the secondary hydroxy groups is selectively silylated. Three stereogenic centers are generated in a single step including a tertiary alcohol.

**Scheme 2.21 Key Step of Total Synthesis of Cleroindicin D**

![Scheme 2.21](image)

With chiral silyl ether 2.86 in hand, Scheme 2.22 shows the end game of the total synthesis of cleroidin D. Subsequent conversion of 2.86 into mesylate 2.87 was performed under standard conditions, affording the desired product in 92% yield. Treatment of 2.87 with five equivalents of HCl in aqueous THF (0 °C to 22 °C) for four hours led to the formation of enantiomerically pure cleroidin D, which was isolated in 45% overall yield as a single diastereomer. Thus enantioselective total synthesis of cleroidin D was achieved in eight steps from commercially available material.

**Scheme 2.22 End Game of Total Synthesis of Cleroindicin D**

![Scheme 2.22](image)

Conversion of 2.87 into the target molecule under aqueous acid condition constitutes a five-step sequence involving removal of the two silyl groups to afford
mesylate 2.89 (Scheme 2.23), conversion of the acetal into the ketone 2.90, and β-
elimination of the mesylate group to furnish the requisite enone 2.91, which undergoes
intramolecular conjugate addition to afford the furan ring of the nature product.

As illustrated in Scheme 2.24, cleroindicin D can be easily and efficiently
converted into cleroindicins F and C under standard dehydration and hydrogenation
conditions.


2.4 Conclusion

In summary, catalytic enantioselective silylation has been extended beyond the previously reported 1,2-diols. The process detailed above is applicable to variety of triol substrates and delivers otherwise difficult-to-access polyoxygenated small molecules of exceptional enantiomeric purity, significantly expanding the utility of catalytic enantioselective silylation reactions. The synthetic utility of this methodology is demonstrated in the total syntheses of cleroindicins D, F and C.

2.5 Experimental and Supporting Information

General information

Infrared (IR) spectra were recorded on a Perkin Elmer 781 spectrophotometer, \( \nu_{\text{max}} \) in \( \text{cm}^{-1} \). Bands are characterized as broad (br), strong (s), medium (m), and weak (w). \(^1\text{H}\) NMR spectra were recorded on a Varian GN-400 (400 MHz) instrument. Chemical shifts are reported in ppm with the solvent reference as the internal standard (CHCl\(_3\): \( \delta \) 7.26; CD\(_3\)OD: \( \delta \) 4.87, 3.31; pyridine-d\(_5\): \( \delta \) 8.74, 7.58, 7.22 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), and coupling constants (Hz). \(^{13}\text{C}\) NMR spectra were recorded on a Varian GN-400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent reference as the internal standard (CHCl\(_3\): \( \delta \) 77.23, CD\(_3\)OD: \( \delta \) 49.15; pyridine-d\(_5\): \( \delta \) 150.35, 135.91, 123.87 ppm). Melting points (mp) were taken with a Laboratory Devices Mel-Temp and are uncorrected. Enantiomeric ratios were determined by gas liquid chromatography (GLC) on a Hewlett Packard HP 6890 with a Beta Dex 120 (30 m x 0.25 mm x 0.25 µm film thickness), or a Gamma Dex 120
(30 m x 0.25 mm x 0.25 µm film thickness) column; or by analytical liquid chromatography (HPLC) on a Shimadzu chromatograph ((Chiral Technologies Chiralpak AS (4.6 x 250 mm), or Chiral Technologies Chiralpak OD (4.6 x 250 mm)). **Optical rotations** were measured on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. High resolution mass spectrometry (HRMS) was performed by the mass spectrometry facility at Boston College.

Chlorotriethylsilane (TESCl) was distilled from 3Å molecular sieves prior to use. Methanesulfonyl chloride (MsCl) was distilled from P2O5 prior to use. Tetrahydrofuran (THF) was dried on alumina columns by a solvent dispensing system prior to use. All other reagents were used as received.

**General procedure for desymmetrization of 1,2,3-triols through catalytic enantioselective silylation with TBSCl**

Catalyst **2.25** (19 mg, 0.06 mmol) and the triol substrate (0.2 mmol) were weighed into a 10 x 75 mm test tube. THF (48 µL) and DIPEA (52 µL, 0.3 mmol) were added with a Gilson Pipetman. The tube was capped with a septum, and the mixture was allowed to cool to −78 °C using an aceton dry-ice bath. TBSCl (45 mg, 0.3 mmol) was dissolved in THF (55 µL, total volume ~ 100 µL) and added to the test tube with a Gilson Pipetman. The test tube was capped with a septum, wrapped with Teflon tape and the mixture was allowed to stir at the appropriate temperature (see below for details) in a Cryocool® apparatus for the reported period of time. The reaction was quenched by addition of DIPEA (25 µL) and methanol (25 µL). The mixture was allowed to warm to 23 °C, diluted with ethyl acetate (20 mL) and washed with 10% citric acid aqueous
solution (10 mL). The aqueous layer was washed with ethyl acetate (2 x 15 mL) and the combined organic layer was dried over MgSO₄, filtered and concentrated to afford a yellow oil. The crude product was purified by silica gel chromatography (10% diethyl ether in hexanes to 1:1 diethyl ether:hexanes) and analyzed by GLC (Supelco Beta, or Gamma Dex 120) or HPLC.

The aqueous layer was basified with 3 N NaOH until pH 12 and washed with CH₂Cl₂ (3 x 15 mL). The combined organic layer was dried over MgSO₄, filtered and concentrated under high vacuum to provide the recovered catalyst 1 as a white solid (mass recovery > 90%). The recovered catalyst was re-used directly for the silylation reactions with the same efficiency and selectivity.

**General procedure for desymmetrization of 1,2,3-triols through catalytic enantioselective silylation with TESCl**

Catalyst 2.25 (12 mg, 0.04 mmol) and the triol substrate (0.2 mmol) were weighed into a 10 x 75 mm test tube. THF (148 µL) and DIPEA (52 µL, 0.3 mmol) were added with a Gilson Pipetman. The tube was capped with a septum, and the mixture was allowed to cool to −78 °C. TESCl (42 µL, 0.25 mmol) was dissolved in THF (158 µL, total volume ~ 200 µL) and added to the test tube with a Gilson Pipetman. The test tube was capped with a septum, wrapped with Teflon tape and the mixture was allowed to stir at −78 °C in a cryocool apparatus for 48 h. The reaction was quenched by addition of DIPEA (25 µL) and methanol (25 µL). The mixture was allowed to warm to 23 °C, diluted with ethyl acetate (20 mL) and washed with 10% citric acid (10 mL). The aqueous layer was washed with ethyl acetate (2 x 15 mL) and the combined organic layer
was dried over MgSO₄, filtered and concentrated to afford a yellow oil. The crude product was purified by silica gel chromatography (10% diethyl ether in hexanes to 1:1 diethyl ether:hexanes) and analyzed by GLC (Supelco Beta, or Gamma Dex 120).

**Characterization Data**

(R)-2-((tert-Butyldimethylsilyloxy)methyl)-3,3-dimethylbutane-1,2-diol (2.60, Table 2.1, entry 1):

**IR** (neat, thin film): 3491 (br), 2955 (m), 2926 (s), 2855 (m), 1463 (w), 1254 (w), 1082 (m), 937 (w), 837 (s), 777 (m) cm⁻¹. \( ^1H \) **NMR** (CDCl₃, 400 MHz): \( \delta \) 3.81 (1H, d, \( J = 10.0 \) Hz), 3.74 (1H, d, \( J = 10.0 \) Hz), 3.66 (2H, m), 3.18 (1H, s), 2.80 (1H, t, \( J = 6.4 \) Hz), 0.93 (9H, s), 0.91 (9H, s), 0.10 (6H, s). \( ^13C \) **NMR** (CDCl₃, 100 MHz): \( \delta \) 75.38, 66.59, 64.66, 36.15, 26.10, 25.66, 18.44, −5.25, −5.32. **HRMS** \([M^+ + H]^+\): Calculated for C₁₃H₃₁O₃Si: 236.2043; Found: 236.2053. **Optical Rotation**: \( [\alpha]^{20}_{D} = -1.2 \) (c = 1.0, CHCl₃).

Compound 2.60 was derivatized to the corresponding aldehyde by PCC oxidation. Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 1 °C/min, 8 psi.); chromatograms are illustrated below for a 93% ee sample:
2-tert-Butylpropane-1,2,3-triol:
White solid. **MP:** 77.0–78.0 °C. **IR** (neat): 3347 (br), 3238 (br), 2958 (m), 2875 (w), 1718 (w), 1468 (w), 1408 (m), 1389 (m), 1233 (w), 1028 (s), 1000 (s), 927 (m), 873 (w), 564 (m) cm\(^{-1}\). **\(^1\)H NMR** (CDCl\(_3\), 400 MHz): \(\delta 3.85 (2H, d, J = 10.8 \text{ Hz}), 3.76 (2H, d, J = 10.8 \text{ Hz}), 2.78 (3H, br), 0.94 (9H, s).** **\(^13\)C NMR** (CDCl\(_3\), 100 MHz): \(\delta 75.73, 66.32, 28.22, 25.51\). **HRMS** [M\(^+\)+NH\(_4\)]: Calculated for C\(_7\)H\(_{20}\)N\(_1\)O\(_3\): 166.1443; Found: 166.1450.

(R)-3-(tert-Butyldimethylsilyloxy)-2-cyclohexylpropane-1,2-diol (2.61, Table 2.1, entry 2):
**IR** (neat, thin film): 3421 (br), 2927 (s), 2854 (m), 1470 (w), 1450 (w), 1253 (m), 1084 (s), 836 (s), 776 (s), 671 (w) cm\(^{-1}\). **\(^1\)H NMR** (CDCl\(_3\), 400 MHz): \(\delta 3.69 (1H, d, J = 10 \text{ Hz}), 3.63 (1H, d, J = 10 \text{ Hz}), 3.62 (1H, dd, J = 11.2, 5.2 \text{ Hz}), 3.54 (1H, dd, J = 11.2, 5.2 \text{ Hz}), 2.82 (1H, s), 2.45 (1H, dd, J = 7.2, 5.2 \text{ Hz}), 1.78-1.48 (6H, m), 1.25-0.74 (5H, m), 0.91 (9H, s), 0.090 (3H, s), 0.086 (3H, s).** **\(^13\)C NMR** (CDCl\(_3\), 100 MHz): \(\delta 74.67, 66.69, 65.81, 43.10, 27.32, 27.16, 27.05, 26.80, 26.11, 18.48, -5.24\). **HRMS** [M\(^+\)+H]: Calculated for C\(_{15}\)H\(_{33}\)O\(_3\)Si: 289.2199; Found: 289.2211. **Optical Rotation:** \([\alpha]^{25}_D\) -1.8 (c = 1.0, CHCl\(_3\)).

Compound 2.61 was derivatized to the corresponding aldehyde by PCC oxidation. Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 \(\mu\)m film thickness), 140 °C hold 110 min, 15 psi.); chromatograms are illustrated below for a 94% ee sample:
**2-Cyclohexylpropane-1,2,3-triol:**

White solid. **MP:** 93.0–95.2 °C. **IR** (neat): 3271 (br), 2919 (m), 2850 (m), 1447 (w), 1120 (w), 1057 (m), 1029 (s), 672 (w), 649 (w), 627 (w), 564 (w) cm⁻¹. **¹H NMR** (CDCl₃, 400 MHz): δ 3.75 (2H, d, J = 10.8 Hz), 3.64 (2H, d, J = 10.8 Hz), 2.92 (1H, br), 2.40 (2H, br), 1.79-1.48 (6H, m), 1.23-0.90 (5H, m). **¹³C NMR** (CDCl₃, 100 MHz): δ 74.88, 66.71, 43.62, 27.17, 26.95, 26.71. **HRMS** [M⁺+NH₄⁺]: Calculated for C₉H₂₂N₁O₃: 192.1600; Found: 192.1598.

**(R)-2-((tert-Butyldimethylsilyloxy)methyl)-3-methylbutane-1,2-diol** (2.62, Table 2.1, entry 3):

**IR** (neat, thin film): 3413 (br), 2956 (m), 2929 (s), 2883 (w), 2857 (m), 1470 (m), 1389 (w), 1362 (w), 1254 (m), 1094 (s), 1021 (w), 836 (s), 777 (s) cm⁻¹. **¹H NMR** (CDCl₃, 400 MHz): δ 3.69 (1H, d, J = 9.6 Hz), 3.64 (1H, dd, J = 11.2, 4.8 Hz), 3.63 (1H, d, J = 9.6 Hz), 3.55 (1H, dd, J = 11.2, 7.2 Hz), 2.82 (1H, s), 2.44 (1H, dd, J = 7.2, 4.8 Hz), 1.86 (1H, septet, J = 6.8 Hz), 0.92 (6H, d, J = 6.8 Hz), 0.91 (9H, s), 0.094 (6H, s). **¹³C NMR** (CDCl₃, 100 MHz): δ 74.86, 66.36, 65.57, 32.37, 26.10, 18.46, 17.24, 17.10, −5.25.
HRMS [M$^+$+NH$_4^+$]: Calculated for C$_{12}$H$_{32}$N$_1$O$_3$Si: 266.2151; Found: 266.2149. **Optical Rotation**: $[\alpha]^{20}_D$ $-1.0$ ($c = 1.0$, CHCl$_3$).

Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 115 °C hold 90 min, 15 psi); chromatograms are illustrated below for a >98% ee sample:

(R)-3-(tert-Butyldimethylsilyloxy)-2-phenylpropane-1,2-diol (2.63, Table 2.1, entry 4):

**IR** (neat, thin film): 3424 (br), 2953 (w), 2884 (w), 2857 (m), 1604 (w), 1509 (m), 1254 (m), 1226 (m), 1084 (s), 1032 (w), 834 (s), 815 (m), 778 (s) cm$^{-1}$. **$^1$H NMR** (CDCl$_3$, 400 MHz): $\delta$ 7.46 (2H, m), 7.36 (2H, m), 7.28 (1H, m), 4.00 (1H, d, $J = 10$ Hz), 3.95 (1H, dd, $J = 11.6, 5.6$ Hz), 3.75 (1H, d, $J = 10$ Hz), 3.72 (1H, dd, $J = 11.6, 7.2$ Hz), 3.39 (1H, s), 2.43 (1H, dd, $J = 7.2, 5.6$ Hz), 0.87 (9H, s), 0.04 (3H, s), 0.01 (3H, s). **$^{13}$C NMR** (CDCl$_3$, 100 MHz): $\delta$ 141.74, 128.46, 127.62, 125.47, 76.10, 69.55, 68.49, 26.05, 18.48, $-5.29$. **HRMS** [M$^+$+NH$_4^+$]: Calculated for C$_{15}$H$_{30}$N$_1$O$_3$Si: 300.1995; Found: 300.1992. **Optical Rotation**: $[\alpha]^{20}_D$ $-0.72$ ($c = 1.3$, CHCl$_3$).
Enantiomeric purity was established by HPLC analysis (Chiralpak OD column (25 cm × 0.46 cm), 99/1 hexanes/i-PrOH, 1 mL/min, 220 nm); chromatograms are illustrated below for a >98% ee sample:

(R)-3-(tert-Butyldimethylsilyloxy)-2-(4-methoxyphenyl)propane-1,2-diol (2.64, Table 2.1, entry 5):

IR (neat, thin film): 3433 (br), 2952 (m), 2928 (m), 2856 (m), 1611 (w), 1512 (m), 1463 (m), 1302 (w), 1248 (s), 1178 (w), 1082 (m), 1007 (m), 833 (s), 777 (s) cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.37 (2H, m), 6.89 (2H, m), 3.95 (1H, d, J = 10 Hz), 3.92 (1H, dd, J = 11.2, 5.2 Hz), 3.80 (3H, s), 3.72 (1H, d, J = 10 Hz), 3.70 (1H, dd, J = 11.2, 7.6 Hz), 3.33 (1H, s), 2.41 (1H, dd, J = 7.6, 5.2 Hz), 0.87 (9H, s), 0.05 (3H, s), 0.02 (3H, s). ¹³C NMR (CDCl₃, 100 MHz): δ 159.11, 133.77, 126.71, 113.89, 75.77, 69.64, 68.62, 55.51, 26.08, 18.49, −5.26. HRMS [M⁺+Na]: Calculated for C₁₆H₂₈O₄Na₁Si: 335.1655; Found: 335.1646. Optical Rotation: [α]²⁰D −0.41 (c = 0.5, CHCl₃).
Enantiomeric purity was established by HPLC analysis (Chiralpak OD column (25 cm × 0.46 cm), 99/1 hexanes/i-PrOH, 1 mL/min, 220 nm); chromatograms are illustrated below for a 95% ee sample:

\[(R)-3-\text{(tert-Butyldimethylsilyloxy)}-2-(4-fluorophenyl)propane-1,2-diol\ (2.65, \text{ Table 2.1, entry 6}):\]

\text{IR (neat, thin film): 3418 (br), 2953 (m), 2928 (m), 2883 (w), 2856 (m), 1463 (w), 1252 (m), 1088 (m), 1070 (m), 1037 (m), 833 (s), 775 (s), 758 (m), 698 (s), 669 (w) cm}^{-1} . 1^H NMR (CDCl$_3$, 400 MHz): δ 7.42 (2H, m), 7.04 (2H, m), 3.95 (1H, d, $J = 10$ Hz), 3.91 (1H, d, $J = 11.2$ Hz), 3.72 (1H, d, $J = 10$ Hz), 3.68 (1H, d, $J = 11. 2$ Hz), 3.37 (1H, br), 2.38 (1H, br), 0.87 (9H, s), 0.04 (3H, s), 0.01 (3H, s). 13C NMR (CDCl$_3$, 100 MHz):

δ 127.34, 127.26, 115.34, 115.13, 75.91, 69.27, 68.28, 26.03, 18.46, −5.29. HRMS [M$^+\text{+NH}_4^+$]: Calculated for C$_{15}$H$_{29}$N$_1$O$_3$Si: 318.1901; Found: 318.1897. \text{Optical Rotation:} \[
[\alpha]_{D}^{20} = \text{−1.3 (c = 1.0, CHCl}_3)\].
Enantiomeric purity was established by HPLC analysis (Chiralpak OD column (25 cm × 0.46 cm), 99.3/0.7 hexanes/i-PrOH, 1 mL/min, 220 nm); chromatograms are illustrated below for a 96% ee sample:

![Chromatograms](image)

**2-(4-Fluorophenyl)propane-1,2,3-triol:**

White solid. **MP:** 65.5–67.0 °C. **IR** (neat): 3246 (br), 2964 (w), 2908 (m), 1606 (w), 1510 (m), 1421 (w), 1234 (m), 1045 (s), 1002 (m), 722 (m), 640 (m), 550 (s), 534 (s) cm⁻¹. **¹H NMR** (CDCl₃, 400 MHz): δ 7.43 (2H, m), 7.07 (2H, m), 3.96 (2H, dd, J = 11.2, 6.0 Hz), 3.77 (2H, dd, J = 11.2, 4.0 Hz), 3.42 (1H, s), 2.25 (2H, br). **¹³C NMR** (CDCl₃, 100 MHz): δ 127.30, 127.22, 115.75, 115.54, 76.39, 68.71. **HRMS** [M⁺+NH₄⁺]: Calculated for C₉H₁₅N₁O₃: 204.1036; Found: 204.1032.

(R)-2-((tert-Butyldimethylsilyloxy)methyl)pent-4-ene-1,2-diol (2.66, Table 2.1, entry 7):
IR (neat, thin film): 3404 (br), 2953 (m), 2929 (m), 2857 (m), 1463 (w), 1252 (m), 1093 (s), 912 (w), 834 (s), 774 (s), 669 (w) cm\(^{-1}\). \(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 5.85 (1H, ddt, \(J = 16.4, 10.8, 7.6 \text{ Hz}\)), 5.13, (1H, m), 5.10 (1H, m), 3.59 (1H, d, \(J = 10 \text{ Hz}\)), 3.57 (1H, dd, \(J = 10.4, 4 \text{ Hz}\)), 3.54 (1H, d, \(J = 10 \text{ Hz}\)), 3.50 (1H, dd, \(J = 10.4, 5.6 \text{ Hz}\)), 2.68 (1H, s), 2.27 (3H, m), 0.88 (9H, s), 0.083 (3H, s), 0.081 (3H, s). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 133.18, 118.69, 73.56, 67.25, 66.79, 39.33, 26.09, 18.47, −5.25. HRMS [M\(^{\text{+}}\)+H]:

Calculated for C\(_{12}\)H\(_{27}\)O\(_3\)Si: 247.1730; Found: 247.1735. Optical Rotation: \([\alpha]^{20}_{D} = -2.3 \) (\(c = 1.0, \text{ CHCl}_3\)).

**Stereochemistry Proof:** Compound 2.66 was derivatized to (S)-(2-allyloxiran-2-yl)methanol. \([\alpha]^{20}_{D} = -8.0 \) (\(c = 0.2, \text{ CHCl}_3\)). Previously reported optical rotation: \([\alpha]^{20}_{D} = -36 \) (\(c = 1.0, \text{ CHCl}_3\)) for enantiopure S enantiomer.\(^{91}\)

Compound 2.66 was derivatized to the corresponding mono acetate. Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 \(\mu\)m film thickness), 110 \(^{\circ}\)C hold 150 min, 15 psi.); chromatograms are illustrated below for a 89% ee sample:

\[\text{HO}_2C\text{(S)-(2-allyloxiran-2-yl)}\text{OH}\]
(S)-3-(tert-Butyldimethylsilyloxy)-2-methylpropane-1,2-diol (2.67, Table 2.1, entry 8):

$^1$H NMR (CDCl$_3$, 400 MHz):  $\delta$ 3.63 (1H, d, $J = 10.0$ Hz), 3.61 (1H, d, $J = 10.8$ Hz), 3.51 (1H, d, $J = 10.0$ Hz), 3.45 (1H, d, $J = 10.8$ Hz), 2.77 (1H, s), 2.36 (1H, s), 1.11 (3H, s), 0.91 (9H, s), 0.09 (6H, s). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 72.19, 69.37, 68.62, 26.10, 21.19, 18.49, −5.24, −5.27. **Optical Rotation:** $\left[\alpha\right]^{20}_D$ 0 (c = 1.0, CHCl$_3$).

Compound 2.67 was derivatized to the corresponding mono acetate. Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 102 °C hold 60 min, 25 psi); chromatograms are illustrated below for a 50% ee sample:

(1S,2S,5R)-1-Methyl-5-(triethylsilyloxy)cyclopentane-1,2-diol (2.72, Table 2.2, entry 1):

IR (neat, thin film): 3379 (br), 2956 (s), 2912 (m), 2876 (m), 1457 (w), 1413 (w), 1375 (w), 1239 (w), 1165 (w), 1065 (s), 991 (s), 842 (s), 730 (s), 674 (w) cm$^{-1}$. $^1$H NMR
(CDCl₃, 400 MHz): δ 3.75 (1H, t, J = 6.0 Hz), 3.62 (1H, dt, J = 7.6, 5.2 Hz), 3.34 (1H, s), 2.70 (1H, d, J = 7.6 Hz), 1.86-1.63 (4H, m), 1.19 (3H, s), 0.96 (9H, t, J = 8.0 Hz), 0.63 (6H, q, J = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 78.03, 77.41, 76.60, 30.90, 30.39, 24.49, 6.96, 5.04. HRMS [M⁺+H]: Calculated for C₁₂H₂₇O₃Si: 247.1730; Found: 247.1731. Optical Rotation: [α]²⁰_D 0 (c = 0.5, CHCl₃).

Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 110 °C to 180 °C, 0.3 °C /min, 15 psi); chromatograms are illustrated below for a >98% ee sample:

(1S,2S,5R)-1-Pentyl-5-(triethylsilyloxy)cyclopentane-1,2-diol (2.73, Table 2.2, entry 2):

IR (neat, thin film): 3450 (br), 2955 (s), 2933 (s), 2876 (m), 1459 (m), 1239 (w), 1089 (s), 1006 (s), 975 (w), 857 (w), 728 (s). ¹H NMR (CDCl₃, 400 MHz): δ 3.79 (1H, t, J = 5.6 Hz), 3.68 (1H, q, J = 6.4 Hz), 3.46 (1H, s), 2.91 (1H, d, J = 6.4 Hz), 1.80-1.66 (4H, m), 1.42-1.26 (8H, m), 0.97 (9H, t, J = 8.0 Hz), 0.89 (3H, t, J = 6.8 Hz), 0.63 (6H, q, J = 8.0 Hz).
Hz). \(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz): \(\delta\) 78.15, 76.64, 75.59, 38.71, 32.70, 31.05, 30.55, 23.39, 22.89, 14.31, 6.97, 5.10. \(\text{HRMS}\) [M\(^+\)+H]: Calculated for C\(_{16}\)H\(_{35}\)O\(_3\)Si: 303.2356; Found: 303.2357. \(\text{Optical Rotation}\): [\(\alpha\)]\(^{20}\)_D −12.2 (c = 1.0, CHCl\(_3\)).

Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 132 °C hold 350 min, 10 psi.); chromatograms are illustrated below for a >98% ee sample:

\[
\text{(1S,2S,6R)-1-Methyl-6-(triethylsilyloxy)cyclohexane-1,2-diol (2.74, Table 2.2, entry 3):}
\]

\[
\text{IR (neat, thin film): 3378 (br), 2953 (m), 2930 (s), 2870 (m), 1458 (w), 1402 (w), 1378 (w), 1158(w), 1059 (s), 969 (m), 896 (w), 837 (w).} \text{\(^{1}\text{H NMR}\) (CDCl\(_3\), 400 MHz): \(\delta\) 3.76 (2H, br), 3.45 (1H, br), 2.99 (2H, br), 1.89-1.75 (4H, m), 1.40-1.20 (8H, m), 0.87 (3H, t, \(J = 6.8\) Hz).} \text{\(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz): \(\delta\) 79.54, 76.25, 37.32, 32.62, 29.98, 23.28, 22.83, 14.26.} \text{\(\text{HRMS}\) [M\(^+\)+NH\(_4\)]: Calculated for C\(_{10}\)H\(_{24}\) N\(_1\)O\(_3\): 206.1756; Found: 206.1761.} \]
IR (neat, thin film): 3430 (br), 2941 (m), 2912 (w), 2875 (m), 1458 (m), 1414 (w), 1362 (w), 1079 (m), 1252 (m), 1041 (s), 1005 (s), 992 (s), 944 (w), 872 (m), 795 (m), 724 (s), 682 (w) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 3.53 (1H, t, \(J = 6.0\)), 3.36 (1H, m), 2.72 (1H, br), 2.64 (1H, br), 1.77-1.58 (6H, m), 1.24 (3H, s), 0.96 (9H, t, \(J = 8.0\) Hz), 0.61 (6H, q, \(J = 8.0\) Hz). \(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 76.52, 75.42, 73.24, 30.43, 30.23, 23.24, 17.52, 7.09, 5.20. HRMS [M\(^+\) + H]: Calculated for C\(_{13}\)H\(_{29}\)O\(_3\)Si: 261.1886; Found: 261.1886. **Optical Rotation**: \([\alpha]\)\(^{20}\)D \(-14.2\) (c = 1.0, CHCl\(_3\)).

Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 \(\mu\)m film thickness), 140 °C hold 80 min, 15 psi.); chromatograms are illustrated below for a >98% ee sample:

<table>
<thead>
<tr>
<th>Peak RetTime Type Width Height Area</th>
<th>Peak RetTime Type Width Height Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 67.703 MN 0.5406 6.15763e4 49.07492</td>
<td>1 67.313 MN 0.5288 1.18416e5 373.95286 1.000e2</td>
</tr>
</tbody>
</table>

(1\(S\),2\(S\),3\(R\))-3-(tert-Butyldimethylsilyloxy)cyclopentane-1,2-diol (2.75, Table 2.3, entry 1):

IR (neat, thin film): 3463 (br), 2953 (s), 2929 (s), 2857 (m), 1471 (w), 1254 (m), 1102 (s), 1004 (w), 887 (w), 836 (s), 778 (m) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 4.14 (1H,
q, J = 4.4 Hz), 3.98 (1H, dq, J = 8.4, 4.4 Hz), 3.75 (1H, dt, J = 7.2, 4.8 Hz), 2.96 (1H, d, J = 7.2 Hz), 2.67 (1H, d, J = 8.4 Hz), 1.88-1.82 (1H, m), 1.79-1.74 (1H, m), 0.91 (9H, s), 0.114 (3H, s), 0.108 (3H, s). 13C NMR (CDCl3, 100 MHz): δ 73.90, 73.84, 72.84, 30.55, 30.38, 26.05, 18.33, −4.40, −4.71. HRMS [M+H]: Calculated for C11H25O3Si: 233.1573; Found: 233.1569. Optical Rotation: [α]25D −18.3 (c = 1.0, CHCl3).

Compound 2.75 was derivatized to the corresponding bis-acetate. Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 μm film thickness), 118 °C hold 130 min, 25 psi.); chromatograms are illustrated below for a 96% ee sample:

1H NMR (CDCl3, 400 MHz): δ 3.92 (1H, m), 3.75 (1H, m), 3.57 (1H, m), 3.08 (1H, br), 2.58 (1H, d, J = 6.4), 1.24-1.86 (6H, m), 0.91 (9H, s), 0.12 (3H, s), 0.09

(1S,2S,3R)-3-(tert-Butyldimethylsilyloxy)cyclohexane-1,2-diol (2.76, Table 2.3, entry 2):

White solid. MP: 73.5–75.2 °C. IR (neat, thin film): 3431 (br), 2930 (m), 2886 (w), 2857 (m), 1471 (w), 1252 (m), 1110 (m), 1047 (s), 990 (m), 873 (m), 832 (s), 774 (s), 665 (w) cm⁻¹. 1H NMR (CDCl3, 400 MHz): δ 3.92 (1H, m), 3.75 (1H, m), 3.57 (1H, m), 3.08 (1H, br), 2.58 (1H, d, J = 6.4), 1.24-1.86 (6H, m), 0.91 (9H, s), 0.12 (3H, s), 0.09
(3H, s). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 73.21, 72.20, 71.83, 30.51, 30.30, 26.03, 18.26, 16.12, −4.51, −4.64. HRMS [M$^+$+H]: Calculated for C$_{12}$H$_{27}$O$_3$Si: 247.1730; Found: 247.1729. **Optical Rotation:** $[\alpha]_{D}^{20} = −13.4$ (c = 1.5, CHCl$_3$).

**Stereochemistry Proof:** Compound 2.76 was derivatized to compound (3aR,4R,7aS)-2,2-dimethylhexahydrobenzo[d][1,3]dioxol-4-ol. Optical rotation: $[\alpha]_{D}^{20} = 10.5$ (c = 0.6, CHCl$_3$). Previously reported optical rotation: $[\alpha]_{D}^{20} = 10.8$ (c = 1.0, CHCl$_3$) for enantiopure (3aR,4R,7aS)-enantiomer.$^{92}$

Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 102 °C hold 300 min, 15 psi.); chromatograms are illustrated below for a >98% ee sample:

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(1S,2S,3R)-3-(tert-Butyldimethylsilyloxy)cycloheptane-1,2-diol (2.77, Table 3, entry 3):

IR (neat, thin film): 3435 (br), 2928 (s), 2857 (m), 1462 (w), 1254 (m), 1071 (s), 1034 (m), 1230 (w), 835 (s), 776 (w), 671 (w) cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 4.08 (1H, m), 3.88 (1H, m), 3.66 (1H, br), 3.10 (1H, d, J = 6.8 Hz), 2.73 (1H, d, J = 10.0 Hz), 1.9-1.35 (8H, m), 0.92 (9H, s), 0.12 (3H, s), 0.09 (3H, s). ¹³C NMR (CDCl₃, 125 MHz): δ 77.00, 75.82, 73.31, 31.97, 31.22, 26.03, 23.23, 21.76, 18.18, −4.57, −4.75. HRMS [M⁺+H]: Calculated for C₁₃H₂₉O₃Si: 261.1886; Found: 261.18960. Optical Rotation: [α]²⁰ₒ −18.8 (c = 0.5, CHCl₃).

Compound 2.77 was derivatized to the corresponding acetonide. Enantiomeric purity was established by GLC analysis (Supelco Gamma Dex 120 (30 m x 0.15 mm x 0.25 μm film thickness), 92 °C hold 210 min, 25 psi.); chromatograms are illustrated below for a >98% ee sample:

(2S,3S,4R)-4-(tert-Butyldimethylsilyloxy)pentane-2,3-diol (2.78, Table 2.3, entry 4):
IR (neat, thin film): 3408 (br), 2956 (m), 2930 (m), 2887 (w), 2858 (m), 1471 (w), 1463 (w), 1254 (m), 1088 (m), 1055 (m), 995 (m), 938 (w), 832 (s), 774 (s), 675 (w) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 3.96 (1H, dq, \(J = 5.2, 6.4\) Hz), 3.84 (1H, quintet, \(J = 6.4\) Hz), 3.38 (1H, dd, \(J = 6.4, 5.2\) Hz), 2.27 (1H, br), 2.03 (1H, br), 1.25 (3H, d, \(J = 6.4\) Hz), 1.20 (3H, d, \(J = 6.4\) Hz), 0.89 (9H, s), 0.092 (3H, s), 0.086 (3H, s). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 78.656, 70.147, 68.658, 26.049, 19.441, 18.911, 18.241, −3.936, −4.645. HRMS [M\(^+\)+H]: Calculated for C\(_{11}\)H\(_{27}\)O\(_3\)Si: 235.1730; Found: 245.1725. Optical Rotation: \([\alpha]^{20}_D\) −15.5 (c = 1.0, CHCl\(_3\)).

Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C/min, 15 psi.); chromatograms are illustrated below for a >98% ee sample:

### Enantioselective total syntheses of cleroindicins D, F, C
**Scheme 2.20:**

To a mixture of 2-4-(2-hydroxyethyl)phenol **2.80** (1.52 g, 11 mmol) and imidazole (824 mg, 12.1 mmol) in THF (5 mL) at 0 °C was added a solution of TBSCI (1.82 g, 12.1 mmol in 5 mL THF) dropwise. The mixture was allowed to stir at 0 °C for 1 h before dilution with Et₂O (50 mL) and aqueous 10% citric acid solution (30 mL). The mixture was partitioned and the organic layer was collected. The aqueous layer was washed with Et₂O (50 mL x 2). The organic layers were combined and dried over anhydrous MgSO₄. The mixture was filtered and solvent was removed in vacuo to yield a colorless oil (~ 3 g). To a solution of the oil in THF (56 mL) and H₂O (17 mL) at 0 °C was added PhI(OAc)₂ (4.25 g, 13.2 mmol) portionwise. The reaction turned to dark brown upon addition of PhI(OAc)₂. After 20 min, the reaction was quenched by addition of saturated aqueous Na₂SO₃ solution (30 mL), and then washed with Et₂O (100 mL x 3). The organic layer was dried over anhydrous MgSO₄, filtered and solvent was removed in vacuo to yield a viscous yellow oil, which was purified by chromatography (10% Et₂O/hexanes to Et₂O, gradient) to yield desired product **2.82** as a pale yellow solid (2.04 g, 69% yield over 2 steps). **MP:** 52.4–53.6 °C. **IR** (neat, thin film): 3368 (br), 3177 (br), 2951 (m), 2928 (m), 2856 (m), 1665 (s), 1612 (s), 1470 (w), 1397 (m), 1250 (m), 1083 (s), 1061 (s), 1005 (m), 831 (s), 769 (s), 712 (m), 659 (m) cm⁻¹. **¹H NMR** (CDCl₃, 400 MHz): δ 6.95 (2H, d, J = 10.4 Hz), 6.12 (2H, d, J = 10.4 Hz), 4.43 (1H, br), 3.92 (2H, t, J = 6.0 Hz),
1.93 (2H, t, \( J = 6.0 \) Hz), 0.90 (9H, s), 0.0 (6H, s). \(^{13}\text{C NMR} \) (CDCl\(_3\), 100 MHz): 185.64, 151.27, 127.52, 69.77, 60.79, 41.70, 26.02, 18.28, −5.34. \( \text{HRMS} [M^{+} + H] \): Calculated for C\(_{14}\)H\(_{25}\)O\(_3\)Si: 269.1573; Found: 269.1568.

\[
\text{O} \quad \text{O} \\
\text{TBSO} \quad \text{TBSO} \\
\text{O} \\
\text{OH} \\
2.82 \quad \text{H}_2\text{O}_2, \text{K}_2\text{CO}_3 \quad \text{THF/H}_2\text{O}, 0 \text{ °C, 6h} \\
92\% \text{ yield} \\
\text{dr} > 20:1 \\
\text{OH} \\
2.83 \\
\text{TBSO}
\]

4-(2-\text{(tert-Butyldimethylsilyloxy)ethyl})-4-hydroxycyclohexa-2,5-diepoxide \ (2.83, Scheme 2.20):

To dienone 2.82 (900 mg, 3.36 mmol) in THF (28 mL) and H\(_2\)O (25 mL) at 0 °C was added H\(_2\)O\(_2\) (30% in H\(_2\)O, 3.8 mL, 34 mmol), followed by K\(_2\)CO\(_3\) (3.7 g, 27 mmol). The mixture was stirred at 0 °C for 4 h. The reaction was then quenched by addition of saturated aqueous Na\(_2\)SO\(_3\) solution (20 mL), washed with EtOAc (50 mL x 4). The organic layer was dried over anhydrous MgSO\(_4\), filtered and solvent was removed in vacuo to yield the crude product as a pale yellow solid which was purified by chromatography (1:1 Et\(_2\)O/hexanes) to yield desired product 2.83 as a white solid (930 mg, 92% yield). MP: 70.0–71.6 °C. \( \text{IR} \) (neat, thin film): 3467 (s), 3030 (w), 2954 (m), 2927 (m), 2884 (w), 2857 (s), 1702 (s), 1334 (w), 1254 (m), 1089 (m), 1072 (m), 1057 (m), 924 (m), 833 (s), 771 (s) 726 (m), 508 (s) cm\(^{-1}\).\(^{1}\text{H NMR} \) (CDCl\(_3\), 400 MHz): \( \delta \) 3.88 (2H, t, \( J = 5.6 \) Hz), 3.60 (1H, d, \( J = 4.0 \) Hz), 3.46 (2H, d, \( J = 4.0 \) Hz), 3.30 (1H, s), 2.01 (2H, t, \( J = 5.6 \) Hz), 0.88 (9H, s), 0.06 (6H, s). \(^{13}\text{C NMR} \) (CDCl\(_3\), 100 MHz): \( \delta \) 198.86, 69.26, 64.40, 58.35, 57.24, 39.16, 26.14, 18.49, −5.25. \( \text{HRMS} [M^{+} + H] \): Calculated for C\(_{14}\)H\(_{25}\)O\(_3\)Si: 301.1471; Found: 301.1465.
2-(2-Hydroxyethyl)-5,5-dimethoxycyclohexane-1,2,3-triol (2.85, Scheme 2.20):

To epoxide 2.83 (400 mg, 1.3 mmol) in EtOAc (13 mL) at 23 °C was added PtO₂ (16 mg, 4 wt%). The reaction was allowed to stir at 23 °C under a hydrogen balloon for 12 h. Solvent was removed and the crude reaction mixture was purified by chromatography (1:1 Et₂O/EtOAc to EtOAc, gradient) to furnish triol 2.84 as a colorless oil (~200 mg). MeOH (2 mL) and pyridinium p-toluenesulfonate (17 mg) was added to the oil. The mixture was heated to 55 °C for 2 h. Solvent was removed in vacuo and the crude reaction mixture was purified by silica gel chromatography (CH₂Cl₂ to 10% MeOH in CH₂Cl₂, gradient) to yield desired tetraol 2.85 as a white solid (125 mg, 40% yield over 2 steps). MP: 124.0–126.0 °C. IR (neat, thin film): 3425 (br), 3238 (br), 2955 (w), 2943 (w), 2903 (w), 1419 (w), 1334 (m), 1311 (m), 1241 (w), 1062 (m), 1025 (s), 993 (m), 948 (s), 892 (w) cm⁻¹. ¹H NMR (CD₃OD, 400 MHz): δ 3.70 (4H, m), 3.65 (2H, t, J = 4.8 Hz), 3.43 (2H, dd, J = 12.0, 4.8 Hz), 3.18 (3H, s), 3.15 (3H, s), 2.02 (2H, m), 1.98 (2H, t, J = 6.0 Hz), 1.72 (2H, t, J = 12.0 Hz). ¹³C NMR (CD₃OD, 100 MHz): δ 100.32, 76.03, 73.67, 70.70, 62.41, 58.83, 48.21, 38.79, 36.88. HRMS [M⁺+Na]: Calculated for C₁₀H₂₀O₆Na: 259.1158; Found: 259.1159.
TES-Ether (2.86, Scheme 2.21):

Catalyst 1 (6 mg, 0.02 mmol) and the tetraol substrate 2.85 (24 mg, 0.1 mmol) were weighed into a 10 x 75 mm test tube. THF (110 µL) and DIPEA (43 µL, 0.25 mmol) were added with a Gilson Pipetman. The tube was capped with a septum, and the mixture was allowed to cool to –78 °C. A solution of TESCl (42 µL, 0.225 mmol) in THF (58 µL, total volume ~ 100 µL) was added to the test tube with a Gilson Pipetman. The test tube was capped with a septum, wrapped with Teflon tape and the mixture was allowed to stir at –78 °C for 48 h. The reaction was quenched by addition of DIPEA (25 µL) and methanol (25 µL) at to –78 °C. The mixture was allowed to warm to 23 °C. The crude reaction mixture was directly purified by silica gel chromatography (10% diethyl ether in hexanes to 1:1 diethyl ether:hexanes) to yield desired product 2.86 as a clear oil (39 mg, 83% yield). IR (neat, thin film): 3462 (br), 2953 (m), 2911 (w), 2877 (m), 2829 (w), 1458 (w), 1414 (w), 1238 (w), 1082 (m), 1048 (s), 1004 (m), 920 (w), 725 (s), 675(w) cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 4.49 (1H, d, J = 4.4 Hz), 3.89 (1H, ddd, J = 11.2, 9.2, 2.4 Hz), 3.71 (1H, m), 3.56 (2H, m), 3.21 (3H, s), 3.16 (3H, s), 2.43 (1H, s), 2.13 (1H, m), 2.09 (1H, m), 1.99 (1H, m), 1.77 (2H, q, J = 12.0 Hz), 1.70 (1H, ddd, J = 14.8, 8.8, 2.8 Hz), 0.97 (9H, t, J = 8.0 Hz), 0.96 (9H, t, J = 8.0 Hz), 0.64 (6H, q, J = 8.0 Hz), 0.62 (6H, q, J = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 99.08, 75.07, 71.47, 69.97, 58.91, 48.04, 47.98, 38.90, 36.43, 35.38, 7.16, 6.94, 5.38, 4.50. HRMS [M⁺]+Na:
Calculated for C_{22}H_{48}O_{6}NaSi_2: 487.2887; Found: 487.2885. **Optical Rotation:** \([\alpha]^{20}_D +1.9\) (c = 1.33, CHCl_3).

Compound 2.86 was derivatized to the corresponding mono benzoate. Enantiomeric purity was established by HPLC analysis (Chiralpak AS column (25 cm × 0.46 cm), 99.5/0.5 hexanes/i-PrOH, 0.5 mL/min, 254 nm); chromatograms are illustrated below for a >98% ee sample:

![Chromatograms](image)

**Mesylate (2.87, Scheme 2.22):**

To TES-ether 2.86 (23 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added DIPEA (30 µL, 0.175 mmol) followed by MsCl (10 µL, 0.125 mmol). The mixture was allowed to warm to 22 °C and stir for 12 h upon which TLC analysis indicated complete conversion.
The crude reaction mixture was directly purified by silica gel chromatography (10% diethyl ether in hexanes to 1:1 diether ether : hexanes) to afford desired product **2.87** as a clear oil (25 mg, 92% yield). **IR** (neat, thin film): 3521 (br), 2954 (s), 2911 (m), 2877 (s), 1459 (w), 1414 (w), 1352 (m), 1328 (m), 1240 (w), 1173 (s), 1091 (s), 1051 (s), 1003 (s), 969 (m), 947 (m), 876 (w), 850 (m), 796 (s) cm⁻¹. **¹H NMR** (CDCl₃, 400 MHz): δ 4.69 (1H, dd, J = 12.0, 4.8 Hz), δ 3.84 (2H, t, J = 6.0 Hz), δ 3.75 (1H, dd, J = 11.6, 4.8 Hz), 3.20 (3H, s), 3.18 (3H, s), 3.06 (1H, s), 2.40-2.34 (1H, m), 2.15 (1H, t, J = 12.0 Hz), 2.07 (1H, q, J = 6.4 Hz), 2.02 (1H, m), 1.91 (1H, dt, J = 14.0, 6.0 Hz), 1.79 (1H, t, J = 12.0 Hz), 0.97 (9H, t, J = 8.0 Hz), 0.96 (9H, t, J = 8.0 Hz), 0.64 (6H, q, J = 8.0 Hz), 0.62 (6H, q, J = 8.0 Hz). **¹³C NMR** (CDCl₃, 100 MHz): δ 98.56, 80.33, 74.85, 70.53, 59.59, 48.24, 48.11, 39.49, 36.69, 36.55, 34.07, 7.14, 7.0, 5.49, 4.43. **HRMS [M⁺+Na]**: Calculated for C₂₃H₅₀O₈NaSi₂S: 565.2663; Found: 565.2639. **Optical Rotation**: [α]²⁰D –4.9 (c = 0.4, CHCl₃).

![Cleroindicin D](image)

**Cleroindicin D (Scheme 2.22):**

To mesylate **2.87** (11 mg, 0.02 mmol) in THF (1 mL) and H₂O (0.9 mL) at 0 °C was added 1 M aqueous HCl solution (100 µL). The mixture was allowed to warm to 22 °C and stir for 4 h after which, saturated aqueous NaHCO₃ solution (2 mL) was added. The mixture was washed with EtOAc (5 mL x 3). The combined organic layers were dried
over anhydrous MgSO₄, filtered and solvent was removed in vacuo to deliver a viscous yellow oil which was purified by chromatography (Et₂O to 1:1 Et₂O/EtOAc to EtOAC) to yield desired product cleroindicin D as a clear oil (1.5 mg, 45% yield). IR (neat, thin film): 3394 (br), 2881 (w), 1708 (s), 1398 (w), 1247 (w), 1051 (s), 1014 (m), 872 (w) cm⁻¹. ¹H NMR (pyridine-d₅, 400 MHz): δ 4.36 (2H, m), δ 3.99 (2H, m), 3.23 (1H, dd, J = 16.8, 4.8 Hz), 3.02 (1H, dd, J = 16.8, 6.4 Hz), 2.87 (1H, dd, J = 16.8, 3.6 Hz), 2.84 (1H, dd, J = 16.8, 3.2 Hz), 2.28 (2H, m). ¹H NMR (CDCl₃, 400 MHz): δ 4.14 (1H, m), δ 4.01 (2H, m), 3.91 (1H, q, J = 8.8 Hz), 2.87 (1H, dd, J = 16.8, 4.4 Hz), 2.61 (1H, dd, J = 16.8, 5.6 Hz), 2.58 (2H, m), 2.14 (2H, m). ¹³C NMR (pyridine-d₅, 100 MHz): δ 208.76, 84.36, 79.55, 71.85, 67.10, 44.34, 43.20, 39.78. ¹³C NMR (CDCl₃, 100 MHz): δ 207.08, 82.97, 78.91, 71.28, 66.37, 42.53, 41.90, 39.07. HRMS [M⁺+H]: Calculated for C₈H₁₃O₄: 173.0814; Found: 173.0811. Optical Rotation: [α]²⁰_D +26.3 (c = 0.095, MeOH); [α]²⁰_D +21.3 (c = 0.15, MeOH).

Cleroindicin F (Scheme 2.24):

To cleroindicin D (3.4 mg, 0.02 mmol) in CH₂Cl₂ (400 µL) at 0 ºC was added diisopropylethylamine (8 µL, 0.044 mmol), followed by addition of a solution of MsCl (1.9 µL, 0.024 mmol) in CH₂Cl₂ (100 µL). The mixture was stirred at 0 ºC for 16 h upon which TLC analysis indicated complete conversion. The crude reaction mixture was
directly purified by silica gel chromatography (Et$_2$O to 1:1 Et$_2$O/EtOAc to EtOAc) to afford desired product cleroindicin F as clear oil (2.8 mg, 92% yield). **IR** (neat, thin film): 3378 (br), 2956 (s), 2924 (s), 2854 (s), 1726 (w), 1688 (s), 1462 (m), 1377 (m), 1261 (w), 1157 (w), 1069 (w) cm$^{-1}$. **$^1$H NMR** (pyridine-d$_5$, 400 MHz): δ 6.96 (1H, d, $J$ = 10.0 Hz), 6.17 (1H, d, $J$ = 10.0 Hz), 4.52 (1H, t, $J$ = 4.8 Hz), 4.07 (1H, m), 3.89 (1H, q, $J$ = 8.0 Hz), 3.01 (1H, dd, $J$ = 16.4, 4.0 Hz), 2.87 (1H, dd, $J$ = 16.4, 4.8 Hz), 2.46 (1H, m), 2.22 (1H, m). **$^1$H NMR** (CDCl$_3$, 400 MHz): δ 6.75 (1H, dd, $J$ = 10.4, 1.6 Hz), 6.03 (1H, d, $J$ = 10.4 Hz), 4.25 (1H, ddd, $J$ = 6.0, 4.8, 1.2 Hz), 4.08 (1H, dt, $J$ = 6.4, 8.8 Hz), 3.96 (1H, dt, $J$ = 6.4, 8.8 Hz), 2.78 (1H, dd, $J$ = 16.8, 4.8 Hz), 2.61 (1H, dd, $J$ = 16.8, 6.0 Hz), 2.33 (1H, ddd, $J$ = 12.8, 8.0, 6.0 Hz), 2.23 (1H, ddd, $J$ = 12.8, 8.0, 6.4 Hz), 2.10 (1H, br). **$^{13}$C NMR** (pyridine-d$_5$, 100 MHz): δ 197.42, 128.48, 82.49, 75.37, 66.89, 41.07, 40.87. **$^{13}$C NMR** (CDCl$_3$, 100 MHz): δ 196.49, 147.57, 129.19, 81.99, 76.09, 66.48, 40.51, 39.89. **HRMS [M$^+$+H]:** Calculated for C$_8$H$_{11}$O$_3$: 155.0708; Found: 155.0700. **Optical Rotation:** $[\alpha]_{D}^{20}$ 0 (c = 0.016, MeOH).

Enantiomeric purity was established by GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C/min, 15 psi); chromatograms are illustrated below for a >98% ee sample:
Cleroindicin C (Scheme 3):

To cleroindicin F (1.5 mg, 0.01 mmol) in THF (400 µL) was added Pd/C (0.8 mg, 50 % wt). The mixture was stirred at 22 °C under H₂ (1 atm. involving a hydrogen balloon) for 1 h. TLC indicated complete conversion. The crude reaction mixture was directly purified by silica gel chromatography (1:1 Et₂O/EtOAc to EtOAC) to afford desired product cleroindicin C as clear oil (1.5 mg, >98% yield). **IR** (neat, thin film): 3398 (br), 2919 (m), 2872 (m), 1713 (s), 1647 (w), 1407 (m), 1337 (w), 1062 (m), 995 (m) cm⁻¹. **¹H NMR** (pyridine-d₅, 400 MHz): δ 4.29 (1H, t, J = 4.4 Hz), 3.94 (2H, m), 2.97 (1H, dd, J = 16.0, 4.4 Hz), 2.78 (1H, dd, J = 16.0, 4.0 Hz), 2.67 (1H, m), 2.36 (1H, m), 2.22 (2H, m), 2.07 (1H, m). **¹H NMR** (CDCl₃, 400 MHz): δ 3.97 (2H, m), 3.88 (1H, dt, J = 7.6, 8.8 Hz), 2.72 (1H, dd, J = 16.0, 4.8 Hz), 2.56 (1H, dd, J = 16.0, 4.8 Hz), 2.48 (1H, m), 2.28 (1H, m), 2.11 (4H, m). **¹³C NMR** (pyridine-d₅, 100 MHz): δ 210.05, 85.03, 77.23, 66.71, 43.53, 41.41, 36.28, 34.78. **¹³C NMR** (CDCl₃, 100 MHz): δ 209.38, 83.75, 77.95, 66.17, 42.62, 40.91, 35.25, 33.72. **HRMS** [M⁺+H]: Calculated for C₈H₁₃O₃: 157.0865; Found: 157.0862. **Optical Rotation**: [α]₂⁰D 25.9 (c = 0.082, MeOH).
2.73
2.74
TBSO
2.75
synthetic cleroindicin D
in pyridine-d$_5$

natural cleroindicin D
in pyridine-d$_5$
synthetic cleroindicin D in pyridine-d$_5$

natural cleroindicin D in pyridine-d$_5$
cleroidcin D in CDCl$_3$
Chapter 3 Kinetic Resolution of 4-Hydroxy-2-cyclopentenones through Catalytic Enantioselective Silylation

3.1 Introduction and Background

As mentioned in chapter 2, catalytic enantioselective silylation has been applied to polyols, including diols, triols and tetraols. In these systems, it has been shown that vicinal hydroxy groups are necessary for reactivity as well as enantioselectivity. A useful advancement would be to extend this catalytic enantioselective protocol to substrates that do not possess multiple hydroxy groups. Hydroxyketones are a class of interesting substrates for enantioselective silylation; instead of having two H-bonding donors, there potentially exists a H-bonding donor and an H-bonding acceptor. Enantioselective silylation of hydroxyketones will also provide valuable information for mechanistic studies of enantioselective silylation reactions.

4-Hydroxy-2-cyclopentenones are important chiral building blocks for enantioselective preparation of natural product targets. Few catalytic enantioselective methods are available for synthesizing enantioenriched 4-hydroxy-2-cyclopentenones. Given these parameters, we decided to study kinetic resolution of 4-hydroxy-2-cyclopentenones through catalytic enantioselective silylation.

Synthetic Utility of 4-Hydroxy-2-cyclopentenones

Enantioenriched 4-hydroxy-2-cyclopentenones (Figure 1) have been extensively used in enantioselective synthesis. The three-component coupling method utilizing 3.1, pioneered by Noyori, has emerged as one of the most general and useful synthetic routes.

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to prostaglandins.\(^{94}\) Access to enantiomerically pure 4-hydroxy-2-cyclopentenone 3.1 typically involves enzymatic desymmetrization of the corresponding \textit{cis}-cyclopenten-1,3-diol or diacetate.\(^{95}\) Substituted hydroxycyclopentenones in enantioenriched forms (3.2 and 3.3 in Figure 3.1) are also used widely in total synthesis. The enantioselective preparation of erythronolide by Stork and co-workers\(^{96}\) and Tanis’s synthesis of (−)-fastigilin\(^{97}\) clearly demonstrate the synthetic utility of these compounds. Due to the dearth of direct enantioselective methods, multi-step syntheses are usually required to prepare these compounds in enantioenriched fashion.\(^{98}\) Thus, development of a practical method for preparation of 4-hydroxy-2-cyclopentenones with good enantiomeric excess will be useful and will increase the efficiency of chemical syntheses.

![Figure 3.1 4-Hydroxy-2-cyclopentenones](image)

\textit{Catalytic Enantioselective Methods Based on Desymmetrization for Preparing 4-Hydroxy-2-cyclopentenone}

There are a few examples of efficient syntheses of 4-hydroxy-2-cyclopentenone 3.1 bearing different protecting groups forms using catalytic asymmetric protocols. Trost


and co-workers developed a palladium-catalyzed enantioselective oxidation of allylic esters and carbonates.\textsuperscript{99} Sterically hindered nitronate \textbf{3.6} (Scheme 3.1) is used as a nucleophilic oxidant\textsuperscript{100} to minimize C-alkylation.\textsuperscript{101} In the presence of nitronate \textbf{3.6}, 0.9 mol \% palladium source and 3 mol \% of Trost ligand \textbf{3.7}, allylic ester \textbf{3.4} can be selectively oxidized to benzoyl-protected 4-hydroxy-2-cyclopentenone \textbf{3.5} with 99\% enantiomeric excess in 61\% yield.

\begin{center}
\textbf{Scheme 3.1} Palladium-catalyzed Enantioselective Oxidation of Allylic Esters
\end{center}

\begin{center}
\text{[Diagram of Scheme 3.1]}
\end{center}

Jacobsen and co-workers reported an efficient synthesis of enantioenriched 4-hydroxy-2-cyclopentenone through a chromium-catalyzed enantioselective epoxide ring opening (Scheme 3.2).\textsuperscript{102} The enantioselective ring opening of meso epoxide \textbf{3.8} is effected by using salenCr(N\textsubscript{3}) complex \textbf{3.11} to afford azide \textbf{3.9}. Basic alumina-promoted azide elimination followed by distillation under reduced pressure provide the desired TMS-protected 4-hydroxy-2-cyclopentenone \textbf{3.10} with 94\% ee in 70\% overall yield from epoxide \textbf{3.8}.


\textsuperscript{101} Trost, B. M.; Surivet, J.-P. \textit{Angew. Chem.; Int. Ed.} \textbf{2000}, 43, 3122–3124.

Scheme 3.2 Chromium-catalyzed Enantioselective Epoxide Ring Opening

More recently, Hoveyda, Snapper and co-workers developed a catalytic enantioselective silylation of meso diols using amino acid-based catalyst 3.15. Meso-1,3-diol 3.12 can be desymmetrized with TBSCI to afford silyl ether 3.13 with 87% ee in 55% yield. Upon oxidation, the enantioenriched TBS ether of 4-hydroxy-2-cyclopentenone 3.14 is obtained. Among all of the protected forms of 4-hydroxy-2-cyclopentenone, TBS silyl ether 3.14 remains the most widely used in organic synthesis.

Scheme 3.3 Desymmetrization of meso 1,3-diols through Catalytic Enantioselective Silylation

These catalytic enantioselective protocols for efficient preparation of 4-hydroxy-2-cyclopentenone with good enantiomeric excess represent attractive alternatives to existing enzyme-base procedures.

**Catalytic Enantioselective Methods Based on Kinetic Resolution for Preparing 4-Hydroxy-2-cyclopentenone**

In Comparison to the great challenge presented in enantioselective preparation of 4-hydroxy-2-cyclopentenone, the racemic form of the compound is readily available from
commercial sources. Under acidic conditions, furfuryl alcohol 3.16 rearranges to rac-3.1 (eq. 3.1). The starting material is commercially available and inexpensive. The reaction proceeds well when scaled up. The product can be easily obtained through continuous extraction of the crude reaction mixture. Given the readily availability of rac-4-hydroxy-2-cyclopentenone, kinetic resolution should present a potentially expeditious and efficient way to access such compounds in an enantioselective fashion.

\[
\begin{align*}
3.16 & \xrightarrow{H_3PO_4/KH_2PO_4, \text{H}_2\text{O, reflux}} 3.17 \\
\text{($\pm$)-3.1} & \text{35/Kg, Aldrich}
\end{align*}
\]

Due to the sensitivity and instability of rac-3.1 (retro aldol-aldol reaction leads to racemization and polymerization), catalytic kinetic resolution of this substrate turns out to be challenging. The only two examples, to date, were developed by Noyori and co-workers. Cationic rhodium-BINAP complex 3.18 (Scheme 3.4) catalyzes isomerization of rac-4-hydroxy-2-cyclopentenone to 1,3-cyclopentanedione 3.17. The starting material is recovered after trapping with TBSCI to afford a more stable and synthetically useful silyl ether 3.14 with 91% ee and 27% yield. The \( k_{\text{rel}} \) value of the enantioselective isomerization is 5. Noyori and co-workers pioneered the area of kinetic resolution of rac-4-hydroxy-2-cyclopentenone. The limitation of this method is the reaction time (14 days) and the moderate enantioselectivity \( (k_{\text{rel}} = 5) \).

Scheme 3.4 Rhodium-catalyzed Enantioselective Isomerization

Later, Noyori and co-workers developed a ruthenium-BINAP catalyzed enantioselective hydrogenation of allylic alcohols.\textsuperscript{105} In the presence of 0.1 mol % of catalyst 3.20, rac-3.1 can be resolved with 98% ee and 32% isolated yield after TBS protection delivering a $k_{rel}$ value of 11.

Scheme 3.5 Ruthenium-catalyzed Enantioselective Hydrogenation

Catalytic kinetic resolutions pioneered by Noyori and co-workers demonstrate the power of such methods to obtain synthetically challenging chiral molecules from readily available racemic mixtures. Developing more enantioselective kinetic resolutions that are applicable to a broader range of 4-hydroxy-2-cyclopentenones will make the methods truly practical.

3.2 Catalyst Screen through Positional Scanning

Initial Results

We initiated our studies by studying the kinetic resolution of rac-4-hydroxy-2-cyclopentenone 3.1 using the catalyst 3.15 found to be optimal for enantioselective silylation of cis-1,3-cyclopentenediol 3.12. As shown in Scheme 3.6, in the presence of 10 mol % catalyst 3.15, product (−)-3.14 is obtained with 66% ee. The reaction proceeded with 5% conversion affording a $k_{\text{rel}}$ value of 6.

Scheme 3.3 Desymmetrization of meso 1,3-diols through Catalytic Enantioselective Silylation

The enantioselective excess of the recovered starting material (ee$_{\text{rsm}}$) and ee of product (ee$_{\text{prod}}$) were determined by chiral GLC analysis. These results were used to calculate the conversion (c, eq 3.2) and $k_{\text{rel}}$ value (eq 3.3) of the reaction based on the method developed by Kagan.$^{106}$

$$c = \frac{\text{ee}_{\text{rsm}}}{(\text{ee}_{\text{prod}} + \text{ee}_{\text{rsm}})} \quad \text{(eq 3.2)}$$

$$k_{\text{rel}} = \frac{\ln[(1-c)(1-\text{ee}_{\text{rsm}})]}{\ln[(1-c)(1+\text{ee}_{\text{rsm}})]} = \frac{\ln[1-c(1+\text{ee}_{\text{prod}})]}{\ln[1-c(1-\text{ee}_{\text{prod}})]} \quad \text{(eq 3.3)}$$

This encouraging initial finding indicates that kinetic resolution of 4-hydroxy-2-cyclopentenone using amino acid-based catalyst is possible, however, with low conversion. By replacing TBSCl with the less sterically hindered TESCl, the catalytic reaction could be improved.

---

reaction proceeds efficiently. For catalyst optimization through positional scanning discussed in the following section, TESCl is used instead of TBSCl.

**Catalyst Optimization: N-Terminus (Silaphilic Portion)**

The catalyst was optimized through a position scanning strategy. The N-terminus, which is the silaphilic portion of the catalyst to afford reactivity, was first investigated. A variety of *iso*-leucine derived catalysts with different Lewis basic functionalities were tested for kinetic resolution of rac-4-hydrox-2-cyclopentenone 3.1.

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<th>ee_{product}[%]</th>
<th>conv.[%]</th>
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As illustrated in Table 3.1, enantioselective silylation is sensitive to the identity of the N-terminus of the catalyst. With 10 mol % N-methylimidazole-based catalyst \textbf{3.15} and TESCl, the enantioselective silylation reaction proceeds with 44% conversion and a $k_{rel}$ value of 6 (entry 1, Table 3.1). By simply changing the methyl on imidazole to an ethyl group to afford catalyst \textbf{3.22}, both conversion and enantioselectivity drop (entry 2). Catalyst \textbf{3.23} bearing a phenyl group on the imidazole ring, changing both sterics and electronics of the catalyst, leads to poor reactivity and selectivity (entry 3). Catalyst \textbf{3.24}, a constitutional isomer of \textbf{3.15}, affords no enantioselectivity (entry 4). Catalyst \textbf{3.25} is also nonselective in the catalytic silylation (entry 5). The results in entries 4 and 5 clearly show that the position with which the imidazole ring is connected to the chiral amino acid-based side chain is essential for enantioselectivity of the kinetic resolution. Catalysts bearing other silaphilic groups such as DMAP \textbf{3.26} or pyridine \textbf{3.27} afford poor selectivity (entries 6 and 7). From the N-terminus screen, N-methylimidazole-derived catalyst turned out to be optimal affording promising reactivity and enantioselectivity.

\textit{Catalyst Optimization: Amino Acid Portion}

With the Lewis basic portion fixed as N-methylimidazole from the N-terminus study, catalysts incorporating different amino acids were tested in the kinetic resolution of \textit{rac-3.1}. Catalyst incorporating proline as the amino acid moiety does not afford any conversion, which clearly indicates the importance of the secondary amine for catalysis. Results of amino acid screen are summarized in Table 3.2.
Butyltheonine, sterically encumbered and with a big extension in the three dimensional structure. More amino acids with sterically demanding substituents. Protected threonines are also sterically hindered amino acid is ben.

When the catalyst bears a bulky tert-leucine 3.37, the enantioselectivity of the reaction is improved and $k_{rel}$ value of 9 is obtained (entry 11). This finding suggests that a sterically hindered amino acid is beneficial to enantioselectivity, leading us to investigate more amino acids with sterically demanding substituents. Protected threonines are also sterically encumbered and with a big extension in the three dimensional structure. O-tert-Butyltheonine, O-benzylthreonine and O-tritylthreonine derived catalysts 3.38, 3.39 and

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<th>entry</th>
<th>catalyst</th>
<th>AA</th>
<th>conv.[%]</th>
<th>$k_{rel}$</th>
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</tbody>
</table>

Iso-leucine-based diastereomeric catalysts 3.15 and 3.28 essentially afford the same reactivity and selectivity (entries 1 and 2 in Table 3.2). Fine tuning the sterics of the catalyst, such as incorporating leucine 3.29, valine 3.30, cyclohexylglycine 3.31 or cyclohexylalanine 3.32 does not lead to significant improvement (entries 3 to 6). Phenyl-substituted or naphthyl-substituted amino acid-based catalysts (3.33 to 3.36) also promote the kinetic resolution with moderate selectivity (entries 7 to 10).
3.40 were tested in the kinetic resolution, 3.38 affords 52% conversion with a synthetically useful $k_{\text{rel}}$ value of 13 (entries 12 to 14). Generally, a $k_{\text{rel}}$ value greater than 10 is considered to be synthetically useful. The stereogenic center in the O-tert-butylthreonine might be responsible for this significant improvement in enantioselectivity. Diastereomeric catalyst 3.41 was tested, however, much lower selectivity was observed ($k_{\text{rel}}$=5, entry 15). This result shows that catalyst 3.38 is the matched case for the kinetic resolution while catalyst 3.41 is mismatched. Without a sterically demanding protecting group on the hydroxy group, threonine derived catalyst 3.42 affords low selectivity ($k_{\text{rel}}$=4, entry 16). Catalyst with a bulky S-tritylpenicillamine 3.43 promotes the kinetic resolution with a $k_{\text{rel}}$ value of 9 (entry 17).

Finally, catalysts derived from amino acids with functionalized side chains such as cysteine, various protected histidines and aspartic acid prove to be inferior to O-tert-butylthreonine-based catalyst 3.38 (entries 18 to 20).

**Catalyst Optimization: C-Terminus**

With N-methylimidazole and O-tert-butylthreonine as fixed portion of the catalyst structure, C-terminus optimization was carried out. Various chiral and achiral amines with steric as well as electronic differences were examined. Diastereomeric catalysts 3.38 and 3.48 afford $k_{\text{rel}}$ values of 14 and 7, respectively (entries 1 and 2, Table 3.3). Thus, catalyst 3.38 is the matched case. Catalysts with phenyl substituted chiral amines 3.49 and 3.50, with electron withdrawing chloro group 3.51 and 3.52, or with electron donating methoxy group 3.53 and 3.54 do not afford any improvement in the catalytic kinetic resolution (entries 3 to 8). Aniline derived catalysts 3.55, 3.56 and 3.57 were also tested (entries 9 to 11). With an electron withdrawing CF$_3$ group on the aniline, the
catalyst promotes the kinetic resolution with similar levels of efficiency and enantioselectivity (44% conversion with a $k_{rel}$ value 13). Achiral amine derived catalyst 3.58 affords moderate selectivity (entry 12). From the C-terminus screen, a catalyst more efficient and enantioselective than 3.38 was not identified.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>R</th>
<th>conv.[%]</th>
<th>$k_{rel}$</th>
<th>entry</th>
<th>catalyst</th>
<th>R</th>
<th>conv.[%]</th>
<th>$k_{rel}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.38</td>
<td></td>
<td>53</td>
<td>14</td>
<td>7</td>
<td>3.53</td>
<td></td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>3.48</td>
<td></td>
<td>52</td>
<td>7</td>
<td>8</td>
<td>3.54</td>
<td></td>
<td>34</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>3.49</td>
<td></td>
<td>49</td>
<td>8</td>
<td>9</td>
<td>3.55</td>
<td></td>
<td>37</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>3.50</td>
<td></td>
<td>46</td>
<td>12</td>
<td>10</td>
<td>3.56</td>
<td></td>
<td>44</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>3.51</td>
<td></td>
<td>41</td>
<td>7</td>
<td>11</td>
<td>3.57</td>
<td></td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>3.52</td>
<td></td>
<td>38</td>
<td>8</td>
<td>12</td>
<td>3.58</td>
<td></td>
<td>43</td>
<td>8</td>
</tr>
</tbody>
</table>

With systematically optimized catalyst 3.38, other parameters of the reaction were also studied.
3.3 Reaction Condition Optimization

**Effect of Silylating Reagent**

As mentioned briefly in the sections above, the size of the silylating reagents effects the outcome of enantioselective silylation of rac-4-hydroxy-2-cyclopentenone 3.1. We systematically studied the effect of silyl chlorides with different substituents for the kinetic resolution.

![Table 3.4 Silylating Reagents Study](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;R&lt;sub&gt;3&lt;/sub&gt;SiCl</th>
<th>ee&lt;sub&gt;rot&lt;/sub&gt;[%]</th>
<th>ee&lt;sub&gt;prod&lt;/sub&gt;[%]</th>
<th>conv.[%]</th>
<th>k&lt;sub&gt;rel&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=R&lt;sub&gt;2&lt;/sub&gt;=Me, R&lt;sub&gt;3&lt;/sub&gt;=t-Bu</td>
<td>&lt;5</td>
<td>80</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=R&lt;sub&gt;2&lt;/sub&gt;=Me, R&lt;sub&gt;3&lt;/sub&gt;=Cy</td>
<td>50</td>
<td>60</td>
<td>45</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=R&lt;sub&gt;2&lt;/sub&gt;=Me, R&lt;sub&gt;3&lt;/sub&gt;=i-Pr</td>
<td>52</td>
<td>42</td>
<td>55</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=R&lt;sub&gt;2&lt;/sub&gt;=Me, R&lt;sub&gt;3&lt;/sub&gt;=n-Bu</td>
<td>61</td>
<td>41</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=R&lt;sub&gt;2&lt;/sub&gt;=R&lt;sub&gt;3&lt;/sub&gt;=Et</td>
<td>92</td>
<td>62</td>
<td>64</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=R&lt;sub&gt;2&lt;/sub&gt;=R&lt;sub&gt;3&lt;/sub&gt;=n-Pr</td>
<td>79</td>
<td>45</td>
<td>60</td>
<td>6</td>
</tr>
</tbody>
</table>

Using bulky TBSCl, the kinetic resolution proceeds with 5% conversion with a k<sub>rel</sub> value of 9 (entry 1 in Table 3.4). Increasing the temperature causes a drop in enantioselectivity. As the size of the silyl chlorides decreases (from tert-butyl to cyclohexyl, iso-propyl and n-butyl), the conversion of the reaction increases but enantioselectivity drops significantly (entries 2 to 4). Triethylsilyl chloride (TESCl) affords significantly better results; starting material (−)-3.1 can be obtained in 92% ee giving a k<sub>rel</sub> value of 14 (entry 5). Further increasing the triethyl substituents to tri-n-
propyl units, the enantioselectivity drops (entry 6). The silylating reagent study revealed that the enantioselective silylation reaction is sensitive to the size of silylating reagents. TESCl is the optimal reagent for kinetic resolution of rac-3.1.

**Solvent Effect**

A variety of solvents were evaluated for catalytic kinetic resolution of rac-4-hydroxy-2-cyclopentenone 3.1. Results are illustrated in Table 3.5. Compared to the reaction in THF, reactions in diethyl ether and tert-butyl methyl ether are much less enantioselective (entries 2 and 3). Use of ethyl acetate also proves to be not as selective as THF (entry 4). Performing reactions in methylene chloride, toluene and hexanes affords poor enantioselectivities (entries 5 to 7).

**Table 3.5 Solvent Effect Study**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conv.[%]</th>
<th>( k_{\text{rel}} )</th>
<th>entry</th>
<th>solvent</th>
<th>conv.[%]</th>
<th>( k_{\text{rel}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>55</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Et(_2)O</td>
<td>52</td>
<td>4</td>
<td>5</td>
<td>CH(_2)Cl(_2)</td>
<td>56</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>t-BuOMe</td>
<td>52</td>
<td>6</td>
<td>6</td>
<td>toluene</td>
<td>68</td>
<td>&lt;2</td>
</tr>
<tr>
<td>4</td>
<td>EtOAc</td>
<td>52</td>
<td>9</td>
<td>7</td>
<td>hexanes</td>
<td>41</td>
<td>3</td>
</tr>
</tbody>
</table>

Other parameters of the reaction including temperature, bases and ratio of reagents were also optimized. It was found that carrying out the reactions at \(-78 \, ^\circ\text{C}\) with 0.8 equivalent TESCl and 1 equivalent (i-Pr)\(_2\)EtN were the optimal conditions for the catalytic kinetic resolution of rac-3.1.
Catalyst Loading and Reaction Time Study

For catalyst and reaction condition optimization, 10 mol % catalyst loading was used. In the presence of optimized catalyst 3.38, TESCl and (i-Pr)₂EtN in THF at –78 ºC, catalyst loading and reaction time were also studied for the enantioselective silylation reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst 3.38 [mol %]</th>
<th>reaction time [h]</th>
<th>ee_{rem} [%]</th>
<th>ee_{prod} [%]</th>
<th>conv. [%]</th>
<th>( k_{\text{rel}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
<td>91</td>
<td>62</td>
<td>60</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>90</td>
<td>63</td>
<td>59</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>3</td>
<td>76</td>
<td>70</td>
<td>53</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>10</td>
<td>80</td>
<td>66</td>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>0.05</td>
<td>10</td>
<td>70</td>
<td>71</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>0.01</td>
<td>20</td>
<td>20</td>
<td>70</td>
<td>20</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 3.6 Catalyst Loading and Reaction Time Study

It is noteworthy, especially considering the catalyst loading in our earlier studies of enantioselective silylation of diols and polyols,\(^{61,66,93}\) that catalyst loading in these kinetic resolutions can be lowered to 0.05 mol % without adversely affecting the \( k_{\text{rel}} \) value (entry 5, Table 3.6, with 0.05 mol % catalyst, \( k_{\text{rel}}=12 \)). With 2 mol % of catalyst 3.38, the kinetic resolution reaction proceeds with 62% conversion in 1 hour, recovered starting material can be obtained in 91% ee with a \( k_{\text{rel}} \) value of 14 (entry 1). Catalyst 3.38 promotes kinetic resolution of rac-4-hydroxy-2-cyclopentenone 3.1 with great efficiency. Such low catalyst loading is rare in organocatalytic reactions.\(^{108}\) In contrast, enantioselective silylation reactions of substrates possessing multiple hydroxy groups

usually requires 20 to 30 mol % catalyst loading and 3 to 5 days. This finding suggests that enantioselective silylation of hydroxyketones may proceed through a distinct mechanism. Detailed studies will be discussed in mechanistic study section.

*Racemization Problem of Recovered 4-Hydroxy-2-cyclopentenone during Purification*

With optimized catalyst and reaction conditions, a $k_{\text{rel}}$ value of 14 can be achieved for the kinetic resolution of rac-4-hydroxy-2-cyclopentenone; starting material is enantioenriched with 91% ee (entry 1 in Table 3.7). However, upon purification to separate the remaining starting material (−)-3.1 from the product 3.21, the recovered starting material (−)-3.1 is racemized to 67% ee while the product 3.21 maintained the same enantiomeric purity (entry 2). This racemization problem could be due to trace desilylation of TES ether 3.21 upon purification using silica gel chromatography. Thus, instead of using slightly acidic silica gel, base-washed silica gel, neutral alumina and basic alumina were also tested. These attempts did not resolve the racemization problem. Recovered starting material (−)-3.1 continued to racemize to a certain extent during purification. Another suspected cause of the racemization could be the thermal instability of 4-hydroxy-2-cyclopentenone.\textsuperscript{109} Derivatization of the remaining starting material to a more stable compound should solve this problem.

\textsuperscript{109} 4-Hydroxy-2-cyclopentenones are sensitive compounds, they are easy to racemize and polymerize. In kinetic resolutions developed by Noyori and co-workers, they derivatized the 4-hydroxy-2-cyclopentenones to a TBS ether before isolation.
Table 3.7 Racemization of Recovered Starting Material Upon Purification

<table>
<thead>
<tr>
<th>entry</th>
<th>reaction time</th>
<th>conv.[%]</th>
<th>ee of (-)-3.1 [%]</th>
<th>ee of 3.21 [%]</th>
<th>( k_{rel} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 h</td>
<td>60</td>
<td>91</td>
<td>62</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>after purification</td>
<td>67</td>
<td>91</td>
<td>62</td>
<td>14</td>
</tr>
</tbody>
</table>

To derivatize the remaining 4-hydroxy-2-cyclopentenone, acetate 3.59 (eq. 3.4) was formed. We chose an acetate group, since the acetate protection is fast and the resulting acetate 3.59 is easily separated from silyl ether 3.21. As shown in eq. 3.2, the derivatized 4-hydroxy-2-cyclopentenone 3.59 can be isolated with 91% ee in 34% yield.

3.4 Substrate Scope of Kinetic Resolution of 4-hydroxy-2-cyclopentenones through Enantioselective Silylation

Substrates of 4-Hydroxy-2-cyclopentenones

As illustrated in Table 3.8, a variety of 4-hydroxy-2-cyclopentenones can be resolved with 2 mol % catalyst loading with synthetically useful levels of selectivity \((k_{rel} \geq 10)\). Kinetic resolution of rac-3.1 proceeds with 60% conversion in 1 h, subsequent acylation delivering 3.59 with 91% ee and 34% isolated yield \((k_{rel} = 14)\) (entry 1 in Table 3.8). Substituted 4-hydroxy-2-cyclopentenones, such as rac-3.2 and rac-3.3, can also be
efficiently resolved; compounds 3.66 and 3.67 can be obtained with 94% ee and 95% ee, respectively (entries 2 and 3). The enantioselective silylation is extremely sensitive to steric of the substrates. With a methyl substituent at the 5 position cis to the hydroxy group, substrate rac-3.60 undergoes kinetic solution with lower selectivity ($k_{rel} = 7$, entry 4). Other substitutions at the 5-position, such as $R^3 =$ Et or allyl group, afford lower selectivities ($k_{rel} = 8$ and 9, respectively, entries 5 and 6). Incorporating substitution other than a methyl group at the 2-position ($R^1 =$Et or allyl) leads to less enantioselective kinetic resolutions ($k_{rel} = 4-6$ versus $k_{rel} = 14$, entries 7 and 8).
Table 3.8 Kinetic Resolution of 4-Hydroxy-2-cyclopentenones through Catalytic Enantioselective Silylation

<table>
<thead>
<tr>
<th>entry</th>
<th>unreacted hydroxyketone</th>
<th>reaction time [h]</th>
<th>conv. [%]</th>
<th>ee_{rel} [%]</th>
<th>ee_{prod} [%]</th>
<th>k_{rel}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-)-3.1</td>
<td>1</td>
<td>60</td>
<td>3.59 91; 34</td>
<td>3.21 62; 60</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>(-)-3.2</td>
<td>4</td>
<td>63</td>
<td>3.66 94; 34</td>
<td>3.74 58; 58</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>(-)-3.3</td>
<td>5</td>
<td>59</td>
<td>3.67 95; 36</td>
<td>3.75 57; 60</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>3.60</td>
<td>2</td>
<td>64</td>
<td>3.68 82; 34</td>
<td>3.76 47; 55</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>3.61</td>
<td>6</td>
<td>69</td>
<td>3.69 80; 39</td>
<td>3.77 57; 59</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>3.62</td>
<td>1</td>
<td>63</td>
<td>3.70 92; 30</td>
<td>3.78 42; 66</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>3.63</td>
<td>6</td>
<td>66</td>
<td>3.71 70; 31</td>
<td>3.79 36; 62</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>3.64</td>
<td>6</td>
<td>68</td>
<td>3.72 83; 31</td>
<td>3.80 39; 63</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>3.65</td>
<td>2</td>
<td>41</td>
<td>3.73 31; 41</td>
<td>3.81 44; 26</td>
<td>3</td>
</tr>
</tbody>
</table>

The kinetic resolution of a 4-hydroxy-2-cyclopentenone bearing substitution at the 3-position (rac-3.65) gives poor selectivity (R² = Me, k_{rel} = 3, entry 9). We hypothesize that substitution at the 3-position results in a disfavored steric interaction with the nucleophilic moiety of the catalyst-silicon complex (a hypervalent silicon complex), which accounts for the low selectivity and reactivity.
As shown in Table 3.6, kinetic resolution can be performed with catalyst loading as low as below 0.1 mol %. Racemic substrates can be resolved on a gram-scale with only 0.08 mol % catalyst loading (i.e. < 3 mg of 3.38) with reactions set up in air on the bench top. The examples in eq. 3.3 and eq. 3.4 are representative. The synthetically valuable TES ethers 3.21 and 3.74 can be obtained in useful yields and enantiomeric purities.

In addition to 4-hydroxy-2-cyclopentenones, acyclic β−hydroxyketones can also be catalytically resolved with moderate enantioselectivities. Catalyst and reaction conditions were also optimized for acyclic β−hydroxyketones. Catalyst 3.38 remained the optimal catalyst for kinetic resolution of this class of substrates. As illustrated in Table 3.9, rac-3.82 can be catalytically resolved with a $k_{rel}$ value of 7; enantioenriched 3.82 can be recovered in 84% ee (entry 1). Additional steric bias on either side of the acyclic β−hydroxyketones does not improve the selectivity of this kinetic resolution (entries 2 and 3).
Table 3.9 Kinetic Resolution of Acyclic β-Hydroxyketones through Catalytic Enantioselective Silylation

<table>
<thead>
<tr>
<th>entry</th>
<th>unreacted hydroxyketone</th>
<th>reaction time [h]</th>
<th>conv. [%]</th>
<th>ee\textsubscript{ran} [%] yield [%]</th>
<th>ee\textsubscript{prod} [%] yield [%]</th>
<th>(k\text{rel})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO_Me_Me</td>
<td>3.82</td>
<td>4</td>
<td>65</td>
<td>84; 27</td>
<td>3.85 47; 60</td>
</tr>
<tr>
<td>2</td>
<td>HO_Et_Et</td>
<td>3.83</td>
<td>4</td>
<td>54</td>
<td>68; 41</td>
<td>3.86 57; 50</td>
</tr>
<tr>
<td>3</td>
<td>HO_n-Pr_Me</td>
<td>3.84</td>
<td>4</td>
<td>27</td>
<td>22; 57</td>
<td>3.87 59; 22</td>
</tr>
</tbody>
</table>

3.5 Limitations of the Methodology and Failed Substrates

The current limitations of the substrate scope of the catalytic kinetic resolution are summarized below.

**Scheme 3.7 Limitations of the Current Methodology: Sensitivity to Sterics**

The reaction is sensitive to steric modification of substrates. As illustrated in Scheme 3.7, methyl-substituted substrate rac-3.3 undergoes enantioselective silylation with good reactivity and enantioselectivity (59% conv.; \(k\text{rel}=14\)). As the size of the
substituent at the 2-position is increased to an allyl group \((rac-3.64)\), the enantioselectivity drops \((k_{rel}=6)\). For the substrate bearing a more sterically demanding \(iso\)-propyl \((rac-3.88)\) or phenyl group \((rac-3.89)\), both reactivity and enantioselectivity of the kinetic resolution suffer \((k_{rel}=4)\).

Enantioselective silylation of \(rac-3.2\) proceeds with 63% conversion and a \(k_{rel}\) value of 14. Diastereomeric compound \(rac-3.60\) with methyl the substituent \(cis\) to the hydroxy group undergoes kinetic resolution with lower enantioselectivity \((k_{rel}=7)\). With \(gem\)-dimethyl substitution at the 5 position \((rac-3.90)\), the kinetic resolution is inefficient. Enantioselective silylation of \(rac-3.65\) with a methyl group at the 3 position proceeds with poor enantioselectivity \((k_{rel}=3)\).

We hypothesized that bulky substituent on the ring causes the substrate-catalyst interaction to become less available due to disfavored steric interactions.

The catalytic kinetic resolution is also sensitive to electronic modifications. Substrates \(rac-3.91\) (Figure 3.1) and \(rac-3.92\), with an electronically withdrawing bromo group at the 2 or 3 positions, undergo enantioselective silylation with inferior conversions and selectivities \((k_{rel}=5\) and 4, respectively).

![Figure 3.2 Electronically Modified Substrates](image)

We hypothesized that the electron withdrawing group changes the electronics of the carbonyl group of the 4-hydroxy-2-cyclopentenones, thus effecting the substrate-
catalyst association. These findings are mechanistically telling and might be useful for elucidating a reasonable transition state model.

3.6 Mechanistic Study

Mechanistically, kinetic resolution of 4-hydroxy-2-cyclopentenones through catalytic enantioselective silylation is interesting. As shown in eq. 3.5, silylation of rac-4-hydroxy-2-cyclopentenone 3.1 proceeds to 60% conversion with only 2 mol % catalyst 3.38 within 1 hour at −78 ºC with good enantioselectivity ($k_{rel}$=14). Even when the catalyst loading is lowered to 0.05 mol %, 50% conversion is achieved in 10 hours and the silylation maintains the same selectivity. This finding of rate acceleration suggests that when the necessary structural requirements are met, catalytic enantioselective silylation can proceed with exceptional level of efficiency. Furthermore, comparison to an authentic sample,\(^\text{110}\) it was shown that the $R$ enantiomer of $\beta$-hydroxyketones gets preferentially silylated over the $S$ enantiomer.

![Diagram](image.png)

The silylation of hydroxyketone rac-3.1 is much faster and more efficient than that of the corresponding cis-cyclopenten-1,3-diol 3.12, which requires 20 mol % catalyst loading and 5 days at −78 ºC (eq. 3.6). The pro-$S$ stereogenic center gets silylated over the pro-$R$ stereogenic center. The dramatic differences between the enantioselective

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silylations of two classes of substrates suggest that, the two transformations may go through distinct mechanisms.

Catalysts with modified structures were also tested for enantioselective silylation of β-hydroxyketones. Results are summarized in Scheme 3.8. Catalyst 3.37 containing a secondary amine and amide promotes the kinetic resolution with 48% conversion and a $k_{rel}$ value of 9. Catalysts with a tertiary amine 3.93, an imine 3.94 and an amide 3.95 in place of the secondary amine fail to promote the silylation. These results clearly illustrate the importance of the secondary amine to afford reactivity. With a methylated amide, catalyst 3.96 affords much lower conversion and enantioselectivity (18% conv.; $k_{rel}=5$). Catalyst 3.97, which incorporates an ester at the C-terminus, is inactive. These findings indicate that the secondary amide is also critical for a positive reaction outcome.
Extensive modeling studies [Merck Molecular Force Field (MMFF94) in Spartan ‘04]\textsuperscript{111} have been carried out to elucidate the reaction mechanism. If we assume that the association between the β-hydroxyketones and the catalyst involves H-bonding, according to modeling calculations, one possible transition state model I is shown in Figure 3.3. One enantiomer of the β-hydroxyketone preferentially interacts with the chiral catalyst through H-bonding; the ketone of the substrate serves as H-bonding acceptor from the amide of the catalyst, while the hydroxy group serves as H-bonding donor to the secondary amine of the catalyst. The N-methylimidazole moiety activates TESCl resulting in silylation of the R enantiomer over the S enantiomer. The Si–O distance is 1.9 Å. The transition state model I is consistent with the limitations of the substrate scope. Since the double bond is facing towards the catalyst chiral backbone while the methylene unit is pointing away from the catalyst, any large substituents at the

R\textsuperscript{1} position (3.88 and 3.89 in Scheme 3.7) would have disfavored steric interactions with the amino acid chiral backbone of the catalyst. Substituents at the R\textsuperscript{2} position (3.65 in Scheme 3.7) would have disfavored interactions with not only the backbone of the catalyst but also the bulky activated silicon species. With electron withdrawing groups at either the R\textsuperscript{1} or R\textsuperscript{2} position (3.91 and 3.92 in Figure 4.2), silylation proceeds with low conversion and poor enantioselectivity. The reason might be that the H-bonding between electron deficient ketone of the substrate and the amide of the catalyst becomes less available.

For enantioselective silylation of diols, the proposed transition state II is shown in Figure 3.3. The calculated Si–O distance is about 3.2 Å. In comparison with the Si–O distance of I (1.9 Å), this distance might be too long for efficient silylation of diols.

**Figure 3.3 Proposed Transition State Models for Enantioselective Silylations**

In transition state I, that substrate-catalyst interaction was assumed to proceed through H-bonding. This does not explain the key differences between silylation of β-hydroxyketones and diols. The reason for which the two transformations give the opposite sense of enantioselectivity, and the dramatic difference in catalyst loading and reaction rate are not clear. With such a flexible catalyst, the distance between silicon and oxygen is not fixed during the cause of the reaction. Simple comparison of the
calculated silicon oxygen distance of the two proposed transition states might be inaccurate. Given these considerations, it might be possible that catalytic enantioselective silylation of β-hydroxyketones proceeds through a completely different mechanism, meaning that substrate-catalyst association can occur through interactions other than H-bonding. Detailed mechanistic studies need to be carried out for further understanding of the transformation.

In the proposed transition state II (Figure 3.3) of enantioselective silylation of diols, the calculated Si–O distance is about 3.2 Å. As illustrated in Figure 3.4, catalysts with an extended tether reduce the Si–O distance between silicon and oxygen atoms to around 1.9 Å, which is significantly shorter than the distance in II. The calculated change of distance in the transition state might be critical to the efficiency of the silylation reactions. Testing catalysts with extended tethers (3.95–3.99) will tell us whether the Si–O distance is the key factor in determining the rate of silylation reactions.

**Figure 3.4 Catalysts with Extended Tether for Higher Reactivity**

3.7 Summary

In conclusion, we have developed a kinetic resolution of β-hydroxyketones through catalytic enantioselective silylation. A variety of 4-hydroxy-2-cyclopentenones,
as well as acyclic β-hydroxyketones can be catalytically resolved with high efficiency. Low catalyst loading (<0.1 mol %), short reaction time (1 h), ease of set up and scale up make this a practical protocol for accessing synthetically useful 4-hydroxy-2-cyclopentenones in an enantiomerically enriched fashion.

For the first time, enantioselective silylation has been extended to substrates without multiple hydroxy groups and the efficiency of such silylation has been increased dramatically. Substrate scope, catalyst modification and modeling calculation have been extensively studied to elucidate the mechanism of enantioselective silylation of β-hydroxyketones.

3.8 Experimental and Supporting Information

**General Information**

Infrared (IR) spectra were recorded on a Perkin Elmer 781 spectrophotometer, \( \nu_{\text{max}} \) in cm\(^{-1}\). Bands are characterized as broad (br), strong (s), medium (m), and weak (w). \(^1\)H NMR spectra were recorded on a Varian GN-400 (400 MHz) instrument. Chemical shifts are reported in ppm with the solvent reference as the internal standard (CHCl\(_3\): \( \delta \) 7.26; CD\(_3\)OD: \( \delta \) 4.87, 3.31; pyridine-d\(_5\): \( \delta \) 8.74, 7.58, 7.22 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), and coupling constants (Hz). \(^{13}\)C NMR spectra were recorded on a Varian GN-400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent reference as the internal standard (CHCl\(_3\): \( \delta \) 77.23, CD\(_3\)OD: \( \delta \) 49.15; pyridine-d\(_5\): \( \delta \) 150.35, 135.91, 123.87 ppm). Melting points (mp) were taken with a Laboratory Devices Mel-Temp and were uncorrected. Enantiomeric ratios
were determined by chiral gas liquid chromatography (GLC) on a Hewlett Packard HP 6890 with a Beta Dex 120 (30 m x 0.25 mm x 0.25 µm film thickness), or a Gamma Dex 120 (30 m x 0.25 mm x 0.25 µm film thickness) column. **Optical rotations** were measured on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. High resolution mass spectrometry (**HRMS**) was performed by the mass spectrometry facility at Boston College.

Chlorotriethylsilane (TESCl) and Diisopropylethylamine (DIPEA) were distilled from 3Å molecular sieves prior to use. (THF) was dried on alumina columns by a solvent dispensing system prior to use. All other reagents were used as received.

**General procedure for the kinetic resolution through catalytic asymmetric silylation**

Catalyst 3.38 (2 mol %) and substrate (0.5 mmol, 1.0 equiv) were weighed into a 16 x 125 mm test tube. The mixture was dissolved in THF (0.4 M, relative to substrate). The test tube was capped with a septum, wrapped with Teflon tape and then cooled to −78 °C under N₂. DIPEA (1.0 equiv) was added via syringe. TESCl (0.75 equiv) in THF solution (0.3 M) was added over 30 min via syringe. The reaction was carefully monitored by GLC and quenched by at proper time by addition of DIPEA (50 µL) and H₂O (200 µL). The mixture was diluted with CH₂Cl₂, dried over anhydrous MgSO₄, filtered and concentrated to ~1 mL. Acetic anhydride (5 equiv), pyridine (5 equiv) and DMAP (10 mol %) were added. The mixture was stirred at 0 °C for 2 h, then diluted with CH₂Cl₂ (15 mL) and subsequently quenched by addition of 10% citric acid (10 mL). The aqueous layer was washed with CH₂Cl₂ (15 mL x 3), dried over anhydrous MgSO₄, filtered and concentrated to afford a yellow oil. The acetate and TES ether were separated by silica gel chromatography and analyzed by chiral GLC.
Procedure for the synthesis of (2S,3R)-3-tert-butoxy-N-((R)-3,3-dimethylbutan-2-yl)-2-((1-methyl-1H-imidazol-2-yl)methylamino)butanamide (3.38)

Fmoc-O-t-butyl-threonine (1.59 g, 4.0 mmol) and (R)-3,3-dimethyl-2-butylamine (590 µL, 4.4 mmol) were dissolved in 30 mL of CH₂Cl₂ in a 100 mL round bottom flask. To this solution were added EDC (843 mg, 4.4 mmol), HOBT (682 mg, 4.4 mmol) and DIPEA (1.4 mL, 8.0 mmol). The mixture was allowed to stir for 2 h at 23 °C after which time 20 mL of 10 % citric acid was added. The organic layer was separated and washed with 20 mL of a saturated solution of NaHCO₃ and then 20 mL of brine, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to yield a white solid. This residue was dissolved in 30 mL of CH₂Cl₂, piperidine (1.5 mL, 15.4 mmol) was then added dropwise to the solution. The mixture was allowed to stir for 1 h at 23 °C and then concentrated in vacuo. The crude product was partitioned between 20 mL of CH₂Cl₂ and 20 mL of 10 % citric acid. The aqueous phase was basified to pH 14 and then extracted with CH₂Cl₂ (3 x 30 mL), the combined organic layer dried over anhydrous MgSO₄. After filtration and removal of the solvent, the unpurified amine was dissolved in 5 mL of CH₂Cl₂, followed by the addition of 1-methyl-2-imidazolecarboxaldehyde (436 mg, 4.0 mmol) and MgSO₄. The mixture was allowed to stir for 12 h at 23 °C, filtered and concentrated to give a white solid, which was dissolved in MeOH and cooled to 0 °C. To this solution was added NaBH₄ (453 mg, 12 mmol. The solution was allowed to stir for 0.5 h at 0 °C and then 1 h at 23 °C, after which time 10 mL of a saturated solution of NaHCO₃ was slowly added to quench the reaction. The product was extracted with CH₂Cl₂ (3 x 15 mL), the
combined organic layer was washed with brine (1 x 10 mL), dried over anhydrous MgSO₄ and concentrated to yield a biege solid. The resulting solid was purified by silica gel chromatography (CH₂Cl₂ to 95:5 CH₂Cl₂:MeOH) to afford the catalyst 3.38 as a white solid (986 mg, 70% yield over 4 steps).

**Characterization Data**

(2S,3R)-3-tert-Butoxy-N-((R)-3,3-dimethylbutan-2-yl)-2-((1-methyl-1H-imidazol-2-yl)methylamino)butanamide (3.38):

![Structure of 3.38]

**MP:** 141.2-142.5 °C. IR: 3333 (br), 2968 (s), 2364 (w), 1665 (s), 1539 (m), 1369 (m), 1193 (m), 1073 (w), 771 (w) cm⁻¹.

**¹H NMR** (CDCl₃, 400 MHz): δ 7.12 (1H, d, J = 10 Hz), 6.89 (1H, d, J = 1.2 Hz), 6.82 (1H, d, J = 1.2 Hz), 3.96 (1H, d, J = 14.0 Hz), 3.83 (1H, d, J = 14.0 Hz), 3.78 (1H, dq, J = 10, 6.4 Hz), 3.71 (3H, s), 3.59 (1H, dq, J = 4.4, 6.4 Hz), 3.14 (1H, d, J = 4.4 Hz), 2.72 (1H, br, s), 1.14 (9H, s), 1.04 (3H, d, J = 6.4 Hz), 1.03 (3H, d, J = 6.4 Hz), 0.88 (9H, s).

**¹³C NMR** (CDCl₃, 100 MHz): δ 170.94, 146.43, 127.12, 121.33, 74.72, 68.74, 65.75, 53.15, 46.05, 34.06, 32.93, 28.60, 26.46, 18.17, 16.16. **HRMS** (m/z + H): Calculated: 352.2923; Found: 352.2917. **Optical Rotation:** [α]²⁵D -29.9 (c = 1.0, CHCl₃).

ORTEP of 3.38
Table 1. Crystal data and structure refinement for 3.38.

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F(000) 388

Crystal size 0.15 x 0.02 x 0.01 mm\(^3\)

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Index ranges -7\(\leq h\leq 12\), -14\(\leq k\leq 15\), -13\(\leq l\leq 8\)

Reflections collected 7249

Independent reflections 4722 [R(int) = 0.0346]

Completeness to theta = 28.40° 99.0 %

Absorption correction Empirical

Max. and min. transmission 0.9993 and 0.9891

Refinement method Full-matrix least-squares on F\(^2\)

Data / restraints / parameters 4722 / 1 / 235

Goodness-of-fit on F\(^2\) 1.051

Final R indices [I>2sigma(I)] R1 = 0.0545, wR2 = 0.1424

R indices (all data) R1 = 0.0709, wR2 = 0.1625

Absolute structure parameter 0.8(14)

Largest diff. peak and hole 0.325 and -0.312 e.Å\(^{-3}\)

Table 2. Atomic coordinates (x 10\(^4\)) and equivalent isotropic displacement parameters (Å\(^2\) x 10\(^3\)) for 3.38. U(eq) is defined as one third of the trace of the orthogonalized U\(^ij\) tensor.
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Table 3. Bond lengths [Å] and angles [°] for 3.38.

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Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å² x 10³) for 3.38. The anisotropic displacement factor exponent takes the form: -2π² [ h₂ a*² U₁₁ + ... + 2 h k a* b* U₁₂ ]

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C(2)-N(1)-C(4)-C(5)  179.11(19)
C(1)-N(1)-C(4)-C(5)  0.8(3)
C(13)-N(4)-C(14)-C(15)  92.1(3)
C(13)-N(4)-C(14)-C(16) -139.4(2)
C(6)-N(3)-C(5)-C(4)  -173.74(18)
N(2)-C(4)-C(5)-N(3)  -116.0(2)
N(1)-C(4)-C(5)-N(3)  64.7(3)
N(4)-C(14)-C(16)-C(19) -71.5(3)
C(15)-C(14)-C(16)-C(19)  53.8(3)
N(4)-C(14)-C(16)-C(17)  50.3(3)
C(15)-C(14)-C(16)-C(17)  175.6(3)
N(4)-C(14)-C(16)-C(18)  167.9(2)
C(15)-C(14)-C(16)-C(18) -66.8(3)
N(1)-C(2)-C(3)-N(2)  0.4(3)
C(4)-N(2)-C(3)-C(2)  -0.5(2)
C(7)-O(2)-C(9)-C(10)  52.6(3)
C(7)-O(2)-C(9)-C(11)  170.36(19)
C(7)-O(2)-C(9)-C(12)  -72.1(3)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for 3.38 [Å and °].
Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y+1/2,-z+2

(5)-4-Oxocyclopent-2-enyl acetate (3.59, Table 3.8)

\[
\text{\textsuperscript{1}H NMR (CDCl}_3, 400 \text{ MHz}): \delta 7.57 (1\text{H, dd}, J = 5.6, 2.4 \text{ Hz}), 6.33 (1\text{H, d}, J = 5.6 \text{ Hz}), 5.85 (1\text{H, m}), 2.83 (1\text{H, dd}, J = 18.4, 6.4 \text{ Hz}), 2.33 (1\text{H, dd}, J = 18.4, 2 \text{ Hz}), 2.10 (1\text{H, s}). \text{\textsuperscript{13}C NMR (CDCl}_3, 100 \text{ MHz}): \delta 204.81, 170.45, 158.93, 137.08, 72.10, 41.18, 21.02. \text{Optical Rotation: } [\alpha]^{20}_D -100.8 \text{ (c = 0.51, CHCl}_3).}
\]

Stereochemistry Proof: Previously reported $[\alpha]^{20}_D$ -111 for enantiomerically pure S enantiomer.$^{110}$

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C/min. 25 psi); chromatograms are illustrated below for a 91 % ee sample:
(R)-4-(Triethylsilyloxy)cyclopent-2-enone (3.59, entry 1 in Table 3.8):

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.45 (1H, dd, $J = 5.6, 2.4$ Hz), 6.18 (1H, d, $J = 5.6$ Hz), 4.97 (1H, m), 2.71 (1H, dd, $J = 18.4, 6.4$ Hz), 2.25 (1H, dd, $J = 18.4, 2.0$ Hz), 0.97 (9H, t, $J = 8.0$ Hz), 0.64 (6H, q, $J = 8.0$ Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 206.50, 163.92, 134.66, 70.77, 45.23, 6.93, 4.96. **Optical Rotation:** $\left[\alpha\right]_{D}^{20} +27.9 (c = 0.51, \text{CHCl}_3)$.

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 104 °C, 4 °C/min, hold 80 min. 25 psi.); chromatograms are illustrated below for a 62 % ee sample:
(1R,5S)-5-Methyl-4-oxocyclopent-2-enyl acetate (3.66, entry 2 in Table 3.8):

**IR** (neat, thin film): 2919 (m), 2850 (w), 1721 (s), 1453 (w), 1373 (m), 1232 (s), 1077 (w), 1024 (m), 912 (w), 822 (w), 680 (w) cm$^{-1}$. **$^1$H NMR** (CDCl$_3$, 400 MHz): $\delta$ 7.47 (1H, dd, $J = 5.6, 2.4$ Hz), 6.29 (1H, d, $J = 5.6$ Hz), 5.47 (1H, m), 2.34 (1H, dq, $J = 2.4, 7.2$ Hz), 2.10 (3H, s), 1.26 (3H, d, $J = 7.6$ Hz). **$^{13}$C NMR** (CDCl$_3$, 100 MHz): $\delta$ 207.15, 170.69, 157.59, 135.90, 79.49, 47.21, 21.09, 13.61. **HRMS** (m/z + H): Calculated: 155.07082; Found: 155.07059. **Optical Rotation**: $[\alpha]^{20}_{D}$ = −91.2 ($c = 0.70$, CHCl$_3$).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C/min. 25 psi); chromatograms are illustrated below for a 94 % ee sample:
(4S,5R)-5-Methyl-4-(triethylsilyloxy)cyclopent-2-enone (3.74, entry 2 in Table 3.8):

IR (neat, thin film): 2957 (m), 2912 (m), 2877 (s), 1921 (s), 1457 (w), 1356 (w), 1237 (w), 1108 (m), 1051 (w), 1005 (w), 894 (w), 856 (w), 798 (m), 746 (m), 672 (w) cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.37 (1H, dd, J = 5.6, 2.0 Hz), 6.16 (1H, dd, J = 5.6, 2.4 Hz), 4.50 (1H, m), 2.26 (1H, dq, J = 2.4, 7.2 Hz), 1.22 (3H, d, J = 7.6 Hz), 0.99 (9H, t, J = 8.0 Hz), 0.66 (6H, q, J = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 208.25, 162.10, 133.50, 78.86, 50.91, 12.95, 6.93, 5.08. HRMS (m/z + H): Calculated: 227.1467; Found: 227.1462. Optical Rotation: [α]²⁰_D +37.3 (c = 1.0, CHCl₃).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 μm film thickness), 110 °C for 65 min. 25 psi.); chromatograms are illustrated below for a 60 % ee sample:
(S)-3-Methyl-4-oxocyclopent-2-enyl acetate (3.67, entry 3 in Table 3.8):

$$\text{IR (neat, thin film): 2925 (w), 1718 (s), 1643 (w), 1374 (m), 1238 (s), 1027 (w), 983 (w), 607 (w) cm}^{-1}. \quad \text{\textbf{\textit{H NMR (CDCl}_3, 400 MHz): } \delta 7.20 (1H, m), 5.74 (1H, m), 2.85 (1H, dd, } J = 18.8, 6.4 \text{ Hz), 2.35 (1H, dd, } J = 18.8, 2 \text{ Hz), 2.08 (3H, s), 1.83(1H, t, } J = 2 \text{ Hz). \textbf{\textit{C NMR (CDCl}_3, 100 MHz): } \delta 205.03, 170.70, 152.58, 145.75, 70.61, 41.42, 21.14, 10.26. \quad \textbf{\textit{HRMS (m/z + H): Calculated: 155.07082; Found: 155.07088. \quad \textbf{\textit{Optical Rotation: } } [\alpha]^{20}_{D} = -82.8 (c = 1.0, CHCl}_3).}

Enantiomeric purity was established by chiral GLC analysis (Supelco Gamma Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C/min. 25 psi); chromatograms are illustrated below for a 95 % ee sample:

(R)-2-Methyl-4-(triethylsilyloxy)cyclopent-2-enone (3.75, entry 3 in Table 3.8):

$$\text{IR (neat, thin film): 2955 (m), 2912 (m), 2877 (m), 1716 (s), 1351 (w), 1241 (w), 1197 (w), 1089 (m), 1066 (m), 1006 (w), 965 (w), 896 (w), 798 (w), 746 (m) cm}^{-1}. \quad \text{\textbf{\textit{H NMR (CDCl}_3, 400 MHz): } \delta 7.09 (1H, m), 4.86 (1H, m), 2.73 (1H, dd, } J = 18.4, 6.4 \text{ Hz), 2.27 (1H, dd, } J = 18.4, 2.0 \text{ Hz), 1.78(1H, t, } J = 7.20 \text{ Hz).}

185
2.0 Hz), 0.97 (9H, t, J = 8.0 Hz), 0.64 (6H, q, J = 8.0 Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 206.45, 157.59, 143.01, 68.77, 45.39, 10.9, 6.91, 4.99. HRMS (m/z + H): Calculated: 227.1467; Found: 227.1463. **Optical Rotation**: $[\alpha]^{20}_D$ +11.6 (c = 1.21, CHCl$_3$).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 110 °C for 65 min. 25 psi); chromatograms are illustrated below for a 57 % ee sample:

(1R,5R)-5-Methyl-4-oxocyclopent-2-enyl acetate (3.68, entry 4 in Table 3.8):

Acylated starting material: 26 mg, 34% yield. IR (neat, thin film): 2982 (w), 2941 (w), 1720 (s), 1456 (m), 1372 (w), 1230 (s), 1188 (m), 1091 (w), 1034 (m), 962 (w), 911 (w), 873 (w) cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.50 (1H, dd, J = 6, 2 Hz), 6.32 (1H, d, J = 6 Hz), 5.92 (1H, m), 2.67 (1H, quin, J = 7.6 Hz), 2.12 (3H, s), 1.08 (3H, d, J = 7.6 Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 208.66, 170.45, 158.22, 135.78, 73.75, 43.29, 20.88, 10.99. HRMS (m/z + H): Calculated: 155.07082; Found: 155.07153. **Optical Rotation**: $[\alpha]^{20}_D$ −87.6 (c = 0.50, CHCl$_3$).
Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C/min. 25 psi); chromatograms are illustrated below for a 82 % ee sample:

![Chromatograms](image)

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(4S,5S)-5-Methyl-4-(triethylsilyloxy)cyclopent-2-enone (3.76, entry 4 in Table 3.8):

![Structure](image)

**IR** (neat, thin film): 2955 (w), 2911 (w), 2877 (w), 1717 (s), 1456 (w), 1372 (w), 1238 (w), 1186 (w), 1132 (m), 1102 (w), 1081 (m), 1005 (m), 977 (w), 858 (s), 778 (m), 723 (s) cm⁻¹. **¹H NMR** (CDCl₃, 400 MHz): δ 7.41 (1H, dd, J = 6.0, 2.0 Hz), 6.17 (1H, d, J = 6.0 Hz), 4.94 (1H, m), 2.49 (1H, quin, J = 7.6 Hz), 1.11 (3H, d, J = 7.6 Hz), 0.99 (9H, t, J = 8.0 Hz), 0.66 (6H, q, J = 8.0 Hz). **¹³C NMR** (CDCl₃, 100 MHz): δ 210.35, 162.91, 133.15, 72.34, 45.58, 11.57, 6.94, 5.06. **HRMS** (m/z + H): Calculated: 227.14673; Found: 227.14769. **Optical Rotation**: [α]²⁰D +47.9 (c = 1.0, CHCl₃).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C/min. 25 psi); chromatograms are illustrated below for a 47 % ee sample:
(1R,5S)-5-Ethyl-4-oxocyclopent-2-enyl acetate (3.69, entry 5 in Table 3.8):

IR (neat, thin film): 2966 (m), 2937 (m), 2878 (m), 1720 (s), 1460 (w), 1374 (m), 1354 (m), 1326 (w), 1236 (s), 1171 (m), 1085 (m), 1024 (s), 943 (m), 798 (m), 607 (w) cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.51 (1H, dd, J = 5.6, 2.4 Hz), 6.30 (1H, dd, J = 5.6, 1.2Hz), 5.66 (1H, dt, J = 1.2, 2.4 Hz), 2.34 (1H, ddd, J = 8, 4.8, 2.4 Hz), 2.11 (3H, s), 1.87 (1H, ddq, J = 14.8, 4.8, 7.6 Hz), 1.63 (1H, ddq, J = 14.8, 7.6, 7.6 Hz), 0.96 (3H, t, J = 7.6 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 206.83, 170.63, 157.91, 136.48, 52.94, 21.79, 21.16, 11.18. HRMS (m/z + H): Calculated: 169.08647; Found: 169.08644. Optical Rotation: [α]₂⁰_D −46.0 (c = 1.0, CHCl₃).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C , 2 °C /min. 25 psi); chromatograms are illustrated below for a 80 % ee sample:
(4S,5R)-5-Ethyl-4-(triethylsilyloxy)cyclopent-2-enone (3.77, entry 5 in Table 3.8):

IR (neat, thin film): 2958 (m), 2877 (m), 1718 (s), 1458 (w), 1356 (w), 1108 (m), 1061 (w), 1006 (w), 821 (w), 745 (m) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.39 (1H, dd, J = 5.6, 2.4 Hz), 6.16 (1H, dd, J = 5.6, 0.8 Hz), 4.67 (1H, m), 2.23 (1H, ddd, J = 7.2, 5.6, 2.4 Hz), 1.78 (1H, dd, J = 14.8, 5.6, 7.6 Hz), 1.63 (1H, ddq, J = 14.8, 7.6, 7.6 Hz), 0.99 (9H, t, J = 8.0 Hz), 0.96 (3H, t, J = 7.6 Hz), 0.66 (6H, d, J = 8.0 Hz). \(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 208.245, 162.285, 134.170, 76.201, 56.720, 21.327, 11.321, 6.981, 5.204. HRMS (m/z + H): Calculated: 241.1624; Found: 241.1615. Optical Rotation: \([\alpha]_{D}^{20} +18.8\) (c = 1.0, CHCl\(_3\)).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C/min. 25 psi); chromatograms are illustrated below for a 56% ee sample:
(1R,5S)-5-Allyl-4-oxocyclopent-2-enyl acetate (3.70, entry 6 in Table 3.8):

\[
\text{IR (neat, thin film): } 2017 \text{ (m), 2848 (w), 2359 (w), 1720 (w), 1372 (w), 1233 (s), 1024 (m), 925 (w) cm}^{-1}. \]

\[
\text{H NMR (CDCl}_3, 400 \text{ MHz): } \delta 7.51 (1H, dd, J = 5.6, 2.4 \text{ Hz}), 6.31 (1H, dd, J = 5.6, 1.6 \text{ Hz}), 5.70 (1H, dddd, J = 6.8, 12.0, 6.8, 6.8 \text{ Hz}), 5.66 (1H, m), 5.05–5.18 (2H, m), 2.37–2.63 (3H, m), 2.10 (3H, s). \]

\[
\text{C NMR (CDCl}_3, 100 \text{ MHz): } \delta 206.110, 170.592, 158.170, 136.076, 134.076, 118.203, 76.786, 51.289, 32.782, 21.155. \]

\[
\text{HRMS (m/z + H): Calculated: 181.08647; Found: 181.08650.} \]

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C , 2 °C /min. 25 psi); chromatograms are illustrated below for a 92 % ee sample:
(4S,5R)-5-Allyl-4-(triethylsilyloxy)cyclopent-2-enone (3.78, entry 6 in Table 3.8):

IR (neat, thin film): 2956 (s), 2877 (s), 1716 (s), 1641 (m), 1592 (w), 1458 (m), 1358 (m), 1239 (w), 1111 (s), 1070 (m), 1016 (m), 916 (m), 855 (w), 745 (m), 674 (w) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.38 (1H, \(dd, J = 5.6, 2.4\) Hz), 6.17 (1H, \(dd, J = 5.6, 0.8\) Hz), 5.70 (1H, \(dddd, J = 6.8, 12.0, 6.8, 6.8\) Hz), 5.04–5.14 (2H, m), 4.67 (1H, m), 2.33–2.54 (3H, m), 0.98 (9H, t, \(J = 8.0\) Hz), 0.65 (6H, q, \(J = 8.0\) Hz). \(^13\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 207.450, 162.526, 134.964, 133.944, 117.572, 75.461, 54.951, 32.486, 6.958, 5.181. HRMS (m/z + Na): Calculated: 275.1443; Found: 275.1446. Optical Rotation: [\(\alpha\)]\(^{20}\)D +23.2 (\(c = 1.0, \text{CHCl}_3\)).

Enantiomeric purity was established by chiral GLC analysis (Alltech Associated Chiral dex GTA (30 m x 0.25 mm) column), 80 °C to 140 °C, 2 °C/min, hold 10 min. 15 psi.); chromatograms are illustrated below for a 41 % ee sample:
(S)-3-Ethyl-4-oxocyclopent-2-enyl acetate (3.71, entry 7 in Table 3.8):

IR (neat, thin film): 2972 (m), 2938 (m), 2360 (w), 1716 (s), 1641 (w), 1372 (m), 1237 (s), 1201 (m), 1026 (s), 979 (m), 946 (w), 880 (w), 607 (w) cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 7.16 (1H, m), 5.75 (1H, m), 2.86 (1H, dd, J = 18.4, 6.4 Hz), 2.37 (1H, dd, J = 18.4, 2.0 Hz), 2.24 (1H, ddq, J = 1.2, 1.2, 7.2 Hz), 2.9 (3H, s), 1.12 (3H, t, J = 7.6 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 204.77, 170.74, 151.52, 151.03, 70.63, 41.81, 21.12, 18.16, 11.73. HRMS (m/z + H): Calculated: 169.08647; Found: 169.08665. Optical Rotation: [α]²⁰D −38.0 (c = 0.50, CHCl₃).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C /min, 25 psi); chromatograms are illustrated below for a 74 % ee sample:
(R)-2-Ethyl-4-(triethylsilyloxy)cyclopent-2-enone (3.79, entry 7 in Table 3.8):

IR (neat, thin film): 2955 (s), 2877 (s), 1712 (m), 1458 (m), 1238 (m), 1072 (s), 1004 (m), 740 (m) cm\(^{-1}\). \(^{1}\)H NMR (CDCl\(_3\), 400 MHz): δ 7.04 (1H, m), 4.87 (1H, m), 2.73 (1H, dd, \(J = 18.4, 6.4\) Hz), 2.31 (1H, dd, \(J = 18.4, 2.0\) Hz), 2.18 (1H, ddq, \(J = 1.2, 1.2, 7.6\) Hz), 1.10 (3H, t, \(J = 7.6\) Hz), 0.98 (9H, q, \(J = 8.0\) Hz), 0.65 (6H, t, \(J = 8.0\) Hz). \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): δ 206.16, 155.94, 148.90, 68.85, 49.90, 18.03, 11.87, 6.94, 5.00. HRMS (m/z + H): Calculated: 241.16238; Found: 241.16197. Optical Rotation: \([\alpha]^{20}_{D}\) +6.8 (c = 0.50, CHCl\(_3\)).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 μm film thickness), 110 °C to 150 °C, 1 °C /min, hold 10 min. 15 psi.); chromatograms are illustrated below for a 36 % ee sample:
(S)-3-allyl-4-oxocyclopent-2-enyl acetate (3.72, entry 8 in Table 3.8):

IR (neat, thin film): 2935 (w), 1742 (s), 1712 (s), 1642 (w), 1372 (w), 1237 (s), 1026 (m), 919 (w) cm\(^{-1}\). \(\text{\(^1H\) NMR} (\text{CDCl}_3, 400 MHz): \delta 7.17 (1H, m), 5.85 (1H, dddd, \(J = 17.2, 9.6, 6.8, 6.8\) Hz), 5.76 (1H,m), 5.11–5.15 (2H, m), 2.96 (2H, d, \(J = 6.8\) Hz), 2.87 (1H, dd, \(J = 18.8, 6.4\) Hz), 2.38 (1H, dd, \(J = 18.8, 2.0\) Hz), 2.07 (3H, s). \(\text{\(^13C\) NMR} (\text{CDCl}_3, 100 MHz): \delta 204.169, 170.685, 152.529, 148.266, 133.406, 117.782, 70.560, 41.681, 29.236, 21.140. \text{HRMS} (m/z + Na): Calculated: 203.0684; Found: 203.0694. \text{Optical Rotation: } [\alpha]^{20}_D \text{ } -49.5 (c = 0.9, \text{CHCl}_3).\n
Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C/min. 25 psi); chromatograms are illustrated below for a 83 % ee sample:
(R)-2- Allyl-4-(triethylsilyloxy)cyclopent-2-enone (3.80, entry 8 in Table 3.8):

IR (neat, thin film): 2956 (m), 2877 (m), 1716 (S), 1642 (w), 1414 (w), 1353 (w), 1239 (w), 1083 (s), 1005 (m), 968 (w), 793 (w), 747 (m) cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 7.08 (1H, m), 5.85 (1H, dddd, 𝐽 = 17.2, 9.6, 6.8, 6.8 Hz), 5.09–5.13 (2H, m), 4.89 (1H, m), 2.92 (2H, d, 𝐽 = 6.8 Hz), 2.77 (1H, dd, 𝐽 = 18.4, 6.4 Hz), 2.31 (1H, dd, 𝐽 = 18.4, 2.0 Hz), 0.98 (9H, t, 𝐽 = 8.0 Hz), 0.64 (6H, q, 𝐽 = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 205.502, 157.430, 145.523, 133.951, 117.299, 68.838, 45.678, 29.143, 6.903, 4.986. HRMS (m/z + H): Calculated: 253.1624; Found: 253.1614. Optical Rotation: [α]₂₀⁺D +6.8 (c = 1.0, CHCl₃).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 μm film thickness), 80 °C to 180 °C, 2 °C /min. 25 psi); chromatograms are illustrated below for a 39% ee sample:
(S)-2-Methyl-4-oxocyclopent-2-enyl acetate (3.73, entry 9 in Table 3.8):

IR (neat, thin film): 3508 (br), 1724 (s), 1629 (m), 1374 (m), 1232 (s), 1024 (m), 1168 (w), 993 (w), 850 (w) cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): δ 6.07 (1H, m), 5.73 (1H, m), 2.88 (1H, dd, $J = 18.4, 6.4$ Hz), 2.30 (1H, dd, $J = 18.4, 2$ Hz), 2.12 (3H, s), 2.11 (3H, s). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 204.12, 172.79, 170.62, 133.55, 73.90, 42.87, 21.01, 16.23. HRMS (m/z + H): Calculated: 155.07082; Found: 155.07009. Optical Rotation: $[\alpha]_{D}^{20} +4.2$ (c = 1.0, CHCl$_3$).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C , 2 °C /min. 25 psi); chromatograms are illustrated below for a 31 % ee sample:
(R)-3-Methyl-4-(triethyldisiloxyl)cyclopent-2-enone (3.81, entry 9 in Table 3.8):

IR (neat, thin film): 2956 (s), 2877 (s), 1719 (s), 1629 (m), 1606 (m), 1094 (s), 1006 (m), 728 (m) cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ δ 5.92 (1H, m), 4.73 (1H, m), 2.72 (1H, dd, J = 18.4, 6.4 Hz), 2.28 (1H, dd, J = 18.4, 2.0 Hz), 2.11 (1H, s), 0.99 (9H, t, J = 8.0 Hz), 0.65 (6H, q, J = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 205.17, 177.52, 131.17, 72.94, 46.30, 16.12, 6.94, 5.01. HRMS (m/z + H): Calculated: 227.14673; Found: 227.14763. **Optical Rotation:** [α]²⁰D –1.7 (c = 1.0, CHCl₃).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 80 °C to 180 °C, 2 °C /min. 25 psi); chromatograms are illustrated below for a 44 % ee sample:
(S)-4-Hydroxypentan-2-one (3.82, entry 1 in Table 3.9):

$$^1$$H NMR (CDCl$_3$, 400 MHz): δ 4.21 (1H, m), 3.06 (1H, br), 2.63 (1H, dd, $J$ = 18, 3.2 Hz), 2.53 (1H, dd, $J$ = 18.0, 8.8 Hz), 2.17 (3H, s), 1.18 (3H, d, $J$ = 6.4 Hz). $$^{13}$$C NMR (CDCl$_3$, 100 MHz): δ 209.59, 64.00, 51.72, 30.87, 22.60.

Optical Rotation: $[\alpha]_{D}^{20}$ +64.6 (c = 1.0, CHCl$_3$).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 55 ºC hold 55 min. 15 psi.); chromatograms are illustrated below for a 84 % ee sample:
(R)-4-(Triethylsilyloxy)pentan-2-one (3.82, entry 1 in Table 3.9):

IR (neat, thin film): 2956 (s), 2877 (s), 1719 (s), 1373 (m), 1239 (w), 1173 (m), 1134 (m), 1090 (m), 1018 (s), 927 (w), 744 (s), 672 (w) cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 4.28 (1H, sex, $J = 6.0$ Hz), 2.65 (1H, dd, $J = 15.2$, 6.8 Hz), 2.44 (1H, dd, $J = 15.2$, 6.4 Hz), 1.18 (3H, d, $J = 6.0$ Hz), 0.938 (9H, t, $J = 8.0$ Hz), 0.58 (6H, q, $J = 8.0$ Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 207.90, 65.58, 53.56, 31.72, 24.36, 7.05, 5.17.

HRMS (m/z + Na): Calculated: 239.1443; Found: 239.1435.

Optical Rotation: $[\alpha]^{20}_D$ +11.1 (c = 1.0, CHCl$_3$).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 μm film thickness), 55 °C hold 55 min, 5 °C /min to 180 °C. 15 psi.); chromatograms are illustrated below for a 47 % ee sample:

(S)-5-Hydroxyhexan-2-one (3.83, entry 2 in Table 3.9):

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 4.22 (1H, m), 3.13 (1H, d, $J = 2.8$ Hz), 2.61 (1H, dd, $J = 17.6$, 3.2 Hz), 2.50 (1H, dd, $J = 17.6$, 8.8 Hz), 2.44 (2H, q, $J = 7.2$ Hz), 1.18 (3H, d, $J = 6.4$ Hz), 1.06 (3H, t, $J = 7.2$ Hz). $^{13}$C NMR (CDCl$_3$,
100 MHz): δ 212.515, 64.084, 50.330, 36.888, 22.620, 7.737. **Optical Rotation:** \([\alpha]^{20}_D +42.1 \ (c = 1.0, \text{CHCl}_3)\).

Enantiomeric purity was established by chiral GLC analysis (Supelco Gamma Dex 120 (30 m x 0.15 mm x 0.25 μm film thickness), 80 °C hold 10 min, 20 °C to 180 °C. 25 psi.); chromatograms are illustrated below for a 68 % ee sample:

\[(S)-5-(\text{Triethylsilyloxy})\text{hexan-3-one} \ (3.86, \text{entry 2 in Table 3.9}):\]

**IR** (neat, thin film): 2956 (s), 2877 (s), 1717 (s), 1459 (w), 1413 (w), 1375 (m), 1134 (m), 1094 (m), 1045 (m), 1005 (m), 766 (w), 743 (s) cm\(^{-1}\).

\(^1H\) **NMR** (CDCl\(_3\), 400 MHz): δ 4.30 (1H, m), 2.64 (1H, dd, \(J = 15.2, 7.2\) Hz), 2.46 (2H, q, \(J = 7.2\) Hz), 2.40 (1H, dd, \(J = 15.2, 5.6\) Hz), 1.17 (3H, d, \(J = 6.0\) Hz), 1.03 (3H, t, \(J = 7.2\) Hz), 0.93 (9H, t, \(J = 8.0\) Hz), 0.57 (6H, q, \(J = 8.0\) Hz). **\(^13C\) NMR** (CDCl\(_3\), 100 MHz): δ 210.349, 65.705, 52.341, 37.831, 24.428, 7.729, 7.028, 5.134. **HRMS** (m/z + H): Calculated: 231.17803; Found: 231.17897. **Optical Rotation:** \([\alpha]^{20}_D -15.7 \ (c = 1.0, \text{CHCl}_3)\).
Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 90 °C hold 50 min. 25 psi.); chromatograms are illustrated below for a 47 % ee sample:

![Chromatograms](image)

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Enantiomeric purity was established by chiral GLC analysis (Supelco Gamma Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 70 °C hold 60 min. 25 psi.); chromatograms are illustrated below for a 22 % ee sample:

![Chromatograms](image)

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**(S)-4-Hydroxyheptan-2-one (3.84, entry 3 in Table 3.9):**

![Structure](image)

\[ \text{\textbf{H NMR}} \text{ (CDCl}_3\text{, 400 MHz):} \delta 4.04 (1\text{H, m}), 2.95 (1\text{H, d, } J= 3.2 \text{ Hz}), 2.62 (1\text{H, dd, } J= 18, 3.2 \text{ Hz}), 2.52 (1\text{H, dd, } J= 18, 8.8 \text{ Hz}), 2.18 (3\text{H, s}), 1.34-1.50 (4\text{H, m}), 0.92 (3\text{H, t, } J= 6.8 \text{ Hz}). \]

\[ \text{\textbf{C NMR}} \text{ (CDCl}_3\text{, 100 MHz):} \delta 209.998, 67.536, 50.245, 38.821, 31.005, 18.919, 14.236. \]

**Optical Rotation:** \([\alpha]^{20}_D \ +8.3 \ (c = 1.0, \text{ CHCl}_3).\)

Enantiomeric purity was established by chiral GLC analysis (Supelco Gamma Dex 120 (30 m x 0.15 mm x 0.25 µm film thickness), 70 °C hold 60 min. 25 psi.); chromatograms are illustrated below for a 22 % ee sample:
(R)-2-(Triethylsilyloxy)heptan-4-one (3.87, entry 3 in Table 3.9):

IR (neat, thin film): 2958 (s), 2876 (s), 1719 (s), 1459 (w), 1415 (w), 1356 (w), 1129 (m), 1068 (m), 1007 (m), 740 (s) cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ 4.30 (1H, quin, J = 5.6 Hz), 2.61 (1H, dd, J = 17.2, 6.8 Hz), 2.47 (1H, dd, J = 17.2, 5.6 Hz), 2.16 (3H, s), 1.28-1.48 (4H, m), 0.94 (9H, t, J = 8.0 Hz), 0.92 (3H, t, J = 7.2 Hz), 0.59 (6H, q, J = 8.0 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ 208.042, 69.059, 51.414, 40.395, 31.823, 18.709, 14.415, 7.121, 5.290. HRMS (m/z + H): Calculated: 245.19368; Found: 245.19359. Optical Rotation: [𝛼]²⁰_D = −7.6 (c = 1.0, CHCl₃).

Enantiomeric purity was established by chiral GLC analysis (Supelco Beta Dex 120 (30 m x 0.15 mm x 0.25 μm film thickness), 70 °C hold 50 min. 25 psi.) of the desilylated product; chromatograms are illustrated below for a 59 % ee sample:
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3.38
OAc

3.69 ppm
3.69
Allyl
OTES
3.78
Allyl

3.80
$$\text{Me} \quad \text{Me}$$

$$3.82$$
$n$-Pr OH O Me

$3.84$
Chapter 4 Design and Development of Practical Methods for Catalytic Enantioselective Tosylation of Alcohols

4.1 Introduction and Background

The p-toluenesulfonylation (tosylation) and methanesulfonylation (mesylation) of alcohols are well recognized as fundamental processes in various fields of organic synthesis.\(^{112}\) Formation of a sulfonyl ester is an effective and most widely used method for activation of a C–O bond. The activated alcohol can be displaced by various nucleophiles to generate C–C, C–N, C–O and C–H bonds in a stereoselective fashion. Thus, enantioselective protocols of sulfonylation would be invaluable for chemical synthesis.

There is an impressive example of catalytic enantioselective sulfonylation of meso 1,2-diols. Onomura, Matsumura and coworkers reported a copper–catalyzed enantioselective tosylation in 2007.\(^{113}\) As shown in Scheme 4.1, in the presence of p-TsCl, 10 mol % Ph–BOX ligand\(^{114}\) and Cu(OTf)\(_2\), meso 1,2-diols undergo tosylation efficiently and with high enantioselectivity. This methodology is applicable to various 1,2-diols. Mono-tosylated products, including cyclic meso diols with different ring sizes (4.2–4.4), heterocyclic diols (4.5–4.7), an unsaturated diol (4.8) and an acyclic diol (4.9) are all obtained with excellent enantiomeric purity in good yield. The proposed working model is based on the recognition of the 1,2-diol moiety by a copper(II) ion associated with the chiral Ph-BOX ligand (4.1) to afford the activated 1,2-diol intermediate I.

(Scheme 4.1) followed by tosylation of one enantiotopic hydroxy group.\textsuperscript{115} The corresponding mesylation of \textit{meso} 1,2-cyclohexanediol using MsCl affords 77\% ee.

\textbf{Scheme 4.1} Copper-catalyzed Enantioselective Sulfonylation of \textit{meso} 1,2-Diols

Later that year, Onomura and co-workers extended copper-catalyzed enantioselective tosylation to \(\alpha\)-hydroxyamides.\textsuperscript{116} They found that in the presence of 10 mol \% Cu(OTf)\textsubscript{2} and (\(R,R\))-Ph-BOX ligand in acetonitrile a variety of \(\alpha\)-hydroxyamides can be efficiently resolved. Tosylated products are obtained in 80\% to 92\% ee, giving \(k_{\text{rel}}\) values ranging from 17 to 61 (substrates 4.10, 4.11 and 4.12, Scheme 4.2). Onomura and co-workers proposed a plausible mechanism based on molecular recognition of preferentially one enantiomer of the \(\alpha\)-hydroxyamides by the Cu(II)-(\(R,R\))-Ph-BOX complex to form intermediate \textbf{II} (Scheme 4.2), in which the C–O bond is activated towards tosylation. Enantioselective tosylation of cyclic lactam 4.13 is ineffective and non-selective (8\% yield, 6\% ee). It is likely that the geometry of the cyclic lactams

\textsuperscript{115} The same strategy has been used for benzylation of diols, see: Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. \textit{J. Am. Chem. Soc.} \textbf{2003}, 125, 2052–2053.

prohibits the formation of the active N,O-chelated intermediate II.

\textbf{Scheme 4.2} Copper-catalyzed Kinetic Resolution of \(\alpha\)-Hydroxyamides through Tosylation

\[
\begin{align*}
\text{OH} & \quad \text{N-Ph} \\
\text{R-C=O} & \quad \text{4.1} \\
\text{10 mol \%} & \quad \text{10 mol \% Cu(OTf)2, p-TsCl} \\
& \quad \text{K}_2\text{CO}_3, \text{MeCN, 23 °C, 12 h} \\
\end{align*}
\]

Although the copper-catalyzed enantioselective tosylation reactions of meso 1,2-diols and \(\alpha\)-hydroxyamides are impressive advances, there are several shortcoming of this methodology. The enantioselective protocol requires strictly anhydrous conditions due to the required use of Cu(OTf)\(_2\), thus making the method costly and cumbersome to perform on large scale, and therefore less practical. Enantioselective tosylation is highly effective and selective only for meso 1,2-diols. Since the copper-catalyzed processes are likely to have a strong preference of five-membered ring chelate derived from 1,2-diols, the protocol might not be applicable to 1,3-diols or various polyols. Thus development of a metal-free protocol of catalytic enantioselective tosylation reaction is critical to achieve maximum utility and will likely be complementary to the copper-catalyzed processes.
4.2 Design and Rationale for Enantioselective Tosylation of Alcohols

In chapter 2, total syntheses of cleroindicins D, F and C demonstrate the synthetic utility of enantioselective silylation of polyols. The key reaction of the synthesis is the catalytic enantioselective silylation of tetrol 4.14 (Scheme 4.3) to selectively protect one of the secondary alcohols to afford chiral silyl ether 4.15. The remaining secondary alcohol can then be converted 4.15 into a sulfonyl ester 4.16. We envision that enantioselective sulfonylation reaction in which one of the enantiotopic hydroxy groups is directly activated to form a chiral sulfonyl ester, would further streamline the synthesis.

![Scheme 4.3 Key Step of Enantioselective Synthesis of Cleroindicin D](image)

Even though sulfonylation and silylation are different types of reactions, sulfonylation is activation of an alcohol to increase its reactivity while silylation is a protection of a hydroxy group to lower its reactivity, the initial thoughts of developing enantioselective sulfonylation for alcohols is inspired from enantioselective silylation. As mentioned in the above chapters, the proposed mechanism of enantioselective silylation of diols involves activation of chlorosilane by imidazole moiety and diol interacting with catalyst’s chiral backbone through H-bonding. One of the enantiotopic alcohols closer to the activated silicon gets selectively silylated (intermediate III, Figure...
The same concept might be applicable to enantioselective sulfonylation of alcohols. If the diol substrates interact with the catalyst through H-bonding while sulfonyl chloride is activated by imidazole moiety by forming a sulfonylimidazolium salt\textsuperscript{117} (intermediate IV in Figure 1), this dual activation of substrate and sulfonyl chloride might lead to an enantioselective tosylation of diols.

4.3 Initial Discovery of Enantioselective Tosylation and Mesylation of 1,2-Diols

We began our study by investigating enantioselective sulfonylation reactions of \textit{cis}-1,2-cyclohexanediol. Chiral catalyst 4.17 (eq. 4.1) was used to test if an asymmetric induction would be observed for mesylation. In the presence of 100 mol \% catalyst and 1 equivalent of MsCl, mono mesylate 4.19 was obtained, however, in a racemic form (eq. 4.1). This finding suggests that catalyst-substrate, or more likely catalyst-MsCl do not have the interaction shown in IV Figure 4.1. It is known that mesylation reaction proceeds through the sulfene formation,\textsuperscript{118} thus catalyst-MsCl association by forming a sulfonlammonium salt becomes unavailable. In comparison to mesylation, \textit{p}-TsCl was


used for enantioselective tosylation of diol $4.18$ in the presence of $100 \text{ mol } \%$ catalyst. In contrast, the desired mono-tosylate $4.20$ was obtained in $70\%$ ee (eq. 4.2). This result is promising and suggests that, unlike mesylation, enantioselective tosylation is more likely to form the active intermediate $\text{IV}$ (Figure 4.1) between catalyst and $p$-TsCl.

At this point, we know that tosylation promoted by catalyst $4.17$ is enantioselective. The next question will be if there is catalytic turn over. By incorporating an organic base $(iPr)_2EtN$ in the presence of $20 \text{ mol } \%$ catalyst at $-30 \, ^\circ \text{C}$, mono-tosylate product was obtained in $60\%$ yield with $76\%$ ee (eq. 4.3). This finding clearly shows that catalyst $4.17$ can promote catalytic enantioselective tosylation.

Even though enantioselectivity and yield of the reaction is still moderate, this result is promising and leaves room for improvement. We were hoping that through
reaction condition optimization and modification of catalyst structure, the outcome of enantioselective tosylation would be improved.

4.4 Reaction Conditions Optimization

**Solvent Effect**

Solvent is one of the most important parameters for enantioselective synthesis. Different solvents were tested for enantioselective tosylation and the data is summarized in Table 4.1. tert-Butyl methyl ether is the best solvent in terms of enantioselectivity and yield for the tosylation reaction (entry 4, Table 4.1); mono-tosylate 4.20 is obtained in 88% ee. Diethyl ether is equally enantioselective, but affords more bis-tosylated by-product 4.21 (entry 3). Toluene is slightly less enantioselective compared to tert-butyl methyl ether (entry 1). Reactions in THF and ethyl acetate afford around 50% ee but only mono-tosylated product 4.20 (entries 2 and 5), while DMF is ineffective for tosylation reaction (entry 8). One trend of solvent study results is noteworthy: the solvent affords better enantioselective also forms more of the bis-tosylated product (entries 1, 3 and 4).

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Chemistry, 120

Table 4.1 Solvent Study of Catalytic Enantioselective Tosylation

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<tr>
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<td>8</td>
<td>DMF</td>
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</table>

[a] Conversion determined by NMR with internal standard.
[b] Mono:bis ratio determined by NMR.

Base Effect

We next examined the effect of different bases for enantioselective tosylation. Organic base (iPr)$_2$EtN affords 84% ee in 82% conversion to desired product 4.20 (entry 1, Table 4.2). Triethylamine is much less effective and enantioselective (entry 2). Proton sponge and affords good enantioselectivity (83% ee) but much lower conversion (entry 3). Weaker bases, such as N,N-dimethylaniline, pyridine and lutidines afford low conversion (entries 4–7). The pKa’s of protonated dimethylaniline, pyridine and lutidines are 5, 5 and 7, respectively, and pKa of a protonated secondary amine is around 11. With a more Lewis basic site on the catalyst, its secondary amine will serve as a general base and will be protonated by HCl generated in tosylation reaction. A base such as aniline, pyridine or lutidine will not accomplish the proton transfer from catalyst•HCl salt, thus deactivating the catalyst. Therefore, the choice of a base with appropriate pKa is

---

critical to the catalytic turn over of the tosylation reaction. Inorganic base, such as potassium carbonate is ineffective for the reaction, presumably due to insolvability (entry 9). No background reactions were detected in the absence of catalyst 4.17. Thus, the fact that different bases afford different enantioselectivities is not due to uncatalyzed background reaction and may indicate that the base might be involved in the enantio-determining (or stereinduction) step.

**Table 4.2 Base Effect Study of Catalytic Enantioselective Tosylation**

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**Additive Study**

Enantioselective tosylation is a relatively slow reaction; it typically takes 3 days with 30 mol % catalyst loading. Enantioselective reactions are often very sensitive to small changes in reaction conditions.$^{121}$ Therefore different additives were tested in order to improve the efficiency of enantioselective tosylation. Sodium iodide and tetrabutylammonium iodide were added to the reaction. We were hoping that through

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halogen exchange, more reactive $p$TsI would form in situ, leading to an increase of the reaction rate. Unfortunately, as shown in Table 4.3, additives do not affect the reactions. A more facile enantioselective tosylation reaction may need a better catalyst.

![Tosylating Reagents Study](image)

Different aryl substituted sulfonyl chlorides were tested. Scheme 4.3 summarizes the results of tosylation reagents with steric differences. Phenyl sulfonyl chloride and $m$-TsCl afford slightly lower enantioselectivity compared to $p$-TsCl. Reaction with mesityl sulfonyl chloride does not convert; a substituent at the ortho position is not tolerated either. This is presumably due to steric hindrance of the sulfonyl chloride, which affects the association with catalyst. Investigation of electronically modified sulfonyl chlorides is currently ongoing.

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**Tosylating Reagents Study**

Different aryl substituted sulfonyl chlorides were tested. Scheme 4.3 summarizes the results of tosylation reagents with steric differences. Phenyl sulfonyl chloride and $m$-TsCl afford slightly lower enantioselectivity compared to $p$-TsCl. Reaction with mesityl sulfonyl chloride does not convert; a substituent at the ortho position is not tolerated either. This is presumably due to steric hindrance of the sulfonyl chloride, which affects the association with catalyst. Investigation of electronically modified sulfonyl chlorides is currently ongoing.
Effect of Lewis Basic Site of Catalyst for Enantioselective Tosylation

To further improve the outcome of enantioselective tosylation reaction, catalysts with different structures were tested. We think that sulfonyl chloride is activated by the
imidazole moiety. In order to improve the reactivity of the reaction, catalysts with different Lewis basic sites were examined (Scheme 4.5). As the size of the groups on the imidazole increases, the conversion drops significantly (50% conv. for 4.22 and <5% conv. for 4.23). With unprotected imidazole catalyst 4.24, no conversion was observed. Presumably the imidazole nitrogen gets tosylated over the diol, thus reducing the nucleophilicity of the catalyst. With a substituent at the 4 position on imidazole ring 4.25, the tosylation reaction is shut down. It is likely that the phenyl group close to the nucleophilic nitrogen of imidazole makes interaction between \( p-TsCl \) and the catalyst less favorable. Catalyst with amino acid side chain connected to the 5 position of imidazole 4.26 is ineffective. Catalysts with other Lewis basic site such as DMAP 4.27, pyridine 4.28 and thiozole 4.29 do not afford any conversion. From the study of different Lewis basic site of catalyst, catalyst 4.17 incorporating a N-methylimidazole turns out to be the optimal.
Effect of Side Chain Modification of Catalyst for Enantioselective Tosylation

With N-methylimidazole identified as the optimal Lewis basic site for enantioselective tosylation, we next examined modifications of amino acid side chain of the catalyst. It has been shown in the previous study that secondary amine and amide of the catalyst is critical to both reactivity and enantioselectivity. Catalyst with a tertiary amine 4.30 (Scheme 4.5) is ineffective. We think that there’s disfavored steric interaction between methyl group of the tertiary amine and tert-Leucine moiety. Catalyst with a tertiary amide 4.31 affords much lower conversion as well as enantioselectivity,
presumably due to steric as well. Catalyst 4.32, with an ester functionality on the side chain, is ineffective. Ester is a weaker H-bonding acceptor, and that may affect the catalyst-substrate association. A substituent in between the imidazole moiety and the amino acid side chain is not tolerated; diastereomeric catalysts 4.33 and 4.34 do not promote the tosylation. From the catalyst screen, 4.17 turns out to be the most efficient catalyst.

**Scheme 4.6** Effect of Side Chain Modification of Catalyst for Enantioselective Tosylation

4.18 + Me₄N⁺ -SO₂Cl⁻ → 30 mol % catalyst → 4.20 + 4.21

85% ee, 82% conv. 4.20:4.21=4:1

4.17

<5% conv.

4.20

Me
N
H
H
Me
N
4.32

<5% conv.

4.30

<5% conv.

4.31

<5% conv.

4.33

<5% conv.

4.34

<5% conv.

4.6 Enantioselective Secondary Tosylation

Enantioselective tosylation of meso 1,2-diols generates certain amount of bistosylated product; the ratio of mono:bis tosylation is around 4 with the optimized reaction conditions and catalyst. There is less than 2% background reaction at −30 °C without catalyst. Given the fact that the secondary tosylation is more sterically...
demanding than the first one, it is more likely that the secondary tosylation is also catalyzed by the catalyst. To test this hypothesis, racemic mono-tosylate 4.20 was subjected to enantioselective tosylation reaction. In the presence of 30 mol % chiral catalyst, 0.75 equivalent of p-TsCl and (i-Pr)₂EtN, racemic mono-tosylate 4.20 is catalytically resolved; recovered starting material is enantioenriched with 45% ee (eq. 4.5). Kinetic resolution of racemic tosylate 4.20 proceeds with 50% conversion with a \( k_{rel} \) value of 4. The finding indicates that the secondary tosylation is also enantioselective and catalyzed by chiral catalyst 4.17. The secondary tosylation improves the enantioselectivity of the desired mono-tosylated product.

Catalytic kinetic resolution of racemic 4.20 promoted by catalyst 4.17 demonstrates that sulfonyl group could potentially interact with the catalyst. More detailed study of the interaction between sulfonyl group and the catalyst is ongoing.

4.7 Current Substrate Scope

With the optimized reaction conditions and the optimal catalyst identified so far, the substrate scope is shown in Scheme 4.7. Enantioselective tosylation of cis-1,2-cyclopentanediol yields the desired product 4.35 with 74% ee. Mono tosylated cis-1,2-cyclohexanediol 4.20 and cis-1,2-cyclohexenediол 4.36 are obtained with 87% ee. Medium size rings, such as cis-1,2-cycloheptanediol and cis-1,2-cyclooctanediol undergo
tosylation to afford product 4.37 and 4.38 with 65% ee and 66% ee. Interestingly, enantioselective tosylation of cis-1,2-cyclooctenediol affords desired product 4.39 with 91% ee and 90% isolated yield. Unlike enantioselective silylations that proceed uniformly well regardless of the ring size of substrates,\textsuperscript{61} enantioselective tosylation is substrate dependent. Acyclic substrates with slightly modified sterics also change the reaction outcome. Meso-2,3-butanediol undergoes tosylation with 72% ee and 60% isolated yield of 4.40, while meso-3,4-hexanediol only converts 15% to product 4.41.

4.8 Outlooks of Catalytic Enantioselective Tosylation of Alcohols

With the optimal catalyst 4.17 identified so far, enantioselective tosylation is applicable to a variety of cyclic and acyclic meso 1,2-diols, with 65%–91% enantiomeric excess and 66%–91% yield (Scheme 4.7). Clearly, a more reactive as well as more
enantioselective catalyst is needed for enantioselective tosylation reaction. The direct of catalyst optimization is shown is Chapter 3.

The substrate scope of the enantioselective tosylation will be explored. Other than meso 1,2-diols, chiral racemic 1,2-diols, 1,3-diols, 1,4-diols as well as polyols will be tested in the near future.

Activated C–O bond can be displaced by various nucleophiles to generate C–C, C–N and C–O bonds in a stereoselective fashion. Furnished products are otherwise difficult to excess by other catalytic protocols.

**Scheme 4.8** Representative Examples of Functionalization of Tosylation Products

C-Based Nucleophiles:

\[ \text{OTs} \rightarrow \text{COOH} \]

N-Based Nucleophiles:

\[ \text{HN} \]

O-Based Nucleophiles:

\[ \text{OH} \]

Representative examples of functionalization are shown in Scheme 4.8. Cuprate addition of a carbon-based nucleophile\(^\text{122}\) followed by oxidation of tosylate \(\text{4.20}\) will deliver cyclic chiral ketone \(\text{4.42}\). It is noteworthy that there are no general effective methods for enantioselective \(\alpha\)-alkylation of cyclic ketones.\(^\text{123}\) Enantioenriched acid \(\text{4.43}\)


can be obtained from cyanide addition and hydrolysis of 4.20.\textsuperscript{124} Nitrogen-based nucleophiles, such as readily available pyrrole, can be added to eight-membered ring tosylate 4.39.\textsuperscript{125} Synthesis of complex bicyclic diene 4.46 involves addition of oxygen-based nucleophile\textsuperscript{126} to the tosylated triol 4.45 followed by enyne metathesis.\textsuperscript{127}

A fully developed catalytic enantioselective tosylation, especially with a more reactive and selective catalyst as well as extended substrate scope, will be truly practical and invaluable for organic synthesis.

4.9 Experimental and Supporting Information

\textbf{General Information}

Infrared (IR) spectra were recorded on a Perkin Elmer 781 spectrophotometer, $\nu_\text{max}$ in cm\textsuperscript{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). \textsuperscript{1}H NMR spectra were recorded on a Varian GN-400 (400 MHz). Chemical shifts are reported in ppm with the solvent reference as the internal standard (CHCl$_3$: $\delta$ 7.26; CD$_3$OD: $\delta$ 4.87, 3.31; pyridine-d$_5$: $\delta$ 8.74, 7.58, 7.22 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), and coupling constants (Hz). \textsuperscript{13}C NMR spectra were recorded on a Varian GN-400 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent reference as the internal standard (CHCl$_3$: $\delta$ 77.23,

CD$_3$OD: $\delta$ 49.15; pyridine-d$_5$: $\delta$ 150.35, 135.91, 123.87 ppm). Melting points (mp) were taken with a Laboratory Devices Melt-Temp and were uncorrected. Enantiomeric ratios were determined by analytical liquid chromatography (HPLC) Shimadzu chromatograph (Chiral Technologies Chiralpak OD (4.6 x 250 mm)). Optical rotations were measured on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. High resolution mass spectrometry (HRMS) was performed by mass spectrometry facility at Boston College. All reagents were used as received.

**General Procedure for Catalytic Enantioselective Tosylation of meso-1,2-diols**

Catalyst **4.17** (19 mg, 0.06 mmol) and the diol substrate (0.2 mmol) were weighed into a 10 x 75 mm test tube. $t$-BuOMe (360 $\mu$L) and DIPEA (44 $\mu$L, 0.25 mmol) were added with a Gilson Pipetman. The tube was capped with a septum, and the mixture was allowed to cool to –78 °C. $p$-TsCl (48 mg, 0.25 mmol) was dissolved in $t$-BuOMe (400 $\mu$L) and added to the test tube with a Gilson Pipetman. The test tube was capped with a septum, wrapped with Teflon tape and the mixture was allowed to stir at –30 °C in a cryocool apparatus for the reported period of time. The reaction was quenched by addition of methanol (25 $\mu$L). The mixture was allowed to warm to 23 °C and directly purified by silica gel chromatography (1:3 diethyl ether:hexanes to 1:1 diethyl ether:hexanes) and analyzed by HPLC.

**Characterization Data**

**(1R,2S)-2-Hydroxycyclohexyl-4-methylbenzenesulfonate (4.20):**
$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.81 (2H, d, $J = 8.4$ Hz), 7.34 (2H, d, $J = 8.4$ Hz), 4.63 (1H, m), 3.82 (1H, m), 2.45 (3H, s), 1.98 (1H, d, $J = 5.2$ Hz), 1.91 (1H, m), 1.73 (1H, m), 1.63-1.44 (4H, m), 1.32-1.25 (2H, m). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 145.01, 134.40, 130.09, 127.89, 83.40, 69.23, 30.48, 27.98, 21.97, 21.87, 20.96. **Optical Rotation:** $[\alpha]^{20}_D$ 6.4 (c = 1.0, CHCl$_3$).

Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm × 0.46 cm), 90/10 hexanes/i-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 87% ee sample:

![Chromatograms](image_url)

(1R,2S)-2-Hydroxycyclopentyl-4-methylbenzenesulfonate (4.35): $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.81 (2H, d, $J = 8.4$ Hz), 7.34 (2H, d, $J = 8.4$ Hz), 4.66 (1H, m), 4.12 (1H, m), 2.45 (3H, s), 2.16 (1H, br), 1.89-1.77 (4H, m), 1.74-1.66 (1H, m), 1.56-1.45 (1H, m). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 145.18, 133.85, 130.12, 128.01, 84.44, 72.98, 30.20, 28.09, 21.86, 19.08. **Optical Rotation:** $[\alpha]^{20}_D$ 4.5 (c = 1.0, CHCl$_3$).
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm × 0.46 cm), 90/10 hexanes/i-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 74% ee sample:

(1R,6S)-6-Hydroxycyclohex-3-enyl-4-methylbenzenesulfonate (4.36):

IR (neat, thin film): 3527 (br), 3034 (w), 2924 (w), 1598 (w), 1350 (m), 1188 (m), 1172 (s), 1096 (m), 1070 (w), 975 (m), 945 (m), 905 (s), 876 (s), 832 (m), 813 (m), 756 (w), 729 (m), 662 (s), 607 (m), 552 (s) cm⁻¹. \( ^1H \) NMR (CDCl₃, 400 MHz): δ 7.79 (2H, d, \( J = 8.4 \) Hz), 7.32 (2H, d, \( J = 8.4 \) Hz), 5.54 (1H, m), 5.44 (1H, m), 4.73 (1H, m), 4.01 (1H, m), 2.42 (3H, s), 2.37 (1H, s), 2.34-2.16 (4H, m). \( ^{13}C \) NMR (CDCl₃, 100 MHz): δ 145.03, 134.93, 130.02, 127.84, 124.08, 122.53, 80.76, 67.15, 31.54, 28.57, 21.76. HRMS [M⁺+NH₄⁺]: Calculated for C₁₃H₂₀N₁O₄S₁: 286.1113; Found: 286.1118. Optical Rotation: \([\alpha]^{20}_D \) 10.6 (c = 1.0, CHCl₃).
Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm × 0.46 cm), 90/10 hexanes/i-PrOH, 0.7 mL/min, 220 nm); chromatograms are illustrated below for a 87% ee sample:

(1R,2S)-2-Hydroxycycloheptyl 4-methylbenzenesulfonate (4.37):

IR (neat, thin film): 3534 (br), 2931 (w), 2864 (w), 1458 (w), 1351 (m), 1172 (s), 1096 (m), 903 (s), 868 (m), 814 (m), 760 (s), 555 (m) cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 7.77 (2H, d, J = 8.4 Hz), 7.30 (2H, d, J = 8.4 Hz), 4.64 (1H, dt, J = 8.8 Hz, J = 2.6 Hz), 3.90 (1H, dt, J = 8.0 Hz, J = 2.8 Hz), 2.41 (3H, s), 2.11 (1H, s), 1.72 (1H, m), 1.77-1.25 (9H, m).

\(^{13}\)C NMR (CDCl\(_3\), 100 MHz): δ 144.98, 130.05, 127.89, 86.96, 72.51, 31.17, 28.78, 26.78, 22.44, 21.84, 21.70.

HRMS [M\(^{+}\)+NH\(_4\)]\(^+\): Calculated for C\(_{14}\)H\(_{24}\)N\(_1\)O\(_4\)S\(_1\): 302.1426; Found: 302.1434. Optical Rotation: [\(\alpha\)]\(^{20}\)_D 6.4 (c = 1.0, CHCl\(_3\)).

Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm × 0.46 cm), 90/10 hexanes/i-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 65% ee sample:
(1R,2S)-2-Hydroxycyclooctyl-4-methylbenzenesulfonate (4.38):

IR (neat, thin film): 3529 (br), 2925 (w), 2860 (w), 1598 (w), 1450 (w), 1188 (w), 1173 (m), 1097 (w), 904 (s), 863 (w), 814 (w), 726 (s), 688 (m), 648 (w), 554 (m) cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.79 (2H, d, \(J = 8.4\) Hz), 7.33 (2H, d, \(J = 8.4\) Hz), 4.74 (1H, m), 3.93 (1H, m), 2.43 (3H, s), 2.28 (1H, s), 2.06 (1H, m), 1.76-1.34 (11H, m).

\(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 144.97, 134.16, 130.02, 127.87, 86.11, 71.78, 30.28, 28.20, 27.00, 25.55, 24.05, 21.89, 21.79. HRMS [M\(^+\)+H]: Calculated for C\(_{15}\)H\(_{23}\)O\(_4\)S\(_1\): 299.1317; Found: 299.1303. Optical Rotation: \([\alpha]_{20}^{20}\)D 9.6 (c = 1.0, CHCl\(_3\)).

Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm × 0.46 cm), 90/10 hexanes/i-PrOH, 0.7 mL/min, 220 nm); chromatograms are illustrated below for a 66% ee sample:
(1R,8S,Z)-8-Hydroxycyclooct-4-enyl-4-methylbenzenesulfonate (4.39):

IR (neat, thin film): 3530 (br), 3019 (w), 2939 (w), 1598 (w), 1352 (w), 1188 (w), 1173 (m), 1097 (s), 1033 (w), 902 (s), 873 (m), 837 (w), 813 (w), 725 (s), 670 (m), 648 (w), 573 (w), 555 (m) cm$^{-1}$.\textsuperscript{1}H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.78 (2H, d, $J = 8.4$ Hz), 7.33 (2H, d, $J = 8.4$ Hz), 5.62 (2H, m), 4.77 (1H, m), 4.01 (1H, m), 2.50 (2H, m), 2.43 (3H, s), 2.33 (1H, s), 2.12-1.54 (6H, m). \textsuperscript{13}C NMR (CDCl$_3$, 100 MHz): $\delta$ 144.99, 133.86, 130.79, 130.02, 129.27, 127.94, 87.88, 73.55, 33.24, 30.78, 21.87, 21.81, 21.35. HRMS [M$^+$+NH$_4$]: Calculated for C$_{15}$H$_{24}$N$_1$O$_4$S$_1$: 314.1426; Found: 314.1429. Optical Rotation: $[\alpha]^{20}_D$ 31.8 ($c = 1.0$, CHCl$_3$).

Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm $\times$ 0.46 cm), 90/10 hexanes/i-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 91% ee sample:
(2R,3S)-3-Hydroxybutan-2-yl-4-methylbenzenesulfonate (4.40):

IR (neat, thin film): 3528 (br), 2985 (w), 1599 (w), 1449 (w), 1189 (w), 1174 (m), 1099 (w), 1019 (w), 901 (s), 814 (w), 786 (w), 726 (s), 648 (w), 555 (s), 465 (w) cm⁻¹.

¹H NMR (CDCl₃, 400 MHz): δ 7.79 (2H, d, J = 8.4 Hz), 7.33 (2H, d, J = 8.4 Hz), 4.54 (1H, m), 3.86 (1H, m), 2.43 (3H, s), 2.22 (1H, br), 1.19 (3H, d, J = 6.4 Hz), 1.09 (3H, d, J = 6.4 Hz).

¹³C NMR (CDCl₃, 100 MHz): δ 145.00, 134.15, 130.03, 127.89, 83.36, 69.47, 21.79, 17.79, 15.03.

HRMS [M⁺+NH₄⁺]: Calculated for C₁₁H₂₀N₁O₄S₁: 262.1113; Found: 262.1114. Optical Rotation: [α]₂₀ D 5.2 (c = 1.0, CHCl₃).

Enantiomeric purity was established by HPLC analysis (Chiralpak OJ-H column (25 cm × 0.46 cm), 90/10 hexanes/i-PrOH, 0.5 mL/min, 220 nm); chromatograms are illustrated below for a 72% ee sample:
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