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YTTRIUM-CATALYZED REACTIONS: TRANSACYLATION, SECONDARY ALCOHOL RESOLUTION, CYANOSILYLATION OF KETONES AND EPOXIDES

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By
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The Ohio State University
2002

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ABSTRACT

New applications of Y-complexes for selective C-O, C-C and C-N bond-forming reactions are described in this thesis. Isopropenyl or vinyl esters react with primary and secondary alcohols in the presence of $\text{Y}_3(\text{O}^{\text{Pr}})_3\text{O}$ (0.05–1 mol%) at room temperature to give the corresponding esters in high yields. Remarkably, the yttrium catalyst promotes selective O-acylation of amino alcohols without formation of the amide. For example, yttrium-catalyzed acylation of 2-piperidinemethanol with isopropenyl acetate gives 2-piperidinemethyl acetate exclusively.

A bifunctional complex with proximal reactive sites on the metal, which can simultaneously enhance the reactivity of both the alcohol and the enol ester, should be the catalyst of choice for this reaction. Accordingly, ligand-assisted catalysis is observed in a salen-yttrium complex-catalyzed asymmetric acylation. The kinetic resolution of 1-indanol catalyzed by 1 mol% of the complex with 91%ee at 76% conversion ($k_{\text{rel}} = 4.8$) is the first example of metal-catalyzed kinetic resolution of a secondary alcohol via acylation.

Salen-yttrium complex also is an active catalyst in cyanosilylation of ketones, and epoxide opening with TMSCN and TMSN$_3$ respectively. Asymmetric ring opening of cyclohexene oxide with TMSCN catalyzed by salen-yttrium complex (2 mol%) gave a trans-$\beta$-trimethylsilyloxy nitrile with up to 66% enantiomeric excess.
Dedicated to my parents
ACKNOWLEDGMENTS

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I would like to thank Professor David Hart for his encouragement, which made me cross the fear of language barrier and complete my student seminar.

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LIST OF ABBREVIATIONS

Ac  acetyl
[α]  specific rotation
box  bis(oxazoline)
Bu  butyl
r-Bu  tert-butyl
°C  degree ceicious
calcd  calculated
δ  chemical shift in parts per million downfield from tetramethylsilane
d  doublet (spectral)
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DME  1,2-dimethoxyethane
dms  dimethylsilyl
DMF  N,N-dimethylformamide
equiv.  equivalent(s)
Et  ethyl
g  gram(s)
GC  gas chromatography
GPC  gel permeation chromatography
h  hour(s)
HRMS  high-resolution mass spectrum
Pr  isopropyl
LDA  lithium diisopropylamide
Hz  hertz
IR  infrared spectroscopy
J  coupling constant (in NMR)
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
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<tr>
<td>L</td>
<td>liter(s)</td>
</tr>
<tr>
<td>μ</td>
<td>micro</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (spectral)</td>
</tr>
<tr>
<td>M</td>
<td>moles per liter</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl (mesyl)</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio (in mass spectrometry)</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>OTf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>part per million (in NMR)</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>pybox</td>
<td>bis(oxazoliny)pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet (spectral)</td>
</tr>
<tr>
<td>Rf</td>
<td>retention factor (in chromatography)</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet (spectral)</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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CHAPTER 1

YTTRIUM-CATALYZED ACYL TRANSFER REACTIONS

1.1 INTRODUCTION

The advantages of ester syntheses via transesterification reactions have been addressed.¹ More efficient catalyst, mild reaction conditions compatible with acid or base-labile functional groups, and easy purification are the paragon for developing new catalysts for transesterification reactions.² Several powerful catalysts have been discovered in acylation of alcohols where an acid anhydride is used as the acylating agent (eq 1).³

\[
\text{ROH} + \text{Ac}_2\text{O} \xrightleftharpoons{\text{cat.} \, l} \text{ROAc}
\]

\[
\text{ROH: pri-, sec-, tert-alcohol; PhOH; cat.} \, l: \text{Sc(NTf}_2)_3, \text{Sc(OTf}_3, \text{Me}_3\text{SiOTf, Bi(OTf)}_3
\]

Enol acetate is another acylating agent widely used in enzymatic methods (eq 2); furthermore, no background reaction in the combination of alcohol and enol acetate exists.⁴ Metal catalysts documented in the acyl transfer reaction of enol acetates are \(\text{Cp}^*\text{Sm(thf)}_2\) and distannoxane (eq 2).⁵
The advantages of enol acetate as an acylating agent are mild (nearly neutral) conditions, and an irreversible reaction driven through enol-keto tautomerization. The utilization of the yttrium alkoxide $Y_5(O^\text{Pr})_{13}O$ is reported in aldol reaction, silylcyanation, aldol-Tishchenko and polymerization of lactones and cyclohexene oxide (Scheme I).

Recently, a new use for yttrium alkoxides was discovered in the transesterification reaction. Yttrium alkoxides 1, 2 were selected from over 15 metal oxides to be the catalyst of choice. Regioselectivity (primary, secondary vs tertiary alcohol) and kinetic enantioselectivity (with optically active lanthanide catalysts) of this reaction are the primary topics of this thesis.
Scheme 1. Y₅(O′Pr)₁₃O (1) Catalyzed Reactions
Scheme 2. Proposed Template Effects of Distannoxane Catalysts in Transesterification

Novel template effects for the distannoxane catalysis have been proposed for distannoxane-catalyzed transesterification of carboxylic esters (Scheme 2). It is also believed that distannoxane-catalyzed acyl transfer of enol esters proceed through the same mechanism. As can be seen from Scheme 2, the transesterification catalyzed by distannoxane can be performed because of the enhanced reactivity of alcohol and enol ester and direct interaction between the alkoxy group and the coordinated carbonyl group.
The reactivities of two reactants are enhanced because of the formation of the alkoxydistannoxane and the coordination of the carbonyl group of enol ester to the electrophilic tin. Distannoxane and \( Y_5(0^\beta Pr)_3O \) (1), both active catalysts, in the transesterification share this structural feature of the metaloxane core. The proximity of two reactive sites on the catalyst has proven to be crucial in the reaction of alcohol and enol acetate (see chapter 2 for detailed discussion). In addition, we believe that rapid exchange of free alcohol with terminal and bridging alkoxides in the cluster of \( Y_5(0^\beta Pr)_3O \) via a proton transfer mechanism is a necessary feature for this cluster to be an efficient catalyst.

1.2 TRANSESTERIFICATIONS CATALYZED BY YTTRIUM COMPLEXES

Structure of \( Y_5(0^\beta Pr)_3O \) (1) was determined by Caulton et al and an easy preparation has been reported (Figure 1; eq 3). As mentioned, yttrium alkoxides 1, 2 were selected from several metal oxides to be the catalyst of choice. Other metal oxides investigated include \( Y(OCH_2CH_2NMMe_2)_3 \), SmI_3. THF, Ti(O^\beta Pr)_4, \( (N[(CH_2CH(CH_3)O)_3]Ti IV Cl \), \( (N[(CH_2CH(CH_3)O)_3]Zr IV Cl \), \( Zr(O^\beta Pr)_4 \), \( Hf(O^\beta C_4H_5)_4 \), \( Nb(O^\beta C_3H_5)_5 \), \( V(O)(O^\beta Pr)_3 \), \( Ta(O^\beta C_2H_5)_5 \), Eu(tfc)_3, tfc = tris[3-(trifluoromethylhydroxymethylene)camphorato], Pr(tfc)_3, \( Y(thd)_3 \) (thd = tris(2,2,6,6-tetramethyl-3,5-heptanedionato), La(thd)_3, Yb(thd)_3. Note that the catalyst is needed for the reaction of alcohol and enol ester; i.e., no acetate formation was observed when a mixture of benzyl alcohol (1 mmol) and vinyl acetate (1 mL) was stirred for 24 h.
Figure 1. Structure of $Y_5(O'Pr)_{13}O$ (1) Determined by Caulton\textsuperscript{13a} et al

\[ \text{Preparation:}^{13a} \quad \text{Me} \quad \begin{array}{c} \text{Me} \cr \text{OH} \end{array} + Y \xrightarrow{\text{cat. HgCl/Hg(OAc)\_2}} \text{Me} \quad \text{Me} \quad Y_5(O'Pr)_{13}O \quad (3) \]

toluene, reflux 36-48 h

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The results of two yttrium alkoxide-catalyzed (1, 2) stoichiometric transesterification reaction of alcohol (1 mmol) and isopropenyl acetate (1 mmol) in benzene (2 mL) are shown in Table 1. Under yttrium alkoxide-catalyzed acylation condition, the primary alcohol reactivity was greater than secondary, but tertiary alcohol was unreactive. Compared to \([Y(\text{thd})_2(O'\text{Pr})]\) (2), the efficacy of \(Y_5(O'\text{Pr})_{13}O\) (1) was dramatically increased in solvent-free transesterification when excess acylating agent was employed (Table 2, entries 1 vs 4, 5 vs 6). The reactions were performed smoothly to give quantitative yield (Table 2, entries 1, 2, 5, 9, 11); furthermore, the purification was extremely easy.

Table 1. Stoichiometric Transesterifications Catalyzed by Y Complexes 1, 2

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>Y complex</th>
<th>time (h)</th>
<th>conv. (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzyl alcohol</td>
<td>(Y_5(O'\text{Pr})_{13}O) (1)</td>
<td>7</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>benzyl alcohol</td>
<td>([Y(\text{thd})_2(O'\text{Pr})]) (2)</td>
<td>14</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>1-phenylethanol</td>
<td>(Y_5(O'\text{Pr})_{13}O) (1)</td>
<td>27</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>1-phenylethanol</td>
<td>([Y(\text{thd})_2(O'\text{Pr})]) (2)</td>
<td>20</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>t-butanol</td>
<td>(Y_5(O'\text{Pr})_{13}O) (1)</td>
<td>96</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>t-butanol</td>
<td>([Y(\text{thd})_2(O'\text{Pr})]) (2)</td>
<td>96</td>
<td>0</td>
</tr>
</tbody>
</table>

a. Conversion was determined by GC.
\[
\text{ROH} + \overset{\text{OAc}}{\text{R'}} = \overset{\text{Me}}{\text{Me}} (3a) \quad \overset{\text{R'} = \text{H}}{\text{R'}} \quad \overset{Y \text{ catalyst, rt}}{\rightarrow} \quad \text{ROAc}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohol</th>
<th>enol acetate</th>
<th>Y cat. (mol%)</th>
<th>time (h)</th>
<th>conversion (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzyl alcohol</td>
<td>3a</td>
<td>1 (0.5)</td>
<td>1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>benzyl alcohol</td>
<td>3c</td>
<td>1 (0.5)</td>
<td>0.08</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>benzyl alcohol(^d)</td>
<td>3c</td>
<td>1 (0.05)</td>
<td>24</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>benzyl alcohol</td>
<td>3a</td>
<td>2 (1)</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>1-phenylethanol</td>
<td>3a</td>
<td>1 (0.5)</td>
<td>1.5</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>1-phenylethanol</td>
<td>3a</td>
<td>2 (5)</td>
<td>43</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>cyclohexanol</td>
<td>3a</td>
<td>1 (0.5)</td>
<td>1.5</td>
<td>&gt;95 (94)(^b)</td>
</tr>
<tr>
<td>8</td>
<td>cyclohexanol</td>
<td>3c</td>
<td>1 (0.5)</td>
<td>1.5</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>1-Ph-1,2-ethanediol</td>
<td>3a</td>
<td>1 (1)</td>
<td>1.5</td>
<td>&gt;99(^c)</td>
</tr>
<tr>
<td>10</td>
<td>1,3-di-Ph-allyl alcohol</td>
<td>3a</td>
<td>1 (1)</td>
<td>1.5</td>
<td>90(^b)</td>
</tr>
<tr>
<td>11</td>
<td>E-cinnamyl alcohol</td>
<td>3a</td>
<td>1 (0.5)</td>
<td>0.16</td>
<td>&gt;99</td>
</tr>
<tr>
<td>12</td>
<td>E-cinnamyl alcohol(^d)</td>
<td>3c</td>
<td>1 (0.05)</td>
<td>48</td>
<td>72</td>
</tr>
<tr>
<td>13</td>
<td>(2S, 3S)-epoxygeraniol</td>
<td>3c</td>
<td>1 (0.5)</td>
<td>0.08</td>
<td>&gt;99 (67)(^b)</td>
</tr>
</tbody>
</table>

a. Conversion was determined by GC. b. Isolated yield. c. Diacetate was obtained as product. d. The reaction was carried out with alcohol (10 mmol), and vinyl acetate (4 mL) at rt.

**Table 2. Yttrium-Catalyzed Solvent-Free Transesterification**
When the reaction was complete, the reaction mixture was concentrated in \textit{vacuo} to remove excess vinyl (or isopropenyl) acetate, and subsequently distilled or filtered through a short column of silica gel. The crude product gave satisfactory $^1$H NMR data.

Remarkably, the transesterification of vinyl acetate (3c) with benzyl alcohol and E-cinnamyl alcohol can be performed at room temperature in the presence of 0.0005 equiv of $Y_5(O'Pr)_{13}O$ (1) (substrate/catalyst = 2000) (Table 2, entries 3, 12).

As can be seen above, the reaction catalyzed by 0.0005 equiv of $Y_5(O'Pr)_{13}O$ (1) gave 57% conversion in 10 min and 70% conversion in 35 min. Such catalytic efficiency for acyl transfer of enol esters is unprecedented.
In general, vinyl acetate (3c) has higher reactivity than isopropenyl acetate (3a); however, opposite reactivity was observed in cyclohexanol (Table 2, entry 7 vs 8).

Presumably, acetaldehyde liberated from vinyl acetate might decrease the catalyst activity when the side-reactions (for example, aldolization) compete with sluggish transesterification.\(^{14}\) Note that Y\(_5\)(O\(\text{OPr}\))\(_{13}\)O is a active catalyst for aldol reaction.\(^6\)

In a study of the functional group compatibility with Lewis acidic yttrium alkoxides, Y\(_5\)(O\(\text{OPr}\))\(_{13}\)O (1) catalyzed transesterification of relatively sensitive electrophilic substrates such as 1,3-diphenylallyl alcohol, E-cinnamyl alcohol, and 2,3-epoxygeraniol gave quantitative reactions. In addition, no allylic rearrangement of the acyl group was found in the acylation of E-cinnamyl alcohol (Table 2, entries 11, 12).

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Moreover, epoxide remained intact under Y₅(O₃Pr)₁₃O catalyzed conditions (Table 2, entry 13).

\[
\begin{align*}
\text{H}_3\text{C} & \text{CH}_3 \text{CH}_3 \text{CH}_3 \text{O} \text{H} + \text{H} \text{Ac} & \xrightarrow{0.5 \text{ mol} \% \ Y₅(O₃Pr)₁₃O} \text{H}_3\text{C} & \text{CH}_3 \text{CH}_3 \text{CH}_3 \text{O} \text{H} \text{Ac} \\
\text{rt, 5 min, 99\% conv.} & \text{(57\% isolated yield)}
\end{align*}
\]

1.3 SELECTIVE ACYLATION AMONG DIFFERENT KINDS OF HYDROXYL GROUPS

Selective esterification of a primary alcohol in the presence of a secondary alcohol has been sought. Significant discrimination between primary and secondary alcohol could not be achieved in acylation; however, excellent selectivity (24:1) was obtained in benzylation (Scheme 3). As mentioned, primary alcohol was quantitatively acylated in 5 min when vinyl acetate was employed as acylating agent under catalysis by Y₅(O₃Pr)₁₃O. Herein, a mixture of benzyl alcohol (1 mmol), α-methylbenzyl alcohol (1 mmol) and vinyl acetate (1mL, 10.9 mmol) in the presence of 0.24 mol% of Y₅(O₃Pr)₁₃O, 100% of the primary alcohol and 25% of the secondary alcohol were esterified. When the acylating agent such as isopropenyl acetate (3a) was employed as limiting agent, the selectivity between primary and secondary alcohol achieved was 2.7/1 under catalysis by Y₅(O₃Pr)₁₃O (1), and 8/1 under catalysis by [Y(thd)₂(O₃Pr)] (2). The selectivity can be improved dramatically (>24:1) when isopropenyl benzoate (3b) was employed as the acylating agent under catalysis by Y₅(O₃Pr)₁₃O (1).
Scheme 3. Yttrium Alkoxide-Catalyzed Selective Esterification of Primary Alcohol in the Presence of Secondary Alcohol

Selective acylation of the least sterically hindered equatorial hydroxyl group (C3-OH) in tert-butyl cholate was achieved (eq 4). In addition, phenol was not acylated under $\text{Y}_5(\text{O}^\text{OPr})_3\text{O}$ (1) catalyzed condition though excess acylating agent was employed (eq 5). This result will have important implications in the design of Y-based chiral catalysts for the transesterification reactions (see chapter 2).
In summary, the selectivity between different kinds of hydroxyl groups can be controlled by stoichiometry, by structure of the enol ester and by the nature of the yttrium catalyst.

1.4 ACYLATION OF AMINES WITH ENOL ESTERS CATALYZED BY YTTRIUM ALKOXIDES

The acylation of amino groups is another reaction that could in principle be catalyzed by yttrium alkoxides. The acylation of amino groups with enol esters catalyzed by Cp*₂Sm(thf)₂ has been reported (eq 6). It has also been stated that enol esters could not...
be employed as acylating agents with primary amine since they react exothermally without a catalyst.\textsuperscript{15a}

\[ \begin{align*}
\text{R}^+\text{N}^+\text{R'}^- + \text{OAc}^- & \xrightarrow{10 \text{ mol\% } \text{Cp}^+_2\text{Sm(THF)}_2} \text{toluene (1 mL), rt, 3 h} \\
\text{H}_3\text{C}=\text{O} & \\
\text{R}'\text{N}^+\text{R'}^- & \\
\end{align*} \]  

**Amine** (yield, %):

- PhNHa (No reaction)
- C6H5NH (No reaction)
- PhNH2 (No reaction)
- C6H5CH2NH2 (>99)

\[ \begin{align*}
\text{P}^-\text{NH} & + \text{PhCH}(_2)^-\text{CHCO}_2\text{Et} \\
\text{NH}_2\cdot\text{HCl} & \xrightarrow{10\% \text{KCN}} \text{Et}_3\text{N (5.5 mmol)} \\
\text{EtOAc (10 mL)} & \xrightarrow{rt, 6 \text{ h}, 85\% \text{isolated yield}} \\
\end{align*} \]

It has also been reported that acylation of \( \alpha \)-amino esters with amido-enol esters required the use of KCN as a catalyst to form dipeptides at room temperature (eq 7).\textsuperscript{15b}

First, benzyl amine and phenylethyl amine were chosen to examine the reactivity of \( \text{Y}_3(\text{O}^\text{Pr})_3\text{O} \) (1), and the results are summarized in Table 3. It came to our attention that primary amines react spontaneously with enol esters 3a-c with no catalyst (Table 3, entries 4, 8, 11, 15).
<table>
<thead>
<tr>
<th>amine</th>
<th>entry</th>
<th>enol ester</th>
<th>cat. (mol%)</th>
<th>time (h)</th>
<th>conversion (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph−NH₂</td>
<td>1</td>
<td>3a</td>
<td>Y₅(OPr)₁₃O (0.5)</td>
<td>0.08</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3a</td>
<td>Y₅(OPr)₁₃O (0.5)</td>
<td>2.16</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3a</td>
<td>Y₅(OPr)₁₃O (0.5)</td>
<td>15</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>none</td>
<td>none</td>
<td>1.3</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>3b</td>
<td>Y₅(OPr)₁₃O (0.5)</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3b</td>
<td>Y₅(OPr)₁₃O (0.5)</td>
<td>15</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>3b</td>
<td>none</td>
<td>0.16</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>3b</td>
<td>none</td>
<td>15</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>3c</td>
<td>Y₅(OPr)₁₃O (0.5)</td>
<td>0.08</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>3c</td>
<td>none</td>
<td>0.08</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>3c</td>
<td>none</td>
<td>0.75</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>3a</td>
<td>Y₅(OPr)₁₃O (1)</td>
<td>0.75</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>3a</td>
<td>Y₅(OPr)₁₃O (1)</td>
<td>23</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>3a</td>
<td>none</td>
<td>1.2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>3a</td>
<td>none</td>
<td>23</td>
<td>73</td>
</tr>
</tbody>
</table>

a. The reaction was carried out with amine (1 mmol), and enol ester (1 mL) at rt.
Benzyl amine was employed (entries 1-11)
Phenylethylamine was employed (entries 12-15)
b. Conversion was determined by GC.

Table 3. Acylation of Amines with Enol Esters

However, the acylation of benzyl amine was inhibited by catalytic amount of
Y₅(OPr)₁₃O, when isopropenyl acetate (3a) was employed as acylating agent (Table 3,
entry 2, 3 vs entry 4). Such inhibition by the catalyst was not observed in the reaction of benzyl amine with isopropenyl benzoate (3b) or vinyl acetate (3c) (Table 3, entry 6 vs 8; entry 9 vs 10). Moreover, no inhibition by the catalyst was observed in the reaction of phenylethyl amine and isopropenyl acetate (3a) (Table 3, entry 13 vs 15). Therefore, the inhibition is dependent on the structure of the enol ester and the amine.

Next, we turned our attention to amino acid esters. Serendipitously, we discovered that the expected amide was observed to be formed in quantitative yield in the absence of any catalysts; somehow, Y₅(O'Pr)₁₃O (1) "inhibited" the amide formation (eq 8, 9).

![Chemical reactions](attachment:chemical_equations.png)

The inhibition of amide formation by the catalyst was also observed under conditions described in eq 10. To a mixture of (R)-phenylglycine methyl ester (1 mmol) and isopropenyl acetate (3a) (1 mL) stirred for 2.83 h with 57.3% conversion, Y₅(O'Pr)₁₃O (1) (6.5 mg; 0.005 mmol) was added. This mixture with 0.5 mol% of Y₅(O'Pr)₁₃O (1)
was stirred for another 24 h at room temperature, and assayed by GC which showed 61.7% overall conversion. After addition of \( Y_3(O'Pr)_{13}O \) (1), thus the amide formation was "inhibited" with only 4.4% conversion for 24 h.

\[
\begin{array}{c}
\text{OAc} - CH_3 + (R)-PhCHCO_2Me \quad \xrightarrow{\text{No catalyst}} \quad (R)-PhCHCO_2Me - NHAc \quad \xrightarrow{0.5 \text{ mol%} Y_3(O'Pr)_{13}O} \quad (R)-PhCHCO_2Me - NHAc
\\(1 \text{ mL}) \quad (1 \text{ mmol}) \quad \text{rt, 2.83 h} \quad 57.3\% \quad 4.4\% \quad 61.7\%
\end{array}
\]

In addition, no inhibition of the amide formation by the catalyst was observed in the reaction of \((L)\)-phenylalanine ethyl ester with vinyl acetate (3c) under the same condition shown in eq 8. It was not necessary to use excess acylating agent for the spontaneous \( N \)-acylation. The amide formation was also performed smoothly at room temperature with stoichiometric amount of \((L)\)-phenylalanine ethyl ester (1 mmol) and isopropenyl acetate (1 mmol) in \( CH_2Cl_2 \) (1 mL) (47 h, 63% conversion), or benzene (1 mL) (22 h, 55% conversion; 47 h, 75% conversion). It is worth noticing no epimerization at \( \alpha \)-carbon of amino acid esters during this amide formation. The absence of any racemization was confirmed by GC analysis of the product on chirasil S-Val column where baseline separation of enantiomers have been observed on an authentic sample of the racemic product. With this remarkable result that \( Y_3(O'Pr)_{13}O \) (1) inhibited the acylation of \( \alpha \)-amino esters with isopropenyl acetate in hand, selective acylation of an alcohol in the presence of an amine was sought as the next target.
1.5 AN UNPRECEDENTED NH$_2$ VS OH CHEMOSELECTIVITY IN AN ACYLATION REACTION

In general, an amino group is more nucleophilic than a hydroxyl group. However, yttrium alkoxide 1 appeared to show reactivity consistent with inhibition of acylation of an amine. We wondered whether selective acylation of an alcohol could be achieved in the presence of an amine. Indeed, this unprecedented functional group transformation has been successfully demonstrated as shown in eq 11, 12, and 14.

\[
\begin{align*}
\delta 2.81 & \text{ (NH}_2\text{-C}(2)\text{-H)} \\
\delta 3.77 & \text{ (HO-C}(3)\text{-H)}
\end{align*}
\]

\[
\begin{align*}
\delta 2.95 & \text{ (NH}_2\text{-C}(2)\text{-H)} \\
\delta 5.28 & \text{ (AcO-C}(3)\text{-H)}
\end{align*}
\]

\[
\begin{align*}
\text{IR} 1730 \text{ cm}^{-1}
\end{align*}
\]

\[
\begin{align*}
\text{IR} 1740 \text{ cm}^{-1} \text{ (O-Ac)} \\
1640 \text{ cm}^{-1} \text{ (N-Ac)}
\end{align*}
\]
A very good yield (82%) of O-acylation was obtained when benzyl 2-amino-2-deoxy-4,6-di-O-phenyl-methyl-α-D-glucopyranoside (0.5 mmol) was treated with 2 mL of isopropenyl acetate (3a) and 3 mol% of Y₃(O'Pr)₁₃O (1) for 2 h at room temperature (eq 11). The structure of the new O-acylation product was confirmed by characteristic peaks in ¹H NMR that the chemical shift of the hydrogen at carbon (3) [δ 3.77, H-C(3)-OH] was downfield shifted because of O-acylation [δ 5.28, H-C(3)-OAc]. The structure of 2-piperidinemethanol acetate was confirmed by IR (ester 1730 cm⁻¹; in comparison with eq 13)¹⁶ and the formation of analytically pure amine oxalate salt (Anal. Calcd for C₁₀H₁₇NO₆: C, 48.56; H, 6.93; N, 5.67. Found: C, 48.70; H, 6.98; N, 5.72) (eq 12).

\[
\text{苯基乙醇} + 1 \text{ mol% } 1, 3a (1 \text{ equiv}) \xrightarrow{\text{rt, } 4\text{ h, } 1\text{M in C₆H₆}} \text{苯基乙基胺} <1% \quad \text{苯基乙基胺} \quad 49% \quad \text{苯基乙基胺} \quad 49% \quad \text{苯基乙基胺} \quad <1% \quad \text{苯基乙基胺} \quad \text{苯基乙基胺} \quad \text{苯基乙基胺} \quad \text{苯基乙基胺}
\]

As can be seen in eq 14, selective O-acylation was observed in a stoichiometric mixture of 1-phenylethanol (1 mmol), 1-phenylethyl amine (1 mmol) and isopropenyl acetate (3a) (1 mmol) in benzene (2 mL) in the presence of Y₃(O'Pr)₁₃O (1) (0.01 mmol). Less than 0.8% (GC) of the N-acyl derivative was detected. The only amine-derived product in the mixture identified by GCMS [m/z 161 (M⁺⁺)] and NMR was the corresponding acetone imine.
In addition, an attempted selective acylation of the allose derivative 4 gave a mixture. Benzyl 2-amino-4,6-O-benzylidene-2-deoxy-allopyranoside (4) (0.5 mmol) was treated with 2 mL of isopropenyl acetate (3a) and 4 mol% of Y$_5$(O'Pr)$_{13}$O (1) for 2 h at room temperature. Rapid intramolecular acyl migration from $O$ to $N$ might be the reason (Scheme 4) for this result. Pure DL-threonine ethyl ester (5) and DL-phenylserine ethyl ester (6) readily polymerize themselves at room temperature; therefore, the reaction with isopropenyl acetate (3a) gave complicated unidentified mixtures. Pseudoephedrine (7) was also subjected to the reaction in order to probe the selectivity between secondary hydroxyl group and secondary amino group; however, pseudoephedrine (7) does not react with enol esters 3a-c under catalysis by Y$_5$(O'Pr)$_{13}$O (1). Presumably, pseudoephedrine (7) might react with yttrium alkoxide 1 to form inert saturated complex. Note that yttrium with chiral ligand 8 was employed as a catalyst in asymmetric hetero Diels-Alder reaction with Danishefsky’s diene (90% yield, 46% ee).$^{17}$ Pseudoephedrine (7) is a more electron-rich ligand to yttrium than β-hydroxyl triflamide 8; therefore, the active sites on Y$_5$(O'Pr)$_{13}$O (1) might be occupied by pseudoephedrine (7) which results in slow alcohol exchange and/or decreased Lewis acidity of the catalyst, both of which are required for the acylation reaction.
Scheme 4. Yttrium-Catalyzed Acylation of Allose Derivative 4: Intramolecular Acyl Migration from O to N

The mechanism for this unusual reaction is unclear. The scenario might be that O-acylation is accompanied with in-situ N-protection because of acetone-imine formation, which was observed during the course of this study (Scheme 5).
Scheme 5. Unprecedented Functional Group Transformation: O-Acylation with in-situ N-Protection

1.6 PROPOSED MECHANISM OF Y₅(O'Pr)₁₃O CATALYZED TRANSACYLATION

It has been reported that rapid exchange of a free alcohol with terminal and bridging alkoxides in the cluster of Y₅(O'Pr)₁₃O (I) takes place via a proton transfer mechanism. Therefore, a possible overall mechanism of Y₅(O'Pr)₁₃O (I) catalyzed acylation can be formulated shown in Scheme 6.
Scheme 6. Proposed Mechanism of Y₅(O'Pr)₁₂O Catalyzed Transacylation

Admittedly intimate details of the formation of the tetrahedral intermediate and its eventual decomposition remain as yet unknown. In addition, it is difficult to proceed with proton transfer from amine (RNH₂, pKa >30) if N-acylation has to go through yttrium activation (eq 15). Thus, acetone liberated from O-acylation reacted with amine to form imine resulting in unprecedented functional group transformation.

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1.7 TRANSACYLATION REACTIONS IN ROOM-TEMPERATURE POLYMERIZATION

The transacylation reaction is potentially useful for the synthesis of a polyester, if the appropriate precursor–divinyl ester–can be prepared (eq 16, 17).

\[
\begin{align*}
\text{cat. } Y_3(O^\text{OPr})_3O & \quad \text{polymer} \quad n \\
\text{HO} & \quad \text{OH} \quad \text{toluene}, \; \text{rt} \\
\end{align*}
\]

From our preliminary study, a promising polymer-like product was observed in the attempted polymerization with diisopropenyl terephthalate (9) (0.37 mmol), 1,3-propanediol (0.5 mmol) and \( Y_3(O^\text{OPr})_3O \) (1) (0.0037 mmol, 1 mol%) in toluene (0.5 mL) at ambient temperature (eq 16). Ether was added into the product mixture and the white solid formed was collected. However, the material was not fully characterized. In addition, divinyl adipate (10) was synthesized according to the procedure described in the literature,\(^{19a}\) and subjected to yttrium-catalyzed room-temperature polymerization (eq 18, 19).
A mixture of divinyl adipate (10 synthesized according to eq 18) (1.9 g; 9.58 mmol), 1,3-propanediol (690.6 mg; 9 mmol) and Y₅(OPr)₁₃O (1) (0.07 mmol) in benzene (2 mL) was stirred for 24 h at ambient temperature to give 2.5 g of product as liquid (eq 19). When hexane was added into the liquid, separate layers were observed and the liquid stayed at the bottom layer; in other words, the liquid did not dissolve in hexane. Formation of a white solid was noticed, when the liquid was added into excess ether. The
liquid portion was an oligomer as confirmed by GPC data shown in the preceding page (page 25). As expected, that GPC (gel permeation chromatography) of this material gave broad peaks and there appears to be no control of molecular weight. Divinyl adipate (10) is probably a poor choice because of the formation of acetaldehyde byproduct and catalyst deterioration could be expected. To overcome the catalyst deterioration caused by the aldolization of acetaldehyde, diisopropenyl terephthalate (9) would be an ideal substrate to examine this protocol. However, the major challenge in this approach to polymer synthesis is the preparation of divinyl esters from readily available precursors. Several attempts were made to synthesize the requisite diisopropenyl esters as described in the next section.

1.8 ATTEMPTED SYNTHESIS OF DIISOPROPENYL TEREPTHALATE

As mentioned, diisopropenyl terephthalate (9) is the substrate of interest to prove the feasibility of $Y_5(O^\text{t}Pr)_13O$ (1) catalyzed room-temperature polymerization. The attempted synthetic routes toward diisopropenyl terephthalate (9) are shown in scheme 6. As a model, isopropenyl benzoate (3b) that gave 24/1 selectivity of pri- vs sec-alcohols in our previous study was successfully prepared from benzoyl chloride and isopropenyl acetate under catalysis by acid.\textsuperscript{18} Although the separation of isopropenyl benzoate from benzoyl chloride was tough, 77% yield based on consumed benzoyl chloride was obtained (eq 20).
However, the acid-catalyzed reaction of terephthaloyl chloride and isopropenyl acetate gave polymerization of terephthaloyl chloride instead of diisopropenyl terephthalate (Scheme 7, route 1). Other possible routes are shown in Scheme 7.

As mentioned, divinyl adipate (10) was prepared via Pd-catalyzed transvinlylation (eq 18). Attempted synthesis of diisopropenyl terephthalate from terephthalic acid and isopropenyl acetate under different conditions reported for transvinlylation failed (Scheme 7, route 2). In general, insolubility of terephthalic acid is the major problem; that is, terephthalic acid is recovered from every attempted reaction. In addition, Pd-catalyzed transvinlylation was a substrate-dependent reaction; moreover, the substrate (organic acid) with pKa between 3.9 and 4.9 showed transvinlylation activity. Obviously, the pKa of terephthalic acid limited the activity of Pd-catalyzed transvinlylation. Furthermore, metal-catalyzed transvinlylation was unsuccessful when isopropenyl acetate (3a) was employed instead of vinyl acetate (3c) even with benzoic acid as the substrate.

The equipment limitation also made the addition of acid to propyne (Scheme 7, route 3) difficult. The reaction vessel need to be purged with nitrogen and then refilled with calculated amount of propyne and heated above 150 °C for the reaction to proceed. This could not be done in our labs and therefore, the diisopropenyl terephthalate (9) was obtained only in low yield (20%) according to the ZnCl2 catalyzed procedure. Diisopropenyl terephthalate (9) was characterized by the data shown in Figure 2.
**Route 1**\(^1\)\(^8\)

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\[\text{Cl} \quad \text{Cl} \quad + \quad \text{OAc} \quad \xrightarrow{\Delta} \quad \text{OAc} \quad \xrightarrow{\text{H}^+} \quad \text{OAc} \quad \xrightarrow{\Delta} \quad \text{OAc} \]

<table>
<thead>
<tr>
<th>condition</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>cat. H(_2)SO(_4), 100 °C, 24 h</td>
<td>trace (&lt;10 mg)</td>
</tr>
<tr>
<td>cat. resin, 98 °C, 50 h</td>
<td>no desired product</td>
</tr>
</tbody>
</table>

**Route 2**\(^1\)\(^9\)

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\[\text{Cl} \quad \text{Cl} \quad + \quad \text{OAc} \quad \xrightarrow{\Delta} \quad \text{OAc} \quad \xrightarrow{\Delta} \quad \text{OAc} \]

<table>
<thead>
<tr>
<th>cat. condition</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>cat. H(_2)SO(_4), cat. Hg(OAc)(_2), 21.5 h</td>
<td>NR</td>
</tr>
<tr>
<td>* cat. (Py)(_2)Pd(OAc)(_2), 4 h</td>
<td>NR</td>
</tr>
<tr>
<td>* cat. p-TsOH, 10 h</td>
<td>NR</td>
</tr>
</tbody>
</table>

* Benzoic acid was employed instead of terephthalic acid.

**Route 3**\(^1\)\(^2\)\(^0\)

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

\[\text{Cl} \quad \text{Cl} \quad + \quad \text{OAc} \quad \xrightarrow{\Delta} \quad \text{OAc} \quad \xrightarrow{\Delta} \quad \text{OAc} \]

<table>
<thead>
<tr>
<th>cat. condition</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mol% PdCl(_2)(CH(_3)CN)(_2), 9 mol% NEt(_3), NMP</td>
<td>NR</td>
</tr>
<tr>
<td>* 1 mol% RuCl(_2)(PPh(_3))(p-cymene), toluene (or Ph(_2)O)</td>
<td>NR</td>
</tr>
<tr>
<td>2 mol% Ru(n5-COD)(_2), 4 mol% P(_2)Bu(_3), toluene</td>
<td>NR</td>
</tr>
<tr>
<td>* 0.9 mol% [Ru(p-cymene)Cl(_2)_2, toluene</td>
<td>NR</td>
</tr>
<tr>
<td>cat. ZnCl(_2), NMP</td>
<td>20% yield</td>
</tr>
</tbody>
</table>

* Benzoic acid was employed instead of terephthalic acid.

**Scheme 7. Attempted Synthetic Routes toward Diisopropenyl Terephthalate (9)**

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Cold-trap technique attempted to introduce calculated amount of propyne into the Parr reactor was unsuccessful. The starting material (either benzoic acid or terephthalic acid) was recovered in significant amount when the addition reaction was carried out with propyne in a Fischer-Porter bottle below 100 °C. Ru-catalyzed addition of acids to propyne also failed (Scheme 7, route 3).

1.9 ROUTES INVOLVING 1,3-HYDRIDE SHIFT TO DIVINYLTerephthalate

Next, we attempted 1,3-hydride shift approach for the synthesis of the enol ester 11.

![Diagram with 1,3-H shift reaction]
In general, 3-benzoyloxybutene (12) was obtained from the reaction of benzoyl chloride and corresponding alcohol. From a practical point of view, benzoic acid and corresponding halide were chosen as starting materials. The synthesis of 3-benzoyloxybutene (12) proceeded smoothly with very good yield (84%) as shown in eq 21; similarly, and di-1-methylallyl terephthalate was obtained with 84% yield when terephthalic acid was treated with DBU.

![Chemical structure of 3-benzoyloxybutene (12)](image)

<table>
<thead>
<tr>
<th>condition</th>
<th>isolated yield of 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBU, toluene, reflux, 19h</td>
<td>84%</td>
</tr>
<tr>
<td>DBU, toluene, 70 °C, 19h</td>
<td>77%</td>
</tr>
<tr>
<td>NaHCO₃, DMF, rt, 48h</td>
<td>5%</td>
</tr>
<tr>
<td>sat'd NaHCO₃, Adogen 464, CH₂Cl₂, rt, 21.5h</td>
<td>NR</td>
</tr>
</tbody>
</table>

Most successful examples of 1,3-hydride shift are reported for enol ether synthesis, and enol ester synthesis via 1,3-hydride shift is unknown. Therefore, 3-benzoyloxybutene (12) was chosen to examine the possibility of 1,3-hydride shift for the formation of enol ester 11, and the results are summarized in Table 4. Under most reaction conditions, the 1,3-hydride shift did not proceed to 2-benzoyloxybutene (Table 4, entries 1-9). The enol ester intermediate was too unstable to survive in the reaction medium and hydrolyzed to give benzoic acid (Table 4, entries 10, 11).
1,3-H shift  

**entry** | **condition** | **conversion**  
---|---|---  
1 | 2.5 mol% [Ir(COD)(Ph₂PMe)₂]⁺PF₆⁻, THF, rt, 5 days | NR  
2 | 2.5 mol% [Ir(COD)(Ph₂PMe)₂]⁺PF₆⁻, CH₂Cl₂, rt, 46h | NR  
3 | cat. 10% Pd-C (2.3 wt%), MeOH, reflux, 17h | NR  
4 | cat. 10% Pd-C (10 wt%), ⁵BuOH, reflux, 2 days | NR  
5 | 10 mol% ⁵BuOK, DMSO, rt, 2.5h | 10%  
6 | 10 mol% ⁵BuOK, DMSO, reflux, 65h | 10%  
7 | 5 mol% [Pd(allyl)Cl]₂, P(o-CH₃C₆H₄)₃, AgOTf, CH₂Cl₂, rt, 6 h | NR  
8 | 1.7 mol% [Ni(allyl)Br]₂, PPh₃, AgOTf, CH₂Cl₂, rt, 4h | NR  
9 | 1.4 mol% [Ni(allyl)Br]₂, PPh₃, AgOTf, CH₂Cl₂, -55 °C, 3.5h, 1 atm ethylene | NR  
10 | 1 mol% Rh(PPh₃)₃Cl, benzene/EtOH, reflux, 29 h | 100⁺  
11 | 1 mol% Rh(PPh₃)₃Cl, toluene, reflux, 4 h | 50⁺  

a. Benzoic acid was the product.  

**Table 4. Attempted 1,3-Hydride Shift of 3-Benzoyloxybutene (12) to Enol Ester**  

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Formation of stable metal allyl intermediate could also complicate this reaction when transition metals are used as catalysts. According to the procedure described in the literature, a mixture of 3-benzoyloxybutene (12) (1.07 mmol) and Rh(PPh$_3$)$_3$Cl (0.014 mmol) in benzene (1.5 mL) and ethanol (3.5 mL) was refluxed for 29 h. The mixture was poured onto ice water and extracted with ether. The ether layer was washed with saturated aqueous NH$_4$Cl solution, dried over MgSO$_4$, and concentrated to give quantitative yield of benzoic acid (Table 4, entry 10). Based on this result, ethanol and aqueous work-up was conjectured to promote hydrolysis of the intermediate of enol ester. Therefore, toluene was employed as the solvent to prevent the intermediate of enol ester from hydrolysis. A mixture of 3-benzoyloxybutene (12) (1.04 mmol) and Rh(PPh$_3$)$_3$Cl (0.014 mmol) in toluene (5 mL) was refluxed for 4 h. After removal of the solvent, white solid of benzoic acid was obtained and the liquid was assayed by GC. Only unreacted 3-benzoyloxybutene (12) was detected (Table 4, entry 11). Metal promoted elimination to give butadiene and benzoic acid could be the most reasonable route to this decomposition.

In summary, promising polymeric materials were observed in the yttrium-catalyzed reactions of divinyl esters and diols although further characterization of these products need to be undertaken (eq 16, 19), before this result can be exploited further.
CHAPTER 2

KINETIC RESOLUTION OF SECONDARY ALCOHOLS

2.1 INTRODUCTION

Optically pure alcohols are important chiral building blocks in modern organic synthesis. Several catalytic approaches that involve nonenzymatic methods for the synthesis of optically pure alcohols have been developed. Among them are: (i) enantioselective addition of nucleophiles to carbonyl compounds,1 (ii) asymmetric hydrogenation of ketones,2 and (iii) kinetic resolution of racemic alcohols by oxidative kinetic resolution,3 and acylative kinetic resolution4 (Scheme 8). The nonenzymatic kinetic resolution of racemic alcohols is considered to be a challenging problem, because the substrate geometry should have a perfect match with the catalyst for high enantioselectivity and such matching is difficult to engineer or predict. Recent breakthroughs in this area relate to the development of nucleophilic catalysis in asymmetric acylation leading to kinetic resolution of secondary alcohols.5-10

In general, the mechanism of nucleophilic catalysis in asymmetric acylation is suggested as the following: first the chiral nucleophile, containing a nitrogen (chiral amine9 13, chiral DMAP6,7 14, 15, 16) or a phosphorus atom (chiral phosphine5 17),
Enantioselective Addition to Carbonyl Compounds:¹

\[
\text{R}_2\text{Zn, cat. L}^* \quad \rightarrow \quad \text{O} \quad \begin{array}{c}
\text{R}^\prime \text{R}
\end{array} \quad \begin{array}{c}
\text{OH}
\end{array}
\]

Asymmetric Hydrogenation of Ketones:²

\[
\text{cat. Ru(II)L}^* \quad \text{hydrogen donor} \quad \rightarrow \quad \text{OH} \quad \begin{array}{c}
\text{R}^\prime \text{R}
\end{array} \quad \begin{array}{c}
\text{OH}
\end{array}
\]

Oxidative Kinetic Resolution:³

\[
\begin{array}{c}
\text{cat. Ru(II)L}^*
\end{array} \quad \begin{array}{c}
\text{O} \quad \text{R}^\prime \text{R}
\end{array} \quad \begin{array}{c}
\text{OH}
\end{array} \quad \begin{array}{c}
\text{OH}
\end{array}
\]

Acylative Kinetic Resolution:⁴

\[
\begin{array}{c}
\text{cat. chiral nucleophile}
\end{array} \quad \begin{array}{c}
\text{Ac}_2\text{O}
\end{array} \quad \begin{array}{c}
\text{R}^\prime \text{R}
\end{array} \quad \begin{array}{c}
\text{OAc}
\end{array} \quad \begin{array}{c}
\text{OH}
\end{array}
\]

Scheme 8. Catalytic Approaches to Optically Pure Alcohols

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acting as a catalyst reacts with acid anhydride to form a reactive chiral acylammonium/acyliminium ion. Resolution of racemic secondary alcohol is then achieved by reaction of the chiral acyliminium ion selectively with one of the enantiomers of the alcohol to form the ester. The other enantiomer which is either unreactive (or at least less reactive) during the acylation is then recovered at the end of the reaction. It is worth noticing that the asymmetric induction from the chiral catalyst is not a result of the direct interaction between the catalyst and alcohol, but between the reactive chiral acyliminium (N-acylpyridinium or P-acylphosphonium) ion and the alcohol. Therefore, acid anhydride or acid halide is the common acylating agent in the base-catalyzed acylation. In addition, asymmetric acylation using chiral reagents such as...
acylating agents 18, and 19 is an alternative strategy to kinetic resolution of racemic alcohol.\textsuperscript{11} From a practical standpoint, the drawback in this reagent selective acylation is the need for stoichiometric amounts of an enantiomerically pure reagent.

Even though nucleophilic catalysis has had great success in the kinetic resolution of secondary alcohols (for example, arylalkyl carbinols, arylalkynyl carbinols and allylic alcohols) via asymmetric acylation, resolution of cyclic alcohols remains a problem. There are few successful examples in cyclic alcohol resolution via an asymmetric acylation process (Figure 3). Examples include the use of asymmetric Lewis acid catalysis (SnX\textsubscript{2}-chiral diamine complex, 20),\textsuperscript{12} an "induced fit" process\textsuperscript{7} and a biomimetic approach using a designed peptide as the catalyst.\textsuperscript{10} Additionally, a novel kinetic resolution of cyclic alcohols through enantioselective S\textsubscript{N}2 displacement of hydroxyl groups by halogens in the presence of chiral BINAP (stoichiometric amount of phosphorus) and N-chlorosuccinimide (NCS) was recently reported (eq 22).\textsuperscript{13}

\[
\begin{align*}
\text{racemic} & \xrightarrow{(S)\text{-BINAP, NCS, THF}} \text{Cl} + \text{OH} \\
\end{align*}
\]

In contrast, Lewis acid-catalyzed asymmetric acylation has drawn much less attention. Therein, lies a reactivity-selectivity dilemma since Lewis acidity (or oxophilicity) of the catalyst has to be well-balanced to accommodate the competing demands of the starting materials and of the products, both of which are Lewis bases.
As mentioned earlier, some progress has been made in the resolution of cyclic alcohols by methods based on Lewis acid catalysis; however, the need for higher amounts (up to 30 mol%) of chiral source for optimum reactions make these approaches less attractive. Following our preliminary studies of yttrium-catalyzed transesterification reaction between alcohols and enol esters, we became interested in kinetic resolution of secondary alcohols. Therefore our goal was set at the development of chiral yttrium complexes and other related stereochemically well-defined chiral Lewis acids for the asymmetric acyl transfer reactions of enol esters. We hoped that the chiral environment around the metal might provide enough diastereoselectivity in the acylation reaction to achieve the goal of alcohol resolution. In scouting of other stereochemically well-defined chiral Lewis acids for asymmetric acyl transfer reactions of enol acetates, we are looking for a metal-catalyzed asymmetric acylation process that operates through a coordinated acyl transfer reagent (Scheme 9, plan 1).
Scheme 9. Lewis Acid Catalysis in Acylative Kinetic Resolution of Secondary Alcohols via Different Activation of Reactants

The rapid exchange of free alcohols with alkoxides in the cluster of $Y_5(O^{'Pr})_3O$ is known and an yttrium-catalyzed acyl transfer reaction of an enol ester has been proposed (see chapter 1, section 1.6, scheme 6) as a viable reaction. We also hoped that the chiral environment around the metal might exert asymmetric induction on the incoming alcohol.
to achieve the goal of alcohol resolution (Scheme 9, plan 2). To our best knowledge, such a process would result in the first example of a metal-catalyzed asymmetric acylation through a metal alkoxide intermediate.

2.2 SCREENING OF CHIRAL LEWIS ACID COMPLEXES: Sn(II) and Cu(II) COMPLEXES

In screening Lewis acids as catalysts, we were encouraged by Procopiou's work, which showed trimethylsilyl trifluoromethanesulfonate (TMSOTf) was an extremely powerful acylation catalyst. Presumably, the reaction involves a pentacoordinate silicon species in step iii (Scheme 10).

\[
\begin{align*}
R'\text{OH} + (R^2\text{CO})_2\text{O} & \xrightarrow{\text{cat. TMSOTf}} R^2\text{COOR}' \\
R'\text{OH} + \text{TMSOTf} & \xrightarrow{i} R'\text{OTMS} + \text{TIOH} \\
(R^2\text{CO})_2\text{O} + \text{TIOH} & \xrightarrow{ii} R^2\text{COOTf} + R^2\text{CO}_2\text{H} \\
\text{TMSOTf} + R^2\text{COOTf} & \xrightarrow{iii} R^2\text{COOR}' + \text{TMSOTf}
\end{align*}
\]

Scheme 10. Mechanism of TMSOTf Catalyzed Acylation of Alcohols
If a chiral metal complex acting as the pentacoordinate silicon species in Procopiou's system selectively activates alcohols (and probably also Lewis acidic enough to coordinate to enol acetates), the goal of alcohol resolution can be achieved.

C₂-symmetric bis(oxazoline) (box) and bis(oxazoliny)pyridine (pybox)–Cu(II)\textsuperscript{15} and Sn(II) complexes have been well studied by Evans.\textsuperscript{15,16} According to Evans' studies, [Sn((S,S)-Ph-pybox)](OTf)\textsubscript{2} (21) has an octahedral geometry in the solid state. In solution both [Sn–(Ph-pybox)\textsubscript{2}]\textsuperscript{2+} and [Sn(Ph-pybox)](OTf)(\textsuperscript{1+}) and triflate ion are in equilibrium.\textsuperscript{16} This clearly indicates a kinetic lability of bisoxazoline derived Sn(II) complexes toward ligand substitution. In addition, it was also reported that Sn(OTf)\textsubscript{2} promoted carboxylic ester formation through mixed anhydrides.\textsuperscript{17} Therefore, Sn(II) and Cu(II) complexes of bisoxazoline 22, 23, pybox 24 were screened in asymmetric acyl
transfer reaction of enol acetates. The preparation of chiral bisoxazoline ligands 22, 23 are shown in Scheme 11. Tin(II)-catalyzed acylation results are summarized in Table 5 and, Cu-catalyzed acylations, in Table 6. As can be seen from Table 5, the acylation reaction was completely shut off in the presence of free hydroxyl groups on the ligand 22 (Table 5, entry 1, 3). Surprisingly, the acyl transfer reaction of enol acetates did not proceed in the presence of [Sn((S,S)-Pr-pybox)][OTf]2 (Table 5, entries 2, 4). The acylation catalyzed by Sn(OTf)2 with TBS-protected ligand 23 was sluggish and ether was observed as side-product; additionally, no enantioselectivity (0% ee) was obtained (Table 5, entry 5).

Scheme 11. Preparation of Chiral Bisoxazoline Ligands 22, 23

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Higher catalytic efficiency was observed in Cu(OTf)₂ than Sn(OTf)₂ (Table 5, entry 5 vs Table 6, entry 3); moreover, 100% conversion was observed in 36 h with 0.0005 equiv of the catalyst although undesired ether was found in significant amounts (Table 6, entry 8, S/C = 2000). Similar reactivity as Cu(OTf)₂ was observed in Cu(SbF₆)₂; however, CuCl₂ did not show any catalytic activity (Table 6, entry 9). In the presence of oxygenated solvent (THF) or ligand 22, the acylation reaction was completely shut off (Table 6, entries 1, 2, 4, 2 vs 3, 3 vs, 4). It appears that Lewis acidity of the catalyst is essential for the acyl transfer reaction of enol acetates.

\[
\text{PhOH} + \overset{\text{CH}_2\text{Cl}_2, \text{rt}}{\text{CH}_3\text{Ac}} \rightarrow \text{PhO} = \overset{\text{PhMe}}{\text{Me}} + \text{PhO} = \overset{\text{MeMePh}}{\text{Ph}}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>mol% Sn(OTf)₂</th>
<th>mol% (chiral ligand)</th>
<th>time</th>
<th>conversion (%)</th>
<th>%ee²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ᵇ</td>
<td>2.5</td>
<td>2.7 (22)</td>
<td>72 h</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>2ᵇ</td>
<td>2.5</td>
<td>3.2 (24)</td>
<td>72 h</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>3ᶜ</td>
<td>10</td>
<td>11 (22)</td>
<td>50 h</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>4ᶜ</td>
<td>10</td>
<td>11 (24)</td>
<td>50 h</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>5ᵈ</td>
<td>5</td>
<td>5.7 (23)</td>
<td>71.5 h</td>
<td>43.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

a. %ee (HPLC) of recovered alcohol.
b. The reactions were carried out with α-methylbenzyl alcohol (1 mmol) and isopropenyl acetate (1.2 mmol) in CH₂Cl₂ (1.7 mL) at room temperature.
c. The reactions were carried out with α-methylbenzyl alcohol (1 mmol) and isopropenyl acetate (1.27 mmol) in CH₂Cl₂ (1 mL) at room temperature.
d. The reaction was carried out with α-methylbenzyl alcohol (1 mmol) and isopropenyl acetate (1.27 mmol) in CH₂Cl₂ (1.45 mL) at room temperature.

Table 5. Transesterifications Catalyzed by Chiral Sn(OTf)₂

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The reactions were carried out with α-methylbenzyl alcohol (1 mmol) and isopropenyl acetate (1.27 mmol) in entries 1-5 and 9-11.

The reaction was carried out with α-methylbenzyl alcohol (10 mmol) and isopropenyl acetate (12.7 mmol) in entry 6.

The reactions were carried out with α-methylbenzyl alcohol (20 mmol) and isopropenyl acetate (22.7 mmol) in entries 7 and 8.

a. %ee (HPLC) of recovered alcohol.

b. Cu(SbF₅)₂ (1 mol%) was prepared by mixing CuCl₂ (1 mol%) and AgSbF₆ (2 mol%).

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol%)</th>
<th>solvent (mL)</th>
<th>time (h)</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>CuCl₂ (5)</td>
<td>CH₂Cl₂ (1.5)</td>
<td>68</td>
<td>NR</td>
</tr>
<tr>
<td>10</td>
<td>Cu(SbF₅)₂ (1)</td>
<td>CH₂Cl₂ (1)</td>
<td>40 min</td>
<td>100 (54% ester)</td>
</tr>
<tr>
<td>11</td>
<td>AgSbF₆ (1)</td>
<td>CH₂Cl₂ (1)</td>
<td>48</td>
<td>38 (12% ester)</td>
</tr>
</tbody>
</table>

Table 6. Transesterifications Catalyzed by Cu Complexes
A possible pathway for the formation of ether side-product in Sn and Cu-catalyzed acylations is proposed in Scheme 12. As can be seen from Scheme 12, the ether formation can be attributed to the strong oxophilicity of the metal. In the Sn and Cu-catalyzed acylations the reactivity-selectivity dilemma in Lewis acid catalysis is observed. As mentioned, the Sn and Cu-catalyzed acylation was completely shut off in the presence of strong donors such as THF or using ligands containing free hydroxyl groups. On the other hand, chiral Sn and Cu-catalyzed acylation did not provide any enantioselectivity but ether formation competed with transesterification due to strong oxophilicity of the metal (Table 5, entry 5; Table 6, entry 6). The Cu(II) complex has a tetrahedral geometry where two labile OTf groups are sitting next to each other (cis); however, [Sn((S,S)-Pr-pybox)][OTf]2 has an octahedral geometry where two labile OTf groups are not adjacent.
groups are far away from each other at axial positions (trans). Therefore, it reminds us that two possible reaction sites on the metal should be close to each other in a viable catalyst.

2.2.1 ATOM-ECONOMIC ALDOL REACTIONS CATALYZED BY Cu(OTf)$_2$

One of the side-reactions is an aldol reaction of enol esters with benzaldehyde catalyzed by Cu(OTf)$_2$ (eq 23-25).$^{19}$

\[
\begin{align*}
\text{PhCHO} + \underset{\text{Me}}{\text{CH}_3\text{CHOAc}} &\rightarrow \underset{\text{Me}}{\text{CH}_3\text{CHOAc}} \quad 5 \text{ mol}\% \text{ Cu(OTf)}_2 \quad \text{CH}_2\text{Cl}_2, \text{rt, 2.5 h} \\
&\rightarrow \underset{\text{Ph}}{\text{Me}} \quad 25, 63\% \text{ isolated yield} \\
\end{align*}
\]

\[
\begin{align*}
\text{PhCHO} + \underset{\text{Ph}}{\text{CH}_2\text{CHOAc}} &\rightarrow \underset{\text{Ph}}{\text{Me}} \quad 5 \text{ mol}\% \text{ Cu(OTf)}_2 \quad \text{benzene, rt, 2.5 h} \\
&\rightarrow \underset{\text{Ph}}{\text{Me}} \quad 25, 44\% \text{ isolated yield} \\
\end{align*}
\]

\[
\begin{align*}
\text{PhCHO} + \underset{\text{H}_3\text{C}}{\text{H}_3\text{COAc}} \underset{\text{Ph}}{\text{Ph}} &\rightarrow \underset{\text{Ph}}{\text{Me}} \quad 1.3 \text{ mol}\% \text{ Cu(OTf)}_2 \quad \text{CH}_2\text{Cl}_2, \text{rt, 2 h} \\
&\rightarrow \underset{\text{Ph}}{\text{Me}} \quad 42\% \text{ isolated yield} \\
\end{align*}
\]

\[
\begin{align*}
\text{PhCHO} + \underset{\text{Me}}{\text{Me}} &\rightarrow \underset{\text{Ph}}{\text{Me}} \quad 5 \text{ mol}\% \text{ Cu(OTf)}_2 \quad \text{CH}_2\text{Cl}_2, \text{rt, 2 h} \\
&\rightarrow \underset{\text{Ph}}{\text{Me}} \quad 25.5\% \text{ isolated yield} \\
\end{align*}
\]

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Scheme 13. Different Approaches\textsuperscript{21} to the Synthesis of 25 and 27
Meanwhile, it has been reported that the crossed aldol reaction of enol acetates with aldehydes can be carried out by using a catalytic amount of cationic species paired with tetrakis(pentafluorophenyl) borate.\textsuperscript{20} Other related approaches to the syntheses of 25 and 27 are shown in Scheme 13.\textsuperscript{21} As can be seen from scheme 13, enol acetate reacted with benzaldehyde to afford aldol-type products as a mixture in the presence of stoichiometric amount of Lewis acid according to Mukaiyama's method.\textsuperscript{21a} In the presence of catalytic amounts of quaternary ammonium chloride, 4-oxo-1,3-dioxin 27 was obtained with 92% yield on toluene refluxing.\textsuperscript{21c} It is worth noticing that chiral cyclic acetal 28 can be a useful starting material in the synthesis of β-hydroxy carboxylic acid (eq 26).\textsuperscript{22}

\[
\begin{align*}
\text{Ph} & \quad \text{cat. CuCl} \\
\text{Me} & \quad \text{Grignard} \\
\text{28} & \quad \text{MgX} \\
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{R}_1 & \quad \text{Me} \\
\end{align*}
\]

Moreover, chiral bisoxazoline-Cu(II) catalyzed enantioselective aldol addition is well established.\textsuperscript{15b} Since our primary goal was acyl transfer to alcohols, these interesting and potentially useful aldol strategies (eq 23-25) were not further pursued. These may become the focus of future investigations.
2.3 SCREENING OF CHIRAL LEWIS ACIDS DERIVED FROM Ti, Mn, Cr, Al, Eu AND Y COMPLEXES

Typical Lewis acid-catalyzed acylation reactions were conducted with alcohol (1 mmol) and isopropenyl acetate (1.27 mmol) in an appropriate solvent (1.5 mL). Conversions were determined by GC and enantiomeric excess of unreacted alcohol was determined by HPLC (Daicel CHIRACEL OD column).

2.3.1 CHIRAL TITANIUM COMPLEX-CATALYZED ACYLATIONS

Chiral titanium alkoxide complexes with O'Pr as labile groups are also of interest to examine the activity in asymmetric acylation. In general, chiral titanium alkoxide complexes were prepared by mixing equimolar amounts of Ti(O'Pr)₄ and tridentate/tetradentate chiral ligands and then these complexes were directly used for acylation. Chiral ligands 30-33 were generously provided by Yong Gao. Titanium alkoxides with a variety of chiral ligands 22, 23, 29, 30, 31, 32, 33 were used in asymmetric acylation and the results are summarized in Table 7.
Toluene is superior to dichloromethane as the solvent (Table 7, entry 1 vs 2). Titanium alkoxide with tetradeutate ligands such as 22, 29, and 30 did not show any catalytic activity (Table 7, entries 3, 4, 5, 13), although excess Ti(O'Pr)₄ was present in the reaction medium (Table 7, entry 3 vs 4). The catalytic ability of Ti(O'Pr)₄ was dramatically decreased in the presence of various chiral ligands (Table 7, entry 2 vs 3, 4, 5, 6; entry 8 vs 9, 10, 11, 12, 13). In other words, ligand decelerated catalysis was observed in Ti-catalyzed acyl transfer reaction of enol acetate or these donor ligands rendered the metal center less electron-deficient and thus discouraging alcohol exchange; therefore, more catalyst loading was required to achieve reasonable conversion (entries 10 vs 15; 11 vs 16; 12 vs 14; 18 vs 20; 19 vs 21). As can be seen, no significant enantioselectivity was obtained, with 10.5%ee being the best result (Table 7, entry 9).
<table>
<thead>
<tr>
<th>alcohol</th>
<th>entry</th>
<th>mol% Ti(ΟPr)$_4$</th>
<th>mol% (chiral ligand)</th>
<th>time</th>
<th>conversion (%)</th>
<th>%ee$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-OH</td>
<td>1$^b$</td>
<td>2</td>
<td>none</td>
<td>26.5 h</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
<td>none</td>
<td>21 h</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
<td>1 (22)</td>
<td>26.5 h</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2</td>
<td>2 (22)</td>
<td>27 h</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2</td>
<td>2 (29)</td>
<td>42 h</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2</td>
<td>2 (23)</td>
<td>49 h</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>2.5</td>
<td>2.5 (23)</td>
<td>38 h</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>2.5</td>
<td>none</td>
<td>27.5 h</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>2.6</td>
<td>2.6 (23)</td>
<td>26 h 20 min</td>
<td>45</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2.5</td>
<td>2.5 (32)</td>
<td>61 h</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>2.5</td>
<td>2.5 (31)</td>
<td>60 h</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>2.5</td>
<td>2.5 (33)</td>
<td>50.5 h</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>2.5</td>
<td>2.5 (30)</td>
<td>50.5 h</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>10</td>
<td>10 (33)</td>
<td>8.5 h</td>
<td>49</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>10</td>
<td>10 (32)</td>
<td>7 h 35 min</td>
<td>43</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>10</td>
<td>10 (31)</td>
<td>7 h 25 min</td>
<td>46</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>2.5</td>
<td>2.5 (23)</td>
<td>24 h</td>
<td>40</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>2.5</td>
<td>2.6 (32)</td>
<td>38 h</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>2.5</td>
<td>2.6 (31)</td>
<td>38.5 h</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>10</td>
<td>10 (32)</td>
<td>11 h</td>
<td>49</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>21</td>
<td>10</td>
<td>10 (31)</td>
<td>11 h</td>
<td>59</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>10</td>
<td>10 (33)</td>
<td>25 h</td>
<td>49</td>
<td>4</td>
</tr>
</tbody>
</table>

The reactions were carried out with alcohol (1 mmol), isopropenyl acetate (1.27 mmol) in toluene (1.5 mL) at room temperature.

$a$. %ee (HPLC) of recovered alcohol. $b$. CH$_2$Cl$_2$ was employed as solvent.

Table 7. Transesterifications Catalyzed by Ti Complexes

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The chiral Schiff base-titanium alkoxide complexes were prepared according to the procedure described in the literature, and detailed information on the catalyst structure has been discussed therein. Based on Oguni’s study, the dominant species in an equimolar mixture of tridentate ligand and Ti(O^Pr)_4 is shown in eq 27.

$$\text{Ti(O^Pr)_4} + \text{H}_2\text{N}^\text{OH} \rightarrow \text{H}_2\text{N}^\text{OH} + 2\text{PrOH} \quad (27)$$

As can be imagined, there will be no coordination site available for enol acetates when tetradentate ligands 22, 29, 30 are employed instead of tridentate ligands 31-33; as a result, tetradentate ligands turn off the acylation. As can be seen from the Table, complexes of 31-33 are reasonable catalysts. In the system of Ti(O^Pr)_4 with tetradentate ligands 22, 29, 30, the two labile O^Pr groups are at axial positions (trans) of the Ti complex with octahedral geometry. As discussed in the system of [(pybox)Sn(OTf)_2], the two possible reaction sites might be too far away to react with each other.
2.3.2 CHIRAL CHROMIUM AND MANGANESE COMPLEX-CATALYZED ACYLATIONS

In the scouting of suitable Lewis acids for kinetic resolution of secondary alcohols, Jacobsen's chiral Mn- and Cr-salen complexes 34,24a 3524b were found without reactivity (Table 8, entries 1, 2). The coordination mode of salen to Cr and Mn is square planar and it is impossible for acyl transfer reaction of enol acetate to proceed at anti orientation if the reaction of alcohol and enol acetate has to go through a unimetallic activation. Note that the acylation should be observed if bimetallic activation involves Cr-catalyzed acylation of alcohols with enol acetates. It is known that epoxide opening with TMSN₃ catalyzed by [(salen)Cr(Cl)] (35) goes through bimetallic activation.²⁴c Besides, a similar observation was made in Ti-salen and Sn(Pr-pybox) complexes. Based on these results and our previous experience with various Y complexes, metal-catalyzed acyl transfer reactions of enol esters most likely go through unimetallic activation, where the two reaction sites are proximal on the catalyst to facilitate the reaction (via the formation of the tetrahedral intermediate).
The reactions were carried out with α-methylbenzyl alcohol (1 mmol) and isopropenyl acetate (1.27 mmol) in toluene (1.5 mL) at room temperature.

a. %ee (HPLC) of recovered alcohol.

b. The reaction was carried out with α-methylbenzyl alcohol (1 mmol) and isopropenyl acetate (1 mL) at room temperature.

c. The reaction was carried out with α-methylbenzyl alcohol (1 mmol) and vinyl acetate (1 mL) at room temperature.

d. Benzene was employed as solvent.

e. Exact structure of 39 is not clear, but calculated mol% is based on the suggested structure as shown in eq 30. 39 (16 mg) was employed in entry 6. 39 (31.6 mg) was employed in entry 7.

Table 8. Chiral Lewis Acid-Catalyzed Acyl Transfer Reactions

<table>
<thead>
<tr>
<th>entry</th>
<th>cat. (mol%)</th>
<th>time (h)</th>
<th>conversion (%)</th>
<th>%ee(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34, Mn (2)</td>
<td>30</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>35, Cr (2)</td>
<td>48</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>36, Al (2)</td>
<td>48</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>37, Eu (1)</td>
<td>47.5</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>37, Eu (1)</td>
<td>70.5</td>
<td>42</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>39, Y (2)(^a)</td>
<td>6</td>
<td>47</td>
<td>1.7</td>
</tr>
<tr>
<td>7</td>
<td>39, Y (4)(^a)</td>
<td>3</td>
<td>56</td>
<td>2.7</td>
</tr>
</tbody>
</table>

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2.3.3 CHIRAL ALUMINUM COMPLEX-CATALYZED ACYLATIONS

Next, we turned our attention to Al complexes such as \((R)-\text{SALBinaphAlOCH}_3\) (36) (Table 8, entry 3). Complex 36 was prepared according to the procedure described in the literature.\(^{25a}\) The maximum coordination number of aluminum is five. In Al-Schiff base complex 36 with saturated coordination, methoxy group will presumably be replaced by alcohol; however, no more Lewis acid site is available for incoming enol acetate. Possibly, because of that no transesterification reaction was observed by using Al-Schiff base complex as a catalyst. However, Al-Schiff base complex such as \((R)-\text{SALBinaphAlOCH}_3\) (36) and \((R)-\text{SALBinaphAlOPr}\) were reported in the polymerization of lactide (eq 28).\(^{25a-c}\) In a plausible mechanism of lactide polymerization catalyzed by Al complex 36, it was suggested that the initiation reaction occurs by insertion to a molecule of lactide in the Al-OCH\(_3\) bond via acyl-oxygen bond cleavage with retention of configuration.\(^{25a}\)

\[
\begin{align*}
\text{ROH} + \text{Lactide} & \xrightarrow{\text{Ln}^+\text{Al-OCH}_3} \text{Lactide}_{n}\text{OCH}_3 \\
\text{ROH} + \text{Lactide} & \xrightarrow{\text{Ln}^+\text{Al-OCH}_3} \text{Lactide}_{n}\text{OCH}_3 + \text{Ln}^+\text{Al-}\text{Lactide}
\end{align*}
\]
Based on this proposed mechanism, we could make the following assumption regarding acyl transfer reaction catalyzed by L₄Al-OMe; insertion of a molecule of isopropenyl acetate in the Al-OMe bond via acyl-oxygen bond would produce Al-enolate species. This is highly unlikely in the presence of excess alcohol. Therefore, the acylation failed in the single site activation of alcohol or enol acetate. In conclusion, bifunctional complex with proximal reactive sites on the metal simultaneously enhancing both reactivity of alcohol and enol acetate should be the catalyst of choice.

2.3.4 CHIRAL EUROPIUM AND YTTRIUM COMPLEX-CATALYZED ACYLATIONS

Based on our preliminary study, [Y(thd)₂(O'Pr)] (2) was found to be an efficient catalyst to give clean a reaction (Table 1, entry 2, 4; page 7). Therefore, a chiral 1,3-dicarbonyl compound was the first choice of ligand to explore the yttrium-catalyzed asymmetric acylation. Readily available chiral shift reagent such as Eu(dcm)₃ (37) with chiral 1,3-dicarbonyl motif was treated with cold dilute sulfuric acid to wash out the metal and to give enantiomerically pure ligand 38 without tedious synthesis (eq 29). In addition, Eu(dcm)₃ (37) was also examined for the reaction (Table 8, entries 4, 5), and no reaction was observed in solvent-free reaction with isopropenyl acetate. Chiral yttrium complex 39 was prepared according to the modified procedure of [Y(thd)₂(O'Pr)] (2) synthesis. A putative structure for 39 was suggested for the resulting complex (eq 30).

55
$^1$H NMR inter alia δ 0.63 (s, 6 H, Me), 0.85 (d, $J = 6.6$ Hz, 6 H, Me), 1.03 (s, 6 H, Me), 1.17 (s, 6 H, Me), 5.68 (s, 1 H, C=CH), 11.44 (s, 1 H, C=C-OH).

$^{13}$C NMR δ 14.5 (q), 18.8 (q), 22.0 (q), 22.3 (q), 28.7 (t), 31.6 (t), 41.7 (d), 45.8 (s), 56.3 (s), 95.9 (d), 199.3 (s).

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The chiral yttrium complex 39 is a reactive catalyst in transesterification (Table 8, entries 6, 7). For example, the acylation of \(\alpha\)-methylbenzyl alcohol (1 mmol) with isopropenyl acetate (1.27 mmol) was catalyzed by 39 (2 mol%) in benzene (1.5 mL) at ambient temperature in 6 h to give the corresponding acetate in 47% conversion. However, the asymmetric induction was poor.

2.4 DEVELOPMENT OF CHIRAL YTTRIUM COMPLEXES

In making every endeavor to develop Lewis acid catalyzed kinetic resolution of secondary alcohols, yttrium was thus found to be superior to other metals (Sn, Cu, Ti, Mn, Cr, Al, Eu). Note that in the first place yttrium alkoxides were selected from 15 different metal oxides to be the catalyst of choice (Chapter 1, Section 1.2 and page 5). We decided to develop an enantiospecific version of this reaction taking into account the low oxophilicity and high Lewis acidity of yttrium.

Based on our preliminary study, phenol was not acylated under catalysis by \(\text{Y}_2(\text{O}^3\text{Pr})_3\text{O}(1)\) (eq 5, page 13). Consequently, salen-type ligands (29, 30 structures shown in page 49) were chosen to examine the asymmetric induction using \(\text{Y}_2(\text{O}^3\text{Pr})_3\text{O}(1)\) as the source of yttrium. As can be seen from Table 9, strong ligand assisted catalysis was observed in yttrium-catalyzed acylation; that is, the catalytic ability of \(\text{Y}_2(\text{O}^3\text{Pr})_3\text{O}(1)\) was significantly enhanced in the presence of salen ligand 29 (entry 8, 9 vs 10). Moreover, no acylation was observed without \(\text{Y}_2(\text{O}^3\text{Pr})_3\text{O}(1)\) which clearly indicated the acylation has to go through yttrium activation (Table 9, entry 7 vs 1). The acylation of \(\alpha\)-
methylbenzyl alcohol (1 mmol) with isopropenyl acetate (1.27 mmol) in the presence of salen ligand 29 (5 mol%) for 22 h at room temperature did not proceed (Table 9, entry 7). Under the same condition, the acylation catalyzed by in-situ prepared salen-yttrium complex—Y$_5$(OPr)$_{13}$O (1) (1 mol%) and salen ligand 29 (5 mol%)—gave quantitative yield of the corresponding acetate in 65 min (Table 9, entry 1).

<table>
<thead>
<tr>
<th>alcohol</th>
<th>entry</th>
<th>mol% (catalyst$^a$)</th>
<th>temp (°C)</th>
<th>time</th>
<th>conversion (%)</th>
<th>%ee$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH</td>
<td>1</td>
<td>1 (1) + 5 (29)</td>
<td>22</td>
<td>1 h 5 min</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (1) + 5 (30)</td>
<td>-5</td>
<td>17 h</td>
<td>28</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 (1) + 5 (29)</td>
<td>-20</td>
<td>13 h</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 (1) + 5 (29)</td>
<td>-38</td>
<td>6.5 h</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1 (1) + 5 (29)</td>
<td>-45</td>
<td>9 h</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1 (1) + 5 (29)</td>
<td>-47</td>
<td>23 h</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>5 (29)</td>
<td>22</td>
<td>22 h</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>HOC$_8$H$_7$OH</td>
<td>8</td>
<td>1 (1)</td>
<td>22</td>
<td>5 h</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>1 (1)</td>
<td>22</td>
<td>24.5 h</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1 (1) + 5 (29)</td>
<td>22</td>
<td>0.5 h</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>1 (1) + 5 (29)</td>
<td>-40</td>
<td>11 h</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1 (1) + 5 (29)</td>
<td>-45</td>
<td>42 h</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

The reactions were carried out with alcohol (1 mmol) and isopropenyl acetate (1.27 mmol).
a. The catalyst for entry 1-6, 10-12 was prepared by the following procedure:
The mixture of Y$_5$(OPr)$_{13}$O (1 (0.01 mmol) and salen-type ligand 29, or 30 (0.05 mmol) in toluene (0.7 mL) was heated to reflux for 10 min, cooled to room temperature and concentrated to dryness to get yellow solids to be directly used for transacylation.
b. %ee (HPLC) of recovered alcohol.

Table 9. Transesterifications Catalyzed by Salen-Y$_5$(OPr)$_{13}$O

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The "in-situ prepared" salen-yttrium complex was made according to the procedure described below: The mixture of \( Y_2(O'Pr)_{13}O \) (1) (0.01 mmol) and salen ligand 29 or 30 (0.05 mmol) in toluene (0.7 mL) was heated to reflux for 10 min, cooled to room temperature and concentrated to dryness to get yellow solids to be directly used for transacylation. Electron-rich donor ligand 29 is expected to render the yttrium center less electron-deficient thus facilitating alcohol exchange (Table 9, entry 2 vs 3, 4).

\[
s^{27} = k_{rel} = \frac{k_{\text{fast}}}{k_{\text{slow}}} = \frac{\ln [(1-c/100)(1-\text{ee}/100)]}{\ln [(1-c/100)(1+\text{ee}/100)]}
\]

c: conversion

ee: enantiomeric excess of the recovered substrate

Compared to titanium isopropoxide Ti(O'Pr)_4 (Table 7, entry 9, \( k_{rel}^{27} = 1.42 \)), yttrium isopropoxide \( Y_2(O'Pr)_{13}O \) (1) is a cluster compound (Figure 1, page 6) which presents 2.6 (13/5) possible active alkoxide group available for alcohol exchange (Table 9, entry 4, \( k_{rel} = 1.78 \); entry 5, \( k_{rel} = 1.76 \); entry 6, \( k_{rel} = 1.57 \)). Herein, the first example of metal-alkoxide complex-catalyzed acylation of alcohols with low enantioselectivity (\( k_{rel} = 1.4-1.8 \)) was first observed. Selectivity factor—\( s \) or \( k_{rel} \)—is calculated based on Kagan's equation shown above which indicates different reactivity of the two enantiomers in a kinetic resolution.
2.4.1 MONONUCLEAR SALEN-YTTRIUM COMPLEXES

In conclusion, two findings that hold promise for Y-salen complexes as catalysts for kinetic resolution of secondary alcohols are the following: (a) no acylation of phenol under yttrium-catalyzed reaction condition, and (b) ligand-assisted catalysis. However, any structural insight into the active yttrium complex in the in-situ preparation from $Y_3(O^tPr)_{13}O$ (1) and salen ligands would be incomplete. Therefore, the development of stereochemically well-defined Y-salen complex was our next goal. Novel chiral Y-salen complex 41 was prepared according to Anwander's silylamide route (Scheme 14). A detailed discussion about this unique structure and further applications are differed until chapter 3.

\[
\text{[YCtjTHF]}_x + \text{LiN(dms)}_2 \rightarrow \text{[Y(N(dms)}_2)_3 \text{2THF]}_4 \quad \text{40}
\]

\[
\text{[Y(N(dms)}_2)_3 \text{2THF]}_4 + \text{Salen ligand 29} \rightarrow \text{41}
\]

Scheme 14. Synthesis of Chiral Salen-Yttrium Complex 41
In general, salen-yttrium complexes are formulated as \([(L)Y(N(SiHMe_2)_2)THF]\) where \(L\) stands for a chiral ligand. Dimethylsilylamide–\(N(SiHMe_2)_2\)–was chosen instead of trimethylsilylamide–\(N(SiMe_3)_2\)–because dimethylsilylamide is less sterically bulky and is more readily replaced by the incoming alcohol. The structure of Y-salen complex 41 recrystallized from pentane was confirmed by X-ray analysis (Figure 4). This stereochemically well-defined yttrium complex 41 also provides insight into the mechanism of the reaction (see chapter 3).

Figure 4. Structure of Y-Salen Complex \([(29)Y(N(SiHMe_2)_2)THF]\) (41)

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The reactions were carried out with alcohol (1 mmol) and isopropenyl acetate (1.27 mmol) in toluene (1.5 mL).

α-methylnaphthalene methanol was employed in entry 1-3.

α-tetralol was employed in entry 4-6.

Table 10. Reactivity of Different Y Complexes
Table 10 shows different reactivities among $Y_2(O^tPr)_{12}O$ (1), in-situ (from $Y_2(O^tPr)_{12}O$ (1) and salen ligands) prepared Y-salen complex and mononuclear Y-salen complex $[(29)Y(N(SiHMe_2)_2)THF]$ (41). Again, ligand-assisted catalysis was observed (Table 10, entry 2, 3 vs 1; entry 5, 6 vs 4). The Y-salen complex 41 was found to be a superb catalyst for transesterification reactions, enabling reactions to be conducted at low temperatures.

2.4.2 OTHER YTTRIUM COMPLEXES

In addition, other Y-complexes such as $[((S,S)-salen)Y(\mu-Cl)THF]_2$ (42) with a different coordination mode was also examined. This complex was prepared according the procedure described in the literature (eq 31). Figure 5 shows the structure of achiral $[(salen)Y(\mu-Cl)THF]_2$ determined by Evans. The salen ligand with ethylenediamine tether is used for this preparation. The chloro-bridged yttrium dimer complex 42 was speculated to form a new type of yttrium complex by cleaving the chloro-bridged dimer with the addition of silver salt (AgOTf), and following phosphine addition. Therefore, we speculated that the new yttrium complexes with phosphine should be good candidates for alcohol resolution. Unfortunately, transesterification did not proceed in the presence of $[((S,S)-salen)Y(\mu-Cl)THF]_2$ (42) with or without additives (AgOTf, phosphines such as $^6$Bu$_3$P or PPh$_3$ and AgOTf/PPh$_3$) (Table 11, entry 1-5).
Figure 5. Structure of Achiral [(salen)Y(μ-Cl)THF]2 Determined by Evans et al.

\[ \text{[(salen)Y(μ-Cl)THF]}_2 \]

Equation (31): 

\[ (S,S)-\text{Salen} \rightarrow [(S,S)-\text{Salen})Y(μ-Cl)THF]_2 \]
Interestingly, the reactivity was slightly increased when different silver salt such as AgOAc was employed (Table 11, entry 6). It seemed that counter ion (OTf vs OAc) has an effect on the reactivity of the corresponding yttrium complex.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol%)</th>
<th>time</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42 (1)</td>
<td>31 h</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>42 (1) + AgOTf (2)</td>
<td>10 days</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>42 (1) + PPh₃ (2)</td>
<td>95 h</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>42 (1) + PPh₃ (2) + AgOTf (2)</td>
<td>79 h</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>42 (1) + nBu₅P (2)</td>
<td>32 h</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>42 (1) + AgOAc (2)</td>
<td>35.5 h</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>HN(SiHMe₂)₂ (11)</td>
<td>16.7 h</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>40 (1)</td>
<td>2.5 h</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>43 (1)</td>
<td>1.2 h</td>
<td>100</td>
</tr>
<tr>
<td>10ᵃ</td>
<td>43 (1)</td>
<td>12 h</td>
<td>53 (0)b</td>
</tr>
</tbody>
</table>

The reactions were carried out with α-methyflbenzyl alcohol (1 mmol) and isopropenyl acetate (1.27 mmol) in toluene (1.5 mL) at room temperature (entry 1-9).

a. The reaction was carried out with 1-indanol (1 mmol) and isopropenyl acetate (1.27 mmol) in toluene (1.5 mL) at -27 °C (entry 10).

b. %ee (HPLC) of recovered alcohol.

**Table 11. Transesterification Catalyzed by Yttrium Complexes 42, 43**
Other Y-amide complexes, \([Y(N(SiHMe_2)_2)_3]_{2\text{THF}}\) (40, synthesized according to Scheme 14, page 60) and \(\{('Bu-box)Y(N(SiHMe_2)_2)_2\}\) (43, synthesized according to the procedure described in the literature\(^\text{32 eq 32}\)) both are efficient catalysts (Table 11, entry 8, 9). In comparison with bisoxazoline-Cu complex, \(\{('Bu-box)Y(N(SiHMe_2)_2)_2\}\) (43) gave cleaner reaction. However, both tetrahedral complexes did not provide any enantioselectivity. The acylation of 1-indanol (1 mmol) with isopropenyl acetate (1.27 mmol) catalyzed by 43 (1 mol%) at -27 °C for 12 h gave the acetate with 53% conversion, and the recovered alcohol assayed by HPLC with 0%ee (Table 11, entry 10). Again, yttrium metal played a key role in transesterification (Table 11, entry 7 vs 8).

\[
[Y(N(dms)_2)_3]_{2\text{THF}} 40 + \quad \text{toluene} \quad \begin{array}{c} \text{rt, 12 h} \end{array} \quad \begin{array}{c} \text{OYVQ} \end{array}
\]

\[
\text{N(dms)_2} = N(SiHMe_2)_2
\]

\(1^H\) NMR \(\delta 0.30 (d, J = 3 \text{ Hz}, 24 \text{ H}, \text{SiHMe}_2), 0.82 (s, 18 \text{ H}, \text{'Bu})\)

\(3.70-3.80 (m, 4 \text{ H}), 3.88 (dd, J = 8.6, 5.1 \text{ Hz}, 2 \text{ H})\)

\(4.64 (s, 1 \text{ H}), 5.06 (sept, J = 3 \text{ Hz}, 4 \text{ H}, -\text{SiHMe})\)

\(12^C\) NMR \(\delta 3.1, 3.3, 26.0, 34.6, 58.5, 68.2, 74.6, 174.2\)

Anal. Calcd for \(C_{23}H_{53}N_4O_2Si_4Y\): C, 44.63; H, 8.63; N, 9.05. Found: C, 43.83; H, 8.33; N, 8.27.
The yttrium complex 44 (synthesis shown in eq 33) also provides another potential entry into a new class of chiral yttrium complexes. Preliminary study showed that \( [Y(\text{OSiPh}_3)_3\cdot\text{THF}_x] \) \(^{33}\) is an active catalyst for acylation of 1-indanol (eq 34). The reaction was carried out with 1-indanol (134.6 mg; 1 mmol), isopropenyl acetate (1.27 mmol), and \( [Y(\text{OSiPh}_3)_3\cdot\text{THF}_x] \) (22.2 mg) in toluene (1.5 mL) at room temperature (eq 34). Exploration in this class of chiral yttrium complexes from \( [Y(\text{OSiPh}_3)_3\cdot\text{THF}_x] \) (44) in asymmetric acylation of alcohols awaits further study.

\[
[Y(N(\text{dms})_2)_3\cdot\text{THF}]\ 40 + \text{Ph}_3\text{SiOH} \underset{\text{toluene, rt, 4 days}}{\xrightarrow{\text{}} [Y(\text{OSiPh}_3)_3\cdot\text{THF}_x] \ 44} (33)
\]

\[
\text{OH} + \overset{\text{16.5 wt\% } [Y(\text{OSiPh}_3)_3\cdot\text{THF}_x]}{\xrightarrow{\text{toluene, rt}}} \text{Ac} \underset{\text{Time conversion (\%)} }{\xrightarrow{\text{45 min } 54 \ \text{2h 40 min } 80 \ \text{19 h } 100}} (34)
\]
2.5 SUMMARY

- **Inactive Catalysts for Transesterification**

\[
\begin{align*}
\text{[(OH-box 22)Cu(OTf)2]} & \\
\text{[(OH-box 22)Sn(OTf)2]} & \\
\text{[((S,S)-Pr-pybox)Sn(OTf)2]} & \\
\text{Salen 29, 30/Ti(O/Pr)4} &
\end{align*}
\]

- **Active Catalysts for Transesterification**

\[
\begin{align*}
\text{[(OTBS-box 23)Sn(OTf)2]} & \\
\text{[(OTBS-box 23)Cu(OTf)2]} & \\
\text{Tridentate ligands 23, 31, 32, 33/Ti(O/Pr)4} & \\
\text{Salen 29, 30/Y3(O/Pr)13O} & \\
\text{[Y(N(dms)2)]2 THF]} & 40 \\
\text{[Y(OSiPh3)3 THF] 44}
\end{align*}
\]

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CHAPTER 3

SCOPE OF SALEN-YTTRIUM COMPLEX-CATALYZED ACYLATIONS

3.1 BIFUNCTIONAL CATALYSIS

Bifunctional (or bimetallic) asymmetric complexes which activate both electrophiles and nucleophiles at defined positions simultaneously have been developed into a new stream of asymmetric catalysts (Schemes 15, 16). The Y-salen complex 41 has an attractive "bifunctional" chelation mode in which both the anionic ligand [N(SiHMe₂)₂] and the neutral ligand (THF) are on a single metal core (Figure 6). These could in principle be replaced by a nucleophile (anionic) and an electrophile (neutral).

Figure 6. Bifunctional property of Salen-Yttrium Complex 41

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CBS (Itsuno-Corey) Catalytic Enantioselective Reduction:\textsuperscript{1d}

\[
\text{PhC} = \text{O} + \text{BH}_3 \text{THF (1.2 equiv)} + \text{N}_2 \text{O} (0.025 equiv) \xrightarrow{\text{THF, 23 °C}} \text{PhCH}_2\text{OH, 99.9%, 94.7%ee}
\]

Lewis base

Lewis acid

Catalytic Enantioselective Cyanosilylation of Ketones:\textsuperscript{1a}

\[
\text{PhC} = \text{O} + \text{Me}_3\text{SiCN} \xrightarrow{\text{Lewis base}} \text{PhCNMe}_3\text{Si}
\]

Scheme 15. Selected Examples of Bifunctional Catalysts

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Heterobimetallic Multifunctional Catalysts

Applications:
1. asymmetric nitro aldol (Henry) reaction

\[ RCHO + CH_3NO_2 \rightarrow RCH(OH)NO_2 \]

2. asymmetric Michael reaction

3. asymmetric hydrophosphonylation of imines

4. asymmetric Diels-Alder reaction

Bimetallic Mechanism for Asymmetric Ring Opening

\[
\begin{array}{c}
\text{10 mol\% YbCl}_3, 12 \text{ mol\% pybox} \\
\text{TMSO}_3, \text{CHCl}_3
\end{array}
\]

up to 92% ee

\[
\begin{array}{c}
\text{(pybox)Yb} \\
\text{CN}
\end{array}
\]

Scheme 16. Selected Examples of Bimetallic Catalysis
• The coordination mode of salen ligand to yttrium is a *out-of-plane* coordination

• The yttrium is 0.95 Å above the plane of ligating atoms-N$_2$O$_2$

• Two silicon atoms are equidistant from yttrium (3.523 Å)
  
  R. Anwander et al *Chem. Commun.* 1996, 1385 (X-ray structure see Figure 8)

![Diagram of 45, Achiral structure](image)

• Two silyl groups of N(dms)$_2$ are not equidistant from yttrium. Y-Si$^1$ = 3.158 Å; Y-Si$^2$ = 3.600 Å

• Chiral back-bone induces asymmetric coordination!
  
  M.-H. Lin; T. V. RajanBabu unpublished result (X-ray structure see Figure 4)

![Diagram of 41, Chiral structure](image)

Figure 7. Unique Structure of Salen-Yttrium Complexes

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As can be seen from Figure 7, an important feature of the Y-salen complexes 41, 45 is the *out-of-plane* coordination mode of the salen ligand to yttrium. In other words, yttrium is 0.95 Å above the plane of ligating-N,O-atoms. Owing to this unique coordination, two possible reactive sites are held closer at cis orientation and the chiral environment is tied-back. It is worth noticing that the electronic property of chiral salen ligand exerts an influence on the selective coordination between two silyl groups of [N(SiHMe$_2$)$_2$].

Figure 8. Structure of Achiral [(salen)Y(N(SiHMe$_2$)$_2$)THF] (45) Determined by Anwander et al.

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Note that one of the silyl groups (Si\(^2\)) is not bonded to yttrium—3.600 Å—but the other (Si\(^1\)) is 3.158 Å—in the chiral Y-salen complex 41. This unusual bonding between Si and Y is so-called agostic interaction.\(^1\)

"The term agostic bonding, originally proposed for the formation of two-electron three-center bonds of the type C-H→M, is now often used in lanthanide chemistry to describe the interaction of a highly electron-deficient, sterically unsaturated metal center with "CH", "SiMe", and "SiH" ligand fragments. Although the agostic bonding is weak and usually not observed in solution, it can have significant implications for the molecular and electronic structure and hence reactivity of the molecule." quoted from Anwander, R. in Principles in Organolanthanide Chemistry.\(^3a\)

The agostic interaction is one obvious difference between achiral Y-salen complex 45 and chiral complex 41. It was reported that an agostic interaction affects the regioselectivity in the palladium-catalyzed dimerization of aryl acetylenes.\(^4\) If the asymmetric induction from chiral Y-salen complex 41 is somehow related to the agostic interaction, this will be the first example of asymmetric agostic interaction affecting enantioselectivity.\(^5\) This agostic interaction shows the availability of an "open" coordination site. The role of such an open site in the asymmetric induction process remains as yet unknown. These unique features of structure of the Y-salen complex 41 provide a working model for coordination catalysis (vide infra) in the present context.
3.2 KINETIC RESOLUTION OF SECONDARY ALCOHOLS

A typical experiment of Y-salen-complex-catalyzed kinetic resolution of alcohols is conducted with alcohol (1 mmol) and isopropenyl acetate (1.27 mmol) in a solvent (1.5 mL), typically toluene. The conversion was determined by GC, enantiomeric excess of the unreacted alcohol was determined by HPLC (Daicel CHIRACEL OD column), and the configuration of major enantiomer was determined by HPLC elution order. Table 12 shows the results of Y-salen-complex-catalyzed (41) kinetic resolution of different kinds of alcohols. As mentioned, selectivity factor $s$ or $k_{rel}$ is calculated based on Kagan's equation (Chapter 2, page 59, and reference cited therein).

The new chiral Y-salen complex 41, presumably acting through both nucleophilic and electrophilic activation at a single metal core, was found to be an efficient catalyst (1 mol%, -25 °C) for kinetic resolution of 1-indanol under nearly neutral reaction condition (91% ee at 77% conversion, $[\alpha]_D = -29^\circ$ (c = 1, CHCl$_3$), $s = k_{fast}/k_{slow} = k_{rel} = 4.8$; Table 12, entry 11). (S)-(+)1-Indanol ($[\alpha]_D = +30^\circ$ (c = 2, CHCl$_3$)) and (R)-(−)-1-indanol ($[\alpha]_D = -29^\circ$ (c = 2, CHCl$_3$)) are available commercially (Aldrich). As can be seen from Table 12, the reactivity was significantly reduced when bulky alcohol with steric demand at $\alpha$-carbon next to the hydroxyl carbon was employed (entry 1 vs 2; 3 vs 6). However, a highly flexible allylic alcohol ($E$-4-phenyl but-3-en-2-ol) was found to be less reactive (entry 7 vs 1). Interestingly, the resolved cyclic alcohols ((R)-1-indanol, entry 10, 11) and acyclic alcohols ((S)-alkyl phenyl carbinols, entry 1, 4, 5; (S)-4-phenyl but-3-en-2-ol, entry 8; (S)-$\alpha$-methyl-naphthalene methanol, entry 9) showed opposite configuration at the chiral carbon.
The reactions were carried with alcohol (1 mmol), and isopropenyl acetate (1.27 mmol) in toluene (1.5 mL).

a. %ee (configuration of major enantiomer) of recovered alcohol was determined by HPLC.

Table 12. Y-Salen Complex (41)-Catalyzed Kinetic Resolution of Secondary Alcohols

<table>
<thead>
<tr>
<th>entry</th>
<th>alcohols (temp °C)</th>
<th>mol% Y (41)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>%ee°, krel = s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMeOH (-3)</td>
<td>1</td>
<td>5.6</td>
<td>65</td>
<td>22.6 (S); s = 1.5</td>
</tr>
<tr>
<td>2</td>
<td>PhOH (22)</td>
<td>1</td>
<td>22</td>
<td>44</td>
<td>9.5; s = 1.4</td>
</tr>
<tr>
<td>3</td>
<td>PhPrOH (0)</td>
<td>1</td>
<td>14</td>
<td>24</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>PhOH (-10)</td>
<td>2.5</td>
<td>7.5</td>
<td>48</td>
<td>17 (S); s = 1.7</td>
</tr>
<tr>
<td>5</td>
<td>PhBuOH (22)</td>
<td>2.5</td>
<td>3.3</td>
<td>44</td>
<td>3.1 (S); s = 1.2</td>
</tr>
<tr>
<td>6</td>
<td>PhBuOH (0)</td>
<td>1</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>PhOH (-4)</td>
<td>1</td>
<td>14</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PhMe=CHMe (-10)</td>
<td>2</td>
<td>9</td>
<td>42</td>
<td>12.7 (S); s = 1.6</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>7.5</td>
<td>61</td>
<td>35.8 (S); s = 2.2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>7.5</td>
<td>75</td>
<td>78 (R); s = 3.6</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>12</td>
<td>77</td>
<td>91 (R); s = 4.8</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>2.7</td>
<td>51</td>
<td>9.6; s = 1.3</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>8</td>
<td>39</td>
<td>14; s = 1.8</td>
<td></td>
</tr>
</tbody>
</table>

Table 12. Y-Salen Complex (41)-Catalyzed Kinetic Resolution of Secondary Alcohols

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The solvent effect was also studied, and toluene was found to be the solvent of choice (Table 13). The acylation did not proceed in the presence of strong donor solvent such as THF (Table 13, entry 2). It indicates that Lewis acid site was probably mostly occupied by THF and the acylation was retarded because enol acetates could not get into the coordination sphere.

Other racemic alcohol substrates 46, 48, 49, 51 and a meso diol 47 were examined. None showed any kinetic selectivity in the acylation reactions. These alcohols showed low reactivity although relatively large catalyst loading was employed.
The reactivity and enantioselectivity both suffered in diastereomeric mixture 46 as the substrate compared to 1-indanol. One of diastereomers reacted faster than the other of diastereomers did (eq 35).

Desymmetrization of diol 47 was expected, but the product was obtained as mixture of mono- and di-acetates. Compared to α-methylbenzyl alcohol, chelating substrates 48, 49 with ancillary oxygen atom presumably blocking the "open" coordination site suffered from low reactivity. Acylation of 48 catalyzed by 2 mol% 41 for 7.5 h at room temperature gave 47% conversion with 5%ee of recovered alcohol (k_{rel} = 1.17).
Similarly, acylation of 49 catalyzed by 2 mol% 41 for 3.5 h at room temperature gave 64.5% conversion with 11.9% ee of recovered alcohol ($k_{rel} = 1.26$). Therefore, it appears that the "open" coordination site is linked to the catalytic ability of Y-salen complex. Trans-azidocyclohexanol (50) was acylated smoothly in the presence of 1 mol% 41 for 6.3 h at ambient temperature to give 70% conversion (vs 1 mol% 40 for 36 h gave 42.7% conversion; ligand assisted catalysis); however, successful separation of two enantiomers 50 was not able to achieved by chiral GC.

From a practical standpoint, it will be ideal to obtain an enantiomerically pure product in quantitative yield. This is an inevitable limitation for kinetic resolution approaches; however, desymmetrization of meso diols is one of the situations where it is possible to get a quantitative yield. Another situation where this is possible is shown in eq 36. Therefore, 51 with related structure was tested as a substrate using Y-salen complex 41. Unfortunately, this substrate did not react with isopropenyl acetate and 2.5 mol% 41 in toluene at ambient temperature for 10 days.
3.3 MODIFICATIONS OF ACYLATING AGENTS

If $\gamma$-coordination of the enol ester is important for selectivity, we should anticipate a dependence of its structure on such selectivity. Scouting optimal acylating agents was therefore considered next. Eight different modified enol acetates were synthesized for this objective (52-59, Figure 9; synthesis, Scheme 17). Many modified enol acetates 52-59 were not as reactive as isopropenyl acetate probably due to steric hindrance. Increased catalyst loading can sometimes be employed to get reasonable reactivity. At this point, isopropenyl acetate is the most optimum acylating agent in terms of reactivity and enantioselectivity (Table 14, 15, 16). In addition, the relative reactivity of modified enol acetates varied with the structure of alcohol (5-membered: 1-indanol; 6-membered: $\alpha$-tetralol; acyclic: $\alpha$-methylbenzyl alcohol; Figure 10).

![Figure 9. A List of Modified Enol Acetates](image-url)
Scheme 17. Synthesis of Enol Esters 52-59
<table>
<thead>
<tr>
<th>entry</th>
<th>enol acetate</th>
<th>mol% Y (41)</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>%ee&lt;sup&gt;a&lt;/sup&gt;; k&lt;sub&gt;rel&lt;/sub&gt; = s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>1</td>
<td>-3</td>
<td>7.5</td>
<td>75</td>
<td>78 (R); s = 3.6</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>1</td>
<td>-25</td>
<td>12</td>
<td>76.5</td>
<td>91 (R); s = 4.8</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>1</td>
<td>-35</td>
<td>12</td>
<td>61</td>
<td>61.5 (R); s = 4.1</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>2.5</td>
<td>22</td>
<td>72</td>
<td>42</td>
<td>7.8 (R); s = 1.3</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>2.5</td>
<td>22</td>
<td>25.17</td>
<td>45.8</td>
<td>7.9 (R); s = 1.3</td>
</tr>
<tr>
<td>6</td>
<td>3c</td>
<td>2</td>
<td>-27</td>
<td>12.5</td>
<td>37</td>
<td>16 (R); s = 2.0</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>3</td>
<td>-3</td>
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<td>58</td>
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<td>-15</td>
<td>12</td>
<td>58.8</td>
<td>18 (R); s = 1.5</td>
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<td>2.5</td>
<td>-15</td>
<td>12</td>
<td>NR</td>
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<td>2.5</td>
<td>-3</td>
<td>6.75</td>
<td>61.8</td>
<td>2 (R); s = 1.0</td>
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<tr>
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<td>2.5</td>
<td>-15</td>
<td>12</td>
<td>18</td>
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</tbody>
</table>

<sup>a</sup> %ee (HPLC) of recovered alcohol.

Table 14. Different Reactivity of Modified Acylating Agents with 1-Indanol
<table>
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<tr>
<th>entry</th>
<th>enol acetate</th>
<th>mol% Y (41)</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>%ee&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>14</td>
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<tr>
<td>8</td>
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<td>21.5</td>
<td>23</td>
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<td>19</td>
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</table>

<sup>a</sup> %ee (HPLC) of recovered alcohol.

Table 15. Different Reactivity of Modified Acylating Agents with α-Tetralol
Table 16. Different Reactivity of Modified Acylating Agents with α-Methylnaphthalene methanol

<table>
<thead>
<tr>
<th>entry</th>
<th>enol acetate</th>
<th>mol% Y (41)</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>%ee&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
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<td>-3</td>
<td>7.5</td>
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<tr>
<td>2</td>
<td>OAc&lt;sub&gt;Ph&lt;/sub&gt;</td>
<td>53</td>
<td>2.5</td>
<td>-3</td>
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<tr>
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<td>OAc&lt;sub&gt;H&lt;/sub&gt;</td>
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<td>4</td>
<td>-3</td>
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<tr>
<td>4</td>
<td>Me&lt;sub&gt;4&lt;/sub&gt;OAc</td>
<td>58</td>
<td>2.5</td>
<td>-2</td>
<td>24</td>
<td>28.5</td>
</tr>
<tr>
<td>5</td>
<td>Me&lt;sub&gt;4&lt;/sub&gt;OAc</td>
<td>58</td>
<td>3.5</td>
<td>-3</td>
<td>15.5</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>Me&lt;sub&gt;4&lt;/sub&gt;OAc</td>
<td>59</td>
<td>3.5</td>
<td>-3</td>
<td>15.5</td>
<td>11.5</td>
</tr>
<tr>
<td>7</td>
<td>OAc&lt;sub&gt;Me&lt;/sub&gt;</td>
<td>57</td>
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<td>-3</td>
<td>17</td>
<td>86.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> %ee (HPLC) of recovered alcohol.

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• relative reactivity of modified enol acetates for acylation of 1-indanol:

\[
\begin{align*}
\text{CH}_3 \quad &\quad \text{OAc} \\
\text{H}_2\text{C} \quad &\quad \text{OAc} \\
\text{CH}_3 \quad &\quad \text{OAc}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 \quad &\quad \text{OAc} \\
\text{H}_2\text{C} \quad &\quad \text{OAc} \\
\text{CH}_3 \quad &\quad \text{OAc}
\end{align*}
\]

• relative reactivity of modified enol acetates for acylation of \( \alpha \)-tetralol:

\[
\begin{align*}
\text{CH}_3 \quad &\quad \text{OAc} \\
\text{H}_2\text{C} \quad &\quad \text{OAc} \\
\text{CH}_3 \quad &\quad \text{OAc}
\end{align*}
\]

• relative reactivity of modified enol acetates for acylation of \( \alpha \)-methylbenzyl alcohol:

\[
\begin{align*}
\text{CH}_3 \quad &\quad \text{OAc} \\
\text{H}_2\text{C} \quad &\quad \text{OAc} \\
\text{CH}_3 \quad &\quad \text{OAc}
\end{align*}
\]

Figure 10. Relative Reactivity of Modified Enol Esters with Different Alcohols

3.4 MATCHED-MISMATCHED REACTIVITY

During an efforts in scouting for the optimal acylating agent among several different modified enolesters for kinetic resolution of secondary alcohols, a "matched-mismatched" pattern reactivity was observed in the reaction of 1-indanol and (-) or (+) menthone enol acetate 58, 59 (Table 14, entry 9 vs 10). Similar substrate matching in transesterification was reported by a Korean group in an enzyme memory-based approach 85.
to enhance the enantioselectivity.\textsuperscript{10} In the lipase-catalyzed transesterification of 2a-c, higher enantioselectivities have been achieved using 1a-c, respectively, as the structurally matched acyl donors (eq 37).\textsuperscript{10}

\[ \text{lipase} \quad \text{A} \quad \text{AcO} \quad \text{OAc} \]

With this interesting observation in hand (Table 14, entry 9 vs 10), we were prompted to seek whether kinetic resolution of (+)/(-) menthone enol acetates or menthones could be achieved by using the same system (eq 38).

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However, one of the most spectacular, as yet unintelligible result ensued: With (+) menthone-derived enol acetate (59) present in the reaction medium, no transesterification occurred!! Another example can be seen in Table 15, entries 8 and 9.

Next, we turned our attention to the reaction of 1-indanol and (-)-menthone enol acetate (58) in the presence of achiral yttrium complex such as \( \text{Y}_5(\text{O'Pr})_{13} \text{O} \) (1) (eq 39).

![Reaction Scheme](image)

Although no significant enantioselectivity was found in the reaction, the configuration of recovered 1-indanol was opposite to the one from the (S,S)-Salen-yttrium (41) catalyzed reaction. Therefore, triangular relationship among the chiral yttrium complex, 1-indanol and menthone enol acetate is suggested (Scheme 18). Clearly these results suggest that the transesterification reaction has to go through an yttrium activation. Based on our previous study, (S,S)-Salen-yttrium complex (41) will give recovered 1-indanol with \( R \) configuration in the reaction of racemic 1-indanol with achiral acylating agents (Table 14, entry 1-7). (-)-Menthone enol acetate (58) on the other hand preferentially reacted with \( (R) \)-1-indanol (eq 39). In conclusion, matched pairs are (S,S)-Salen-Y complex/(S)-1-indanol, and (-)-menthone enol acetate/(R)-1-indanol. As a result, we were pleased to see increased enantioselectivity in the unreacted 1-indanol (S) when \( (R,R) \)-Salen-Y complex was employed with (-) menthone enol acetate which changed the reactivity.
between 1-indanol and (-)-menthone enol acetate from mismatched into matched (Scheme 18). Note that under these conditions the selectivity almost doubled ($k_{rel}$ changed from 1.5 to 2.7).

Scheme 18. Matched-Mismatched Reactivity Affects Enantioselectivity
3.5 CONCENTRATION EFFECTS

The effect of concentration of enol ester and the yttrium catalyst was briefly investigated and the results are shown in Table 17. In a typical experiment, Y-salen complex 41 (1 mol%) catalyzed acylation was conducted with 1-indanol (1 mmol), and isopropenyl acetate (3a) (1.27 mmol) in toluene (1.5 mL) (Table 17, entry 2).

\[
\begin{align*}
\text{Y catalyst (41)} & \\
toluene, -25 °C & \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>concentration [M] enol acetate in toluene</th>
<th>mol% Y (41)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>%ee\textsuperscript{a}, k\textsubscript{rel} = s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{b}</td>
<td>1.7</td>
<td>1</td>
<td>12</td>
<td>95</td>
<td>97 (R); s = 2.81</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
<td>1</td>
<td>12</td>
<td>76.5</td>
<td>91 (R); s = 4.81</td>
</tr>
<tr>
<td>3</td>
<td>0.3</td>
<td>1</td>
<td>12</td>
<td>45</td>
<td>43 (R); s = 4.83</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
<td>0.75</td>
<td>17</td>
<td>62.7</td>
<td>68.7 (R); s = 4.64</td>
</tr>
<tr>
<td>5</td>
<td>1.7</td>
<td>0.5</td>
<td>17</td>
<td>39</td>
<td>35 (R); s = 4.76</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
<td>0.5</td>
<td>12</td>
<td>24.5</td>
<td>19 (R); s = 4.59</td>
</tr>
</tbody>
</table>

The reactions were carried out with 1-indanol (1 or 2 mmol).

\textsuperscript{a} %ee (HPLC) of recovered alcohol. \textsuperscript{b} The reaction was carried out at -27 °C.

Table 17. Concentration Effect of Enol Acetate (3a) and Y-Salen Complex 41 in Kinetic Resolution of 1-Indanol

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Under the typical condition but with limited amount of acylating agent, the reaction was complete with same selectivity factor (s, k_{ed}), when all acylating agent was consumed (Table 17, entry 3). Under the condition with double amount of alcohol, and acylating agent but fixed amount of solvent (1.5 mL), the reaction proceeded with higher conversion but poorer selectivity (Table 17, entry 1). Clearly the rate of the reaction increases with increasing concentration of the catalyst (entries 2, 4, and 6). More careful kinetic studies need to be performed to confirm what appears to be a first-order dependence on the catalyst.

### 3.6 PROPOSED MECHANISM OF SALEN-YTTRIUM COMPLEX-CATALYZED ACYLATION REACTIONS

A proposal for the mechanism of this unique acyl transfer process is shown in Scheme 19. It was reported that 2-propanol reacted with [Y{N(SiMe$_3$)$_2$}] to yield oxo-alkoxide aggregate [Y$_3$(O'Pr)$_3$O]. Furthermore, the silylamide group [N(SiHMe$_2$)$_2$] was found to be labile with respect to hydroxyl group exchange (eq 40).
Scheme 19. Proposed Mechanism of Y-Salen 41 Catalyzed Acylation Reactions
Therefore, formation of yttrium alkoxide A can be expected in the first step. Subsequently, THF could be replaced by an enol acetate 3a to form species B because of large amount of 3a present in the reaction medium compared to catalytic amounts of THF. It is worth noticing that the reactivity of both alcohol and enol acetate is enhanced because of the formation of intermediate B. The activated alkoxide and coordinated enol acetate are vicinal and ready to proceed via a nucleophilic addition to form the tetrahedral intermediate C. The intermediate C could be very unstable and a small reorganization within the Y-coordination sphere could result in a more stable intermediate D (i.e., with better enolate ligands and more coordinate saturation). Therefore the product ester is released to give a relatively stable intermediate D in which L could be the just liberated ester. (Or, the intermediate C could be very unstable because of inverted electronic property on the yttrium; therefore, the product ester was released to give relatively stable intermediate D.) Because pKa's of the relevant conjugate acids would determine the several equilibria here, proton transfer from more acidic alcohol to the enolate D would form an alkoxide intermediate, letting Y to enter the catalytic cycle (B \rightarrow C \rightarrow D \rightarrow E \rightarrow B).

One possible explanation for the previously observed "matched-mismatched" reactivity could be offered as follows: (+)-Menthone enol acetate (59) would form (+)-menthene enolate- yttrium species D; however, the subsequent proton transfer could not proceed due to disfavored chair-like transition state I. Therefore, the catalytic cycle was blocked because the transformation from D to E was blocked. As a result, no acylation was found once (+)-menthene enol acetate (59) was present in the reaction medium. In other words, the enolate of (+)-menthene acts as a suicide-catalyst inhibitor.
Scheme 20. Proposed Proton Transfer via Chair-like Transition State
The proposed proton transfer mechanism via the chair-like transition state is shown in Scheme 20. Alcohol with lone-pair electrons at oxygen atom would presumably coordinate to yttrium enolate D to form chair-like transition states F, G. The re-enolate-Y approach to alcohol as shown F would be disfavored because menthone enolate was orientated above the cyclohexyl ring of Y-salen complex; therefore, si-enolate-Y approach as shown G should be favored. According to favored si-enolate-Y approach, (-)-menthone enolate H, and (+)-menthone enolate I are presumably the most likely chair-like transition states responsible for proton transfer from alcohol to the corresponding menthone enolates. As can be seen from Scheme 20, the isopropyl group of menthone enolate would bump into the salen ligand on yttrium; therefore, the proton transfer failed in I. In addition, this chair-like transition state is also related with the structure of alcohol (Table 14, entry 9 vs 10; Table 15, entry 8 vs 9; Table 16, entry 5 vs 6). In conclusion, there are at least three chiral species with more than three chiral centers involved in the observed "matched-mismatched" reactivity of salen-yttrium complex, and situation could be more complicated than presented here. Further studies are needed to delineate these intriguing observations.

3.7 CHIRAL LIGAND SYNTHESIS

The Schiff base ligands (61, 62, 63, 66, 67, 68, 69) were prepared by condensation of the chiral diamine (1 mmol) with the corresponding substituted salicylaldehyde (2 mmol) in methanol (10 mL).
Scheme 21. Synthesis of Sugar Motif Ligand 62, 63
The chiral diamine with the sugar motif was prepared from 2-acetamido-2-deoxy-\(\alpha\)-\(D\)-glucopyranoside (Scheme 21).\(^{13}\) Salen-type ligand 60 was prepared according to Jacobsen's procedure, and sulfonamide-Schiff base ligands (64, 65) were prepared based on Walsh's procedure (Scheme 22).\(^{14}\) Acetamide 70 and phosphine oxide 71 were prepared according to the procedure described in the literature (Scheme 23).\(^{15}\)

\[
\text{Salen Ligand 60: }^{14a}
\]

\[
\text{Sulfonamide-Schiff base Ligands 64, 65: }^{14b}
\]

Scheme 22. Synthesis of Salen Ligand 60 and Sulfonamide-Schiff Base Ligands 64, 65

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OH FeCl₃H₂O
H₂O, 50 °C, 2 h

N-benzylchinonidinium
chloride

CH₃CN, reflux, 4 h

OH

OH

OH

OH

(OH)

Wienzytanchonidinium chloride (S)-binol (99% ee)

H gO ,

50°C , 2 h

Wienzytanchonidinium chloride (R)-binol (99% ee)

Acetamide 70:¹⁵c

Phosphine oxide 71:¹⁵d

Scheme 23. Synthesis of Chiral Acetamide 70 and Chiral Phosphine Oxide 71

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3.8 MODIFICATIONS OF CHIRAL LIGANDS

Since the salen ligand system was found to be the most optimum in our early studies, our next goal was to modify the chiral diamine backbone. For this we chose cyclohexyl 29, diphenyl 61, binaphthyl 30, 66, 67, 68, 69 and a sugar motif 62, 63. The corresponding salicylaldehyde imine derivatives were prepared. In addition, sulfonamide-Schiff base conjugate ligands 64, 65, acetamide 70, and phosphine oxide 71 were also prepared. Chiral Y-salen complexes were prepared according to Anwander's silylamide route\(^{16}\) (Scheme 24). Dimethylsilylamide—N(SiHMe\(_2\))\(_2\)—was chosen instead of trimethylsilylamide—N(SiMe\(_3\))\(_2\)—because dimethylsilylamide is less sterically bulky and readily replaced. The exact structures of Y-salen complexes were unclear because \(^1\)H NMR in C\(_6\)D\(_6\) spectrum of Y-salen complexes revealed broad, poorly resolved, overlapping signals. Because of that, we have limited information about the structure of Y-salen complexes. Gratifyingly, the structure of Y-salen complex 41, recrystallized from pentane, was confirmed by X-ray analysis (Figure 4). In general, salen-yttrium complexes are formulated as \([(L)Y(N(SiHM e_2))_2(THF)]\) where L stands for chiral ligand(s). Under catalysis by Y-salen complex 41, kinetic resolution of 1-indanol and \(\alpha\)-methylnaphthalene methanol gave the best results (Table 12, entries 9 and 11, 1-indanol, \(k_{\text{rel}} = 4.8\); \(\alpha\)-methylnaphthalene, \(k_{\text{rel}} = 2.2\)). Consequently, 1-indanol and \(\alpha\)-methylnaphthalene methanol were examined under typical conditions (described in page 75) catalyzed by different yttrium complexes with modified chiral backbone. Table 18 shows the results of acylation of 1-indanol, and the results of \(\alpha\)-methylnaphthalene methanol are summarized in Table 19.
Scheme 24. Synthesis of Chiral Yttrium Complexes with Modified Ligands

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### Table 18. Acylation of l-Indanol Catalyzed by Yttrium Complexes with Modified Chiral Ligands

<table>
<thead>
<tr>
<th>entry</th>
<th>([L]Y(N(dms)₂)THF] (mol%)</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>%ee¹</th>
<th>k_rel = s</th>
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<tr>
<td>2</td>
<td>60 (1)</td>
<td>-5</td>
<td>10</td>
<td>4.7</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>60 (1)</td>
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<td>12</td>
<td>4.6</td>
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<tr>
<td>4</td>
<td>61 (1)</td>
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<td>8.8 (R); s = 1.62</td>
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<td>84.7 (R); s = 2.6</td>
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<td>7</td>
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<td>12</td>
<td>40.3</td>
<td>25.7 (R); s = 2.83</td>
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<td>8</td>
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<td>6.5</td>
<td>21.5</td>
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</tr>
<tr>
<td>9</td>
<td>63 (1)</td>
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<td>10</td>
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<td>64 (1)</td>
<td>-2</td>
<td>9</td>
<td>80</td>
<td>25.5 (S); s = 1.38</td>
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<td>-12</td>
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<td>63</td>
<td>17.6 (S); s = 1.43</td>
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<tr>
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<td>88</td>
<td>92 (S); s = 3.16</td>
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<td>84.7 (S); s = 3.5</td>
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<tr>
<td>16</td>
<td>65 (1)</td>
<td>-27</td>
<td>16</td>
<td>13.9</td>
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</table>

¹ %ee (HPLC) of recovered alcohol.
<table>
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<th>entry</th>
<th>[[L]Y(N(dms)$_2$)THF] (mol%)</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>%ee$^a$, $k_{rel} = s$</th>
</tr>
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<tr>
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<td>93</td>
<td>ND</td>
</tr>
<tr>
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<td>66 (1.5)</td>
<td>-26</td>
<td>12</td>
<td>30.5</td>
<td>2 (S); $s = 1.12$</td>
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<td>67 (1)</td>
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<td>8</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>68 (1)</td>
<td>-4</td>
<td>8.25</td>
<td>28.8</td>
<td>3.8 (S); $s = 1.25$</td>
</tr>
<tr>
<td></td>
<td>R = 3-Br, 5-Bu</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R = 3-OMe 68</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>68 (1.5)</td>
<td>-26</td>
<td>12</td>
<td>8</td>
<td>ND</td>
</tr>
<tr>
<td>22</td>
<td>70 (2.5)</td>
<td>-4</td>
<td>12.5</td>
<td>72</td>
<td>8 (R); $s = 1.13$</td>
</tr>
<tr>
<td>23</td>
<td>71 (2)</td>
<td>-3</td>
<td>12.5</td>
<td>89</td>
<td>36 (R); $s = 1.40$</td>
</tr>
<tr>
<td>24</td>
<td>29 (1)</td>
<td>-3</td>
<td>7.5</td>
<td>75</td>
<td>78 (R); $s = 3.58$</td>
</tr>
<tr>
<td>25</td>
<td>29 (1)</td>
<td>-25</td>
<td>12</td>
<td>76.5</td>
<td>91 (R); $s = 4.81$</td>
</tr>
</tbody>
</table>

*a. %ee (HPLC) of recovered alcohol.*

Table 18. (continued) Acylation of 1-Indanol Catalyzed by Yttrium Complexes with Modified Chiral Ligands
Table 19. Acylation of α-Methylnaphthalene methanol Catalyzed by Yttrium Complexes with Modified Chiral Ligands

<table>
<thead>
<tr>
<th>entry</th>
<th><a href="%5BL%5DYN(dms)2">%</a>THF (mol%)</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>%ee</th>
<th>k_rel = s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29 (1)</td>
<td>-3</td>
<td>7.5</td>
<td>61</td>
<td>35.8</td>
<td>s = 2.2</td>
</tr>
<tr>
<td>2</td>
<td>61 (1.5)</td>
<td>-3</td>
<td>10</td>
<td>67</td>
<td>35;</td>
<td>s = 1.9</td>
</tr>
<tr>
<td>3</td>
<td>62 (1)</td>
<td>-2</td>
<td>9.5</td>
<td>27.4</td>
<td>20;</td>
<td>s = 3.94</td>
</tr>
<tr>
<td>4</td>
<td>62 (1.5)</td>
<td>-3</td>
<td>9</td>
<td>69.3</td>
<td>60.4;</td>
<td>s = 2.97</td>
</tr>
<tr>
<td>5</td>
<td>64 (1)</td>
<td>-3</td>
<td>10</td>
<td>26</td>
<td>7.8;</td>
<td>s = 1.69</td>
</tr>
<tr>
<td>6</td>
<td>64 (1.5)</td>
<td>-3</td>
<td>11</td>
<td>28.5</td>
<td>9.7;</td>
<td>s = 1.8</td>
</tr>
<tr>
<td>7</td>
<td>64 (3)</td>
<td>-3</td>
<td>10.5</td>
<td>54.5</td>
<td>21.8;</td>
<td>s = 1.75</td>
</tr>
<tr>
<td>8</td>
<td>65 (1)</td>
<td>-3</td>
<td>10</td>
<td>27</td>
<td>11.3;</td>
<td>s = 2.09</td>
</tr>
<tr>
<td>9</td>
<td>65 (1.5) (R = 4-Me 64)</td>
<td>-3</td>
<td>11</td>
<td>28.5</td>
<td>15;</td>
<td>s = 2.54</td>
</tr>
<tr>
<td>10</td>
<td>65 (3) (R = 2,4,6-Pr 65)</td>
<td>-3</td>
<td>10.5</td>
<td>41.8</td>
<td>16;</td>
<td>s = 1.82</td>
</tr>
</tbody>
</table>

a. %ee (HPLC) of recovered alcohol.
\[
\text{Me}_2\text{OH} + \overset{\text{OAc}}{\text{CH}_3} \xrightarrow{[[\text{L}Y(N(dms)_2)\text{THF}]} \text{toluene} \rightarrow \text{Me}_2\text{OAc}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>([[[\text{L}Y(N(dms)_2)\text{THF}]} \text{(mol%)})</th>
<th>temp (\degree\text{C})</th>
<th>time (h)</th>
<th>conv. (%)</th>
<th>%ee, (k_{\text{rel}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>30 (1)</td>
<td>22</td>
<td>10.5</td>
<td>46</td>
<td>7; (s = 1.26)</td>
</tr>
<tr>
<td>12</td>
<td>66 (1)</td>
<td>22</td>
<td>10.5</td>
<td>90</td>
<td>33.4; (s = 1.34)</td>
</tr>
<tr>
<td>13</td>
<td>66 (2)</td>
<td>-3</td>
<td>8</td>
<td>81</td>
<td>27; (s = 1.39)</td>
</tr>
<tr>
<td>14</td>
<td>67 (1)</td>
<td>22</td>
<td>10.5</td>
<td>70</td>
<td>1.75; (s = 1.03)</td>
</tr>
<tr>
<td>15</td>
<td>67 (2)</td>
<td>-4</td>
<td>8</td>
<td>5.3</td>
<td>ND</td>
</tr>
<tr>
<td>16</td>
<td>68 (1)</td>
<td>22</td>
<td>10.5</td>
<td>38.7</td>
<td>3.8; (s = 1.17)</td>
</tr>
<tr>
<td>17</td>
<td>68 (2)</td>
<td>-4</td>
<td>8.25</td>
<td>30.4</td>
<td>2.1; (s = 1.12)</td>
</tr>
<tr>
<td>18</td>
<td>69 (1)</td>
<td>22</td>
<td>10.5</td>
<td>2.3</td>
<td>ND</td>
</tr>
<tr>
<td>19</td>
<td>70 (3)</td>
<td>-4</td>
<td>12.5</td>
<td>86</td>
<td>59; (s = 1.9)</td>
</tr>
<tr>
<td>20</td>
<td>71 (2)</td>
<td>-3</td>
<td>12.5</td>
<td>49</td>
<td>30; (s = 2.5)</td>
</tr>
</tbody>
</table>

a. \%ee (HPLC) of recovered alcohol.

Table 19. (continued) Acylation of \(\alpha\)-Methylnaphthalene methanol Catalyzed by Yttrium Complexes with Modified Chiral Ligands

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With respect to chiral diamine scaffold, the backbone of cyclohexyl 29 was superior to diphenyl 61, sugar motif 62 and binaphthyl 66 in the acylation of 1-indanol. However, sugar motif 62 gave better enantioselectivity even though lower turnover number than cyclohexyl 29 in the acylation of α-methylnaphthalene methanol. (1-indanol: see Table 18, entry 4 vs 24; entry 7, 18 vs 25; α-methylnaphthalene methanol: see Table 19, entry 1 vs 3; entry 1 vs 2, 13) As can be seen from Table 18 entries 4, 7, and 25, the catalytic ability of Y complexes with the backbone connecting 3,5-di-tert-butyl-salicylaldehyde in acylation of 1-indanol varies with the flexibility of the backbone. Under catalysis by 1 mol% Y complex for 12 h, diphenyl 61 gave 31% conversion at -3 °C, sugar motif 62 gave 40% conversion at -25 °C and cyclohexyl 29 gave 77% conversion at -25 °C. Therefore, the flexibility of the backbone connecting 3,5-di-tert-butyl-salicylaldehyde has an influence on the reactivity of salen-yttrium complexes and rigid backbones gave better results. In addition, it is reported that the flexibility of ligand is a factor affecting Al-C bond reactivity of tetradentate Schiff-base organoaluminum complexes such as [Al(Schiff base)C₂H₅] complexes shown below. Hydrolysis of SALOPHEN is extremely slow. For the more flexible SALEN and SALPN complexes, the relative rates of hydrolysis are significantly faster.

![SALEN](image1.png)  
SALEN  

![SALPN](image2.png)  
SALPN  

![SALOPHEN](image3.png)  
SALOPHEN  

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Substituent effects on salicylaldehyde of the salen-type ligands were also investigated. The electronic property of salicylaldehyde seemed to have crucial effect on the catalytic ability of the salen-yttrium complex (Table 19, entry 11, 12, 14, 16, 18). The salicylaldehyde with electron donating group was superior to electron withdrawing group; in this respect, the metal center with electron demand could be related to the electron movement in tetrahedral intermediate C (Scheme 19). In addition, the sterically demanding substituent at 3-position of salicylaldehyde or ortho-position of sulfonamide seemed to play a role in enantioselectivity.

After scrutinizing fourteen different chiral ligands, we concluded that our first salen-yttrium complex 41 was the best among the ones we prepared.

3.9 ATTEMPTS TO BLOCK THE EXTRA COORDINATION SITE

As mentioned earlier, the agostic interaction showed the availability of an "open" coordination site on the yttrium catalyst. The extra coordination site could contribute to increased number of diastereomeric intermediates resulting in deterioration of enantiocontrol. Therefore, we attempted to block the extra coordination site by addition of strongly coordinating ligands such as phosphine oxide ("Bu₃P=O). As can be seen from Table 20, strong donor ligands ("Bu₃P=O and Ph₂P(O)Me) appear to bind to yttrium more tightly limiting available reaction sites. As a result, the reaction rate was slower but the selectivity factor was unaffected (entry 5, 7 vs 11). There was a striking difference between entry 5 (1 mol% "Bu₃P=O, 54.8% conversion) and entry 6 (2 mol% "Bu₃P=O, no
reaction). This unambiguously reveals that there are three available coordination sites on the yttrium. Because tri-n-butylphosphine oxide replace THF and is irreversibly bound, no enol ester can go into Y-coordination sphere resulting in the lack of reaction with excess $^{t}Bu_3P=O$ (Table 20, entry 6). As mentioned, two of these coordination sites were identified as nucleophilic reaction site and electrophilic reaction site. The role of the third coordination site must await further study.

Strong donor ligands such as a nucleophilic carbene could replace THF on the salen-yttrium complex [(29')Y(N(dms)$_2$)THF] and this could be expected to be robust with respect to ligand exchange. The available reaction sites would thus be minimized resulting in increased selectivity. The syntheses of 1,3-diisopropylimidazol-2-ylidene, carbene-yttrium complex 72, and the acylation of 1-indanol catalyzed by carbene-yttrium complex 72 are shown in Scheme 25. The carbene-yttrium complex 72 was prepared according to the procedure described in the literature, and the putative structure of 72 was suggested as shown based on Herrmann's report. With the sterically demanding $^{t}Pr$ groups on the carbene, carbene-metal bond distance could be longer (Y-C: [(29')Y(N(dms)$_2$)(carbene)] compared to Y-O: [(29')Y(N(dms)$_2$)THF]). Increased selectivity was expected because of limited number of reaction sites and the increased steric demand in the carbene-yttrium complex 72. In the event, there was little difference on the rate (78.4% conversion vs 84% conversion (Table 20, entry 11)) but significant drop in enantioselectivity ($k_{en} = 2.23$ (Scheme 25) vs 3.69 (Table 20, entry 11)).

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Table 20. Additive Effect in Salen-Yttrium Catalyzed Acylation of 1-Indanol

<table>
<thead>
<tr>
<th>entry</th>
<th>additives (mol%)</th>
<th>temp (°C)</th>
<th>time</th>
<th>conv. (%)</th>
<th>%ee a; s = k_{rel}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\eta$Bu$_3$P=O (1)</td>
<td>22</td>
<td>2 h 25 min</td>
<td>80.4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$\eta$Bu$_3$P=O (2)</td>
<td>22</td>
<td>3 h 10 min</td>
<td>62.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ph$_2$P(O)Me (1)</td>
<td>22</td>
<td>2 h</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph$_2$P(O)Me (2)</td>
<td>22</td>
<td>2 h 40 min</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>$\eta$Bu$_3$P=O (1)</td>
<td>-15</td>
<td>12 h</td>
<td>54.8</td>
<td>50 (S); $k_{rel}$ = 3.83</td>
</tr>
<tr>
<td>6</td>
<td>$\eta$Bu$_3$P=O (2)</td>
<td>-15</td>
<td>12 h</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Ph$_2$P(O)Me (1)</td>
<td>-15</td>
<td>12 h</td>
<td>30.5</td>
<td>22 (S); $k_{rel}$ = 3.76</td>
</tr>
<tr>
<td>8</td>
<td>Ph$_2$P(O)Me (2)</td>
<td>-15</td>
<td>12 h</td>
<td>25.3</td>
<td>18 (S); $k_{rel}$ = 3.77</td>
</tr>
<tr>
<td>9</td>
<td>$\eta$Bu$_3$P (1)</td>
<td>-16</td>
<td>12 h</td>
<td>43</td>
<td>34 (S); $k_{rel}$ = 3.63</td>
</tr>
<tr>
<td>10</td>
<td>$\eta$Bu$_3$P (2)</td>
<td>-16</td>
<td>12 h</td>
<td>67.7</td>
<td>68 (S); $k_{rel}$ = 3.71</td>
</tr>
<tr>
<td>11</td>
<td>none</td>
<td>-15</td>
<td>12 h</td>
<td>84</td>
<td>92 (S); $k_{rel}$ = 3.69</td>
</tr>
</tbody>
</table>

a. %ee (HPLC) of recovered alcohol.
Scheme 25. Synthesis of Carbene-Yttrium Complex 72 and Carbene-Yttrium Complex

72 Catalyzed Acylation of 1-Indanol
3.10 SCANDIUM COMPLEXES

Next, we turned our attention to scandium metal with a small coordination sphere. The resulting salen-scandium complex 74 was synthesized according to the extended silylamide route (Scheme 26). It is worth noticing that salen-scandium complex 74 has no THF molecule on it. The exact structure of salen-scandium complex 74 was unclear because $^1$H NMR in $C_6D_6$ spectrum of salen-scandium complex 74 (and other yttrium complexes) revealed broad, poorly resolved, overlapping signals. However, the salen-scandium complex 74 was prepared according to the procedure described for Anwander's disulfonamide scandium complex synthesis (eq 41), so the most likely structure of salen-scandium complex 74 must be what is shown in Scheme 26.

$$
\text{Ln}[N(SiMe_2)_2]_3(\text{THF})_n + \text{racemic} \rightarrow \text{toluene} \rightarrow \text{Ln} = \text{Sc}; n = 1 \\
\text{Ln} = \text{Y, La, Nd}; n = 2
$$

As can be seen from Scheme 26, salen-scandium complex 74 catalyzed acylation of 1-indanol did not give any enantioselectivity ($k_{\text{cat}} = 1.07$).
\[
\text{ScCl}_3 \cdot 6\text{H}_2\text{O} + \text{SOCl}_2 \xrightarrow{\text{THF, reflux, 8 h}} [\text{ScCl}_3 \text{THF}_2]
\]

\[
[\text{ScCl}_3 \text{THF}_2] + \text{LiN(dms)}_2 \xrightarrow{\text{hexane}} [\text{Sc(N(dms)}_2)_3 \text{THF}] 73
\]

\[
[\text{Sc(N(dms)}_2)_3 \text{THF}] 73 + \text{toluene} \rightarrow \text{Bu}(\text{S,S}) 29 \xrightarrow{\text{Bu}} \text{Sc} + \text{N(SiHMe}_2)_2
\]

\[
\frac{\text{OH}}{\text{Ac}} + \text{OAc} \xrightarrow{2\text{ mol% 74, toluene}} \xrightarrow{-1^\circ\text{C, 17 h}} \text{OAc}
\]

Scheme 26. Synthesis of Salen-Scandium Complex 74 and Salen-Scandium Complex 74

Catalyzed Acylation of 1-Indanol

The unambiguous ligand-assisted catalysis was also observed in Sc-catalyzed acylation. For example, the acylation of 1-indanol catalyzed by 1 mol% Sc-salen complex 74 at

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room temperature gave 100% conversion (1 h), while \([\text{Sc}(N(SiHMe}_2)_2]_3\text{THF}\) (73) catalyzed (5 mol%) acylation gave only 43% conversion in 22 h.

In the cases of salen-scandium complex 74 and carbene-yttrium complex 72, the electrophilic reaction site (Lewis acid site) is either missing (in 74) or occupied by non-dissociable ligand (carbene). As a result, the enantioselectivity suffers severely in both cases. However, note that the selectivity factor was retained in the presence of external phosphine oxide (Table 20). Therefore, our attention turned to the use excess chiral salen ligand as external additive to examine the enantioselectivity, and results are summarized in Table 21. The different reactivity pattern between in-situ prepared salen-yttrium complex and isolated, well-defined salen-yttrium complex \([(29)Y(N(SiHMe}_2)_2]\text{THF}\) is clearly shown in entry 2 and 3. The former appears to be more reactive. When excess salen ligand 29 with the chirality same as salen-yttrium complex was present in the reaction medium, the conversion was slightly low (53% vs 77%) but the selectivity factor was the same (entry 3, 4, 6, 7). However, no enantioselectivity \((k_{el} = 1.1)\) was found in the presence of salen ligand 29' of the opposite chirality compared to salen-yttrium complex (entry 5). In this regard, we are forced to reconsider whether this stereochemically well-defined salen-yttrium complex \([(29)Y(N(SiHMe}_2)_2]\text{THF}\) has sufficient structural rigidity throughout the reaction.

As mentioned earlier, phenolic hydroxyl group was not acylated during yttrium-catalyzed acylation. Furthermore, phenoxide is known to be highly coordinating ligand to yttrium.\(^{20}\) Therefore, the imine group on salen ligand can be conjectured to be the weaker donor among the coordinated atoms.
\[
\begin{align*}
\text{entry} & & \text{Y catalyst (mol\%)} & & \text{additive (mol\%)} & & \text{conv. (\%)} & & %\text{ee}^a; s = k_{rel} \\
1 & & [YN(dms)_2]_3 \text{2THF} (1) & & \text{none} & & 58 & \\
2 & & [YN(dms)_2]_3 \text{2THF} (1) & & (S,S) 29 (1) & & 100 & \\
3 & & (S,S) 41 (1) & & \text{none} & & 76.5 & 91 (R); k_{rel} = 4.8 \\
4 & & (S,S)-\text{Salen-Y 41} (1) & & (S,S) 29 (1) & & 52.7 & 55.9 (R); k_{rel} = 5.14 \\
5 & & (S,S)-\text{Salen-Y 41} (1) & & (R,R) 29' (1) & & 53.7 & 3.5 (S); k_{rel} = 1.1 \\
6 & & (S,S)-\text{Salen-Y 41} (1) & & (S,S) 29 (2) & & 55.4 & 55.5 (R); k_{rel} = 4.42 \\
7 & & (S,S)-\text{Salen-Y 41} (1) & & (S,S) 29 (3) & & 48.2 & 45 (R); k_{rel} = 4.38 \\
\end{align*}
\]

\(a. %\text{ee (HPLC) of recovered alcohol.}\)

Table 21. Salen-Yttrium Complex with Excess External Salen Ligand Catalyzed Acylation of 1-Indanol

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As a result, the imine group bearing chiral source would be readily replaced by strong donors and the resulting yttrium catalyst became achiral even when the phenoxide of the salen is still coordinating to the yttrium (Table 21, entry 5).

Among the chiral pool for asymmetric acylation (Scheme 24), chiral phosphine oxide 71 was examined, but only modest result was obtained in acylation of 1-indanol with \( k_{\text{rel}} = 1.4 \) (Table 18 (continued), entry 23) and \( \alpha \)-methylnaphthalene methanol with \( k_{\text{rel}} = 2.5 \) (Table 19 (continued), entry 20). It was reported that rare earth salen derivatives with excellent solubility in non-polar solvents such as toluene or n-hexane indicate the formation of non-oligomerized products.\(^{19c}\) Most yttrium complexes derived from the chiral ligands in Scheme 24 dissolved well in toluene which was the solvent of choice for acylation. However, [\((71)\text{Y(N(SiHMe}_2\text{)_2})\text{THF}\)] did not dissolve in toluene or hexane, and the resulting acylation was carried out in the mixture of toluene (0.5 mL) and CH\(_2\)Cl\(_2\) (1 mL). Thus far, we are not sure whether [\((71)\text{Y(N(SiHMe}_2\text{)_2})\text{THF}\)] exist in an oligomerized form, and the resulting asymmetric acylation was possibly hampered because of this oligomerized state. There is some uncertainty about the structures of yttrium complexes derived from the chiral ligands in Scheme 24 except for [\((29)\text{Y(N(SiHMe}_2\text{)_2})\text{THF}\)]. Spectroscopic techniques are generally not satisfactory for these compounds. However, literature precedents and established reactivity patterns of the Y-amide precursors give sufficient confidence in formulating the structures of the complexes as described here. Certainly the x-ray structure of the complex 41 further validates these propositions.
4.1 INTRODUCTION

Asymmetric cyanation of carbonyl compounds is of considerable importance because cyano group of cyanohydrin is readily transformed into various functional groups such as carboxylic acid, ester, aldehyde and amine without loss of the optical purity. It was reported that asymmetric addition of trimethylsilyl cyanide (TMSCN) to aldehydes catalyzed by basic (anionic chiral nucleophile) or Lewis acidic (Al, Ti, Sm, V, Y) reagents achieved good enantioselectivity (~90%ee). As can be seen from Figure 11, nucleophile (CN⁻) and electrophile (aldehyde) were orientated at defined position in Shibasaki's bifunctional Al catalyst and Belokon's bimetallic Ti catalyst; as a result, the re-face of aldehyde was exposed to incoming cyanide attack. Belokon's vanadium complex proceeded through the same mechanism as the bimetallic Ti complex. In Oguni's Ti catalyst, the re-face of aldehyde was shielded by tert-butyl group; therefore, cyanide approaching only from the si-face of the activated aldehyde resulted in an R-configuration of the cyanohydrin. Note that facial discrimination of the carbonyl group by the metal is decisive in the enantioselectivity of cyanosilylation of carbonyls.
Figure 11. Selected Examples of Asymmetric Cyanosilylation of Aldehydes
The first addition of TMSCN to carbonyls catalyzed by a chiral nucleophile was reported by Kagan.\textsuperscript{1a,b} Chiral mono-lithium phenolate catalyst derived from BINOL\textsuperscript{1a} or SALEN\textsuperscript{1b} reacted with TMSCN to form pentavalent silicon complex acting as a Lewis acid to coordinate to a carbonyl group and resulted in enantioselective transfer of cyanide to the aldehyde. It was proposed that BMPD-Y\textsubscript{3}(O\textsuperscript{O}Pr\textsubscript{13}O as chiral Lewis acid coordinated to a carbonyl group, and TMSCN reacting via the isocyanosilane form added to the activated aldehyde by the mechanism like "silatropic ene reaction".\textsuperscript{1j} Transhydrocyanation from acetone cyanohydrin to aldehydes and ketones catalyzed by lanthanoid(III) alkoxides has also been reported; but an enantiospecific version of this reaction has not been developed.\textsuperscript{2c}

![Chemical reaction diagram]

**Chiral Catalysts:**

**Matsumoto**\textsuperscript{3d}

**Belokon**\textsuperscript{3c}

**Shibasaki**\textsuperscript{3a,b}

**Figure 12. Examples of Catalytic Asymmetric Cyanosilylation of Ketones**

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In contrast to cyanosilylation of aldehydes, no addition of TMSCN to ketones was observed in the absence of catalyst. It was reported that lithium salts were able to promote the addition of TMSCN to ketones.\textsuperscript{2a,b} \textit{Yb}({CN})\textsubscript{3} with little Lewis acidity was found as an efficient catalyst for cyanosilylation of enolizable ketones.\textsuperscript{2d} Enantioselective cyanosilylation of ketones would provide a straightforward entry toward chiral quaternary \textalpha-\texthyphen{hydroxy carbonyl derivatives; however, catalytic asymmetric synthesis of ketone cyanohydrin met with only limited success (Figure 12). For examples, Matsumoto's chiral titanium alkoxide catalyzed trimethylsilylcyanation of acetophenone was carried out under high pressure (0.8 GPa) with 5-93\% yields and ee up to 60\%.\textsuperscript{3d} Belokon's bimetallic Ti complex was the first transition metal based catalyst (0.5 mol\%) for asymmetric addition of TMSCN to ketones at atmospheric pressure with ee up to 72\%.\textsuperscript{3c} To date, Shibasaki's bifunctional catalyst (10 mol\%) containing titanium and phosphine oxide gives the best results in asymmetric cyanosilylation of aromatic ketones with 72-89\% yields and 69-95\%ee, and of aliphatic ketones with 72-92\% yields and 76-91\%ee.\textsuperscript{3b}

4.2 \textbf{SALEN-YTTRIUM COMPLEX CATALYZED TRIMETHYLSILYLICYANATION OF KETONES}

As mentioned, \{BMPD (1 mol\%)-Y\textsubscript{3}(O\textsuperscript{17}Pr\textsubscript{13}O (1 mol\%)] was an efficient catalyst for cyanosilylation of benzaldehyde at -78 °C using slow addition technique with 98\% yield and 90\%ee. Salen-yttrium complex 41 was also an active catalyst for
cyanosilylation of benzaldehyde; however, the reaction of benzaldehyde (1 mmol) and TMSCN (1 mmol) in toluene (0.5 mL) for 21 h at ambient temperature afforded α-hydroxyphenylacetonitrile (83%) even in the absence of catalyst. Thus a background reaction is likely to be a significant problem in aldehyde additions. Therefore, our earlier attempts to explore salen-yttrium in this arena focused on cyanosilylation of ketones.

\[
\begin{align*}
\text{Ph-\text{CH}_3} & \quad + \quad \text{TMSCN} \quad \xrightarrow{\text{Y catalyst}} \quad \text{OTMS Ph-\text{\text{CH}_3}} \\
(42)
\end{align*}
\]

<table>
<thead>
<tr>
<th>Y catalyst (mol%)</th>
<th>time</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>36.5 h</td>
<td>NR</td>
</tr>
<tr>
<td>Y(N(dms)(_2))(_2)(_3) 2THF (2)</td>
<td>23 h 40 min</td>
<td>99</td>
</tr>
<tr>
<td>Y(_5)(O(\text{Pr})(_3))(_3)O (1)</td>
<td>23 h 20 min</td>
<td>88</td>
</tr>
<tr>
<td>Y(_5)(O(\text{Pr})(_3))(_3)O (1)</td>
<td>38.5 h</td>
<td>99+</td>
</tr>
</tbody>
</table>

Yttrium complexes unambiguously showed catalytic ability in trimethylsilylcyanation of acetophenone (eq 42). A study of solvent effect shown in Table 22 revealed that the salen-yttrium complex (41)-catalyzed reaction proceeded slightly slower in polar solvent such as CH\(_2\)Cl\(_2\) (30 h, 82%), Ether (31 h, 98%) and THF (30.3 h, 92%), and hexane (12.3 h, 100%) seemed to be the solvents of choice in terms of reactivity. A low temperature reaction done in toluene showed no enantioselectivity (eq 43). The results of other chiral yttrium complex-catalyzed trimethylsilylcyanation of acetophenone are summarized in Table 23. The reactivity dependent on the flexibility of the ligand backbone was observed (Table 22, entry 5 vs Table 23, entry 1).
The reactions were carried out with acetophenone (1 mmol) and TMSCN (1 mmol) in solvent (1.5 mL) at room temperature.

**Table 22. Solvent Effect in Salen-Yttrium Complex (41)-Catalyzed Trimethylsilylcyanation of Acetophenone**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>time</th>
<th>conversion (%)</th>
<th>%ee of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hexane</td>
<td>12 h 20 min</td>
<td>100</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>30 h</td>
<td>81.9</td>
<td>2.7</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>31 h</td>
<td>97.7</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>30 h 20 min</td>
<td>91.6</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>23.5 h</td>
<td>96</td>
<td>0</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>entry</th>
<th>L: [[L]YN(N(dms)₂)THF] (mo%)</th>
<th>time</th>
<th>conv. (%)</th>
<th>%ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61 (2) Ph Ph</td>
<td>44.5 h</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>61 (2) Bu Bu<code> Bu Bu</code></td>
<td>50.5 h</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>61 (2) Bu Bu<code> Bu Bu</code></td>
<td>4 days</td>
<td>99+</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>64 (2)</td>
<td>48 h</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>64 (2)</td>
<td>53 h</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>64 (2) R<code> R</code></td>
<td>4 days</td>
<td>99+</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>65 (2) R = 4-Me 66</td>
<td>44 h</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>65 (2) R = 2,4,6-Pr 65</td>
<td>49 h</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>65 (2) R = 2,4,6-Pr 65</td>
<td>4 days</td>
<td>99+</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>66 (2)</td>
<td>8 h 15 min</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>66 (2)</td>
<td>22 h</td>
<td>100</td>
<td>4.3</td>
</tr>
<tr>
<td>12</td>
<td>67 (2)</td>
<td>22 h</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>67 (2)</td>
<td>46 h 10 min</td>
<td>89</td>
<td>2.6</td>
</tr>
<tr>
<td>14</td>
<td>67 (2) R = 3,5-Bu 65</td>
<td>69 h</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>68 (2) R = 3,Br,5-Bu 67</td>
<td>9 h</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>68 (2) R = 3-O-Me 68</td>
<td>23 h</td>
<td>97</td>
<td>6.5</td>
</tr>
<tr>
<td>17</td>
<td>68 (2) R = 5-N-O₂ 68</td>
<td>46 h 20 min</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>69 (2)</td>
<td>6 h 50 min</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>69 (2)</td>
<td>22 h 40 min</td>
<td>100</td>
<td>5.8</td>
</tr>
<tr>
<td>20</td>
<td>(((S,S)-Salen)Y(μ-Cl)THF₂ 42 (1)</td>
<td>16 h 20 min</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>(((S,S)-Salen)Y(μ-Cl)THF₂ 42 (1)</td>
<td>47 h 20 min</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>(((S,S)-Salen)Y(μ-Cl)THF₂ 42 (2.6)</td>
<td>18.5 h</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>(((S,S)-Salen)Y(μ-Cl)THF₂ 42 (2.6)</td>
<td>46 h</td>
<td>60</td>
<td>1</td>
</tr>
</tbody>
</table>

The reactions were carried out with acetophenone (1 mmol) and TMSCN (1 mmol) in toluene (1.5 mL) at room temperature.

Table 23. Catalysis of Trimethylsilylcyanation of Acetophenone by Chiral Yttrium Complexes

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The yttrium-catalyzed trimethylsilylcyanation of acetophenone seemed to be sensitive to the electronic properties on the yttrium catalyst (Table 23, entry 10, 12, 15, 18). It is worth mentioning that $[((S,S){\text{-Salen}})Y(\mu-{\text{Cl}}){\text{THF}}_2]$ was ineffective in acylation but active in trimethylsilylcyanation of acetophenone (Table 23, entry 20-23). Not only acetophenone but also other aromatic and aliphatic ketones were examined. The cyanosilylation of ketones with sterically demanding isopropyl group at $\alpha$-carbon of the carbonyl group proceeded smoothly (Table 24, entry 3). The catalytic ability of yttrium complexes varied with the structure of substrates; in particular, substrates with six-membered ring skeleton reacted slowly (Table 24, entry 6 vs 7, 9, 11). As can be seen, bromo, nitro, and chloro functional groups were compatible with the yttrium catalyst (Table 24, entry 4, 5, 12). The reaction of $p$-hydroxyacetophenone (75), $E$-4-phenyl-3-buten-2-one (76) or tert-butylacetoacetate (77) as substrates were complicated. Note that $p$-hydroxyacetophenone (75) with phenol functional group and enolizable tert-butylacetoacetate (77) with 1,3-dicarbonyl skeleton both were strong donor to the yttrium. $^{13}$C NMR spectrum of the crude product revealed TMS and ketone carbonyl signals in the reaction of $p$-hydroxyacetophenone (75). In the reaction of $E$-4-phenyl-3-buten-2-one (76), $^1$H NMR spectrum of the crude product revealed no olefinic hydrogen signal.

\begin{align*}
\text{HO} & \quad \text{Me} \\
75 & \\
\text{Ph} & \quad \text{Me} \\
76 & \\
\text{\begin{bmatrix} \\
\text{Me} & \text{O} & \text{O} & \text{Bu} \\
\text{Me} & \text{O} & \text{Bu} \\
\text{OH} & \text{O} & \text{O} & \text{Bu} \\
\end{bmatrix}} & \quad \text{\begin{bmatrix} \\
\text{Me} & \text{O} & \text{O} & \text{Bu} \\
\text{Me} & \text{O} & \text{Bu} \\
\text{OH} & \text{O} & \text{O} & \text{Bu} \\
\end{bmatrix}}
\end{align*}

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The reactions were carried out with ketone (1 mmol) and TMSCN (1 mmol) in toluene (1.5 mL) at room temperature.

<table>
<thead>
<tr>
<th>entry</th>
<th>ketones</th>
<th>time</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = Me</td>
<td>23.5 h</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>R = Et</td>
<td>35.5 h</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>R = Pr</td>
<td>85 h</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>R’ = Br</td>
<td>17.5 h</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>R’ = NO₂</td>
<td>17.5 h</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>17.5 h</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>16 h 15 min</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>67.5 h</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>17 h 15 min</td>
<td>37</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>38.5 h</td>
<td>100</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>64 h</td>
<td>47</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>61 h</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 24. Salen-Yttrium Complex (41)-Catalyzed Cyanosilylation of Ketones
The reactions were carried out with ketone (1 mmol) and TMSCN (1 mmol) in CH$_2$Cl$_2$ (1 mL) at room temperature.

Table 25. [(71)Y(N(dms)$_2$)THF] Catalyzed Cyanosilylation of Ketones

<table>
<thead>
<tr>
<th>entry</th>
<th>ketones</th>
<th>time (h)</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R$^*$ = Br</td>
<td>4</td>
<td>100 (6.4%ee)</td>
</tr>
<tr>
<td>2</td>
<td>R$^*$ = NO$_2$</td>
<td>4.5</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1.4</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>21.6</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>41.7</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>5.75</td>
<td>100</td>
</tr>
</tbody>
</table>
As mentioned, Shibasaki's Al complex shown in Figure 11 catalyzed cyanosilylation of aldehydes afforded ee up to 98%. Yttrium complex [(71)Y(N(dms)_2)THF] with same chiral phosphine oxide ligand 71 was also an efficient catalyst, and the results are shown in Table 25. Thus far, yttrium complex [(L)Y(N(dms)_2)THF] catalyzed cyanosilylation of ketones was performed in single-portion addition with stoichiometric amount of ketone (1 mmol) and TMSCN (1 mmol); unfortunately, only very little enantioselectivity (%ee <10) was observed for this reaction with these conditions.

4.3 FUTURE PROSPECTS

Chelating carbonyl substrates such as 2-acetylfuran or 2'-methoxyacetophenone could be the substrates of choice to examine whether cyanide transfer proceeded through yttrium. Note that cyanosilylation of carbonyls could be catalyzed by base;\textsuperscript{1a,b} however, N(dms)_2 liberated from chiral yttrium complexes [(L)Y(N(dms)_2)THF] could possibly act as base to promote the reaction. Additionally, the salen ligand liberated from the salen-yttrium complex [(L)Y(N(dms)_2)THF] during acylation could be implicated. If it was the scenario, the reaction probably proceeded through Kagan's mechanism, although the salen-yttrium complex [(L)Y(N(dms)_2)THF] was provided as catalyst in the reaction medium. In any case if a possible involvement of yttrium can be established, ligand modification could be the next issue to be addressed.

The chiral information is inherited from the diamine scaffold in most chiral yttrium complexes with salen-like ligands. As can be seen from Figure 7, the chiral...
diamine backbone induced asymmetric coordination of N(dms)$_2$ potentially acting as Lewis base (nucleophilic site). However, the enantioselectivity of cyanosilylation of carbonyls originate from the facial discrimination of the carbonyls as electrophiles. Scouting yttrium complexes [(L)Y(N(dms)$_2$)THF] with chiral ligand L exerting asymmetric induction on electrophilic site (THF) need to be considered if this mechanism is to be exploited for the addition of cyanide.
CHAPTER 5

SALEN-YTTRIUM COMPLEX-CATALYZED ASYMMETRIC RING OPENING OF MESO EPOXIDES WITH TMSCN AND TMSN₃

5.1 INTRODUCTION

The development of asymmetric ring opening of meso epoxides with TMSCN and TMSN₃ catalyzed by chiral metal complexes has attracted considerable attention because of the synthetic utility of these reactions for the synthesis of valuable chiral building blocks. Examples of chiral Lewis acid catalysis in this arena are shown in Scheme 27. As can be seen, the asymmetric ring opening of meso epoxides with carbon nucleophile (TMSCN) met with only limited success. From a practical standpoint, one limitation is that the application of the protocol require more than 10 mol% chiral source to achieve good enantioselectivity. In contrast, the asymmetric opening of meso epoxides by azide (TMSN₃) are better developed. In Jacobsen's study, the active catalyst in enantioselective opening of meso epoxides by TMSN₃ was in fact a [(salen)CrN₃] complex; and, the reaction is known to proceed through a bimetallic mechanism. In Nugent's study, trimethylsilyl trifluoroacetate was employed as an additive to enhance the Lewis acidity of zirconium alkoxide catalyst.

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Scheme 27. Metal-Catalyzed Asymmetric Ring Opening of Meso Epoxides
Enantioselective opening of cyclohexene oxide with TMSN₃ catalyzed by zirconium alkoxide in the presence of trimethylsilyl trifluoroacetate gave (1S,2S)-1-azido-2-[(trimethylsilyl)oxy]cyclohexane in 86% enantiomeric excess. The enantioselectivity was increased up to 93%ee utilizing the bulkier azide reagent, 'PrMe₂SiN₃.

5.2 SALEN-YTTRIUM COMPLEX-CATALYZED ASYMMETRIC RING OPENING OF MESO EPOXIDES WITH TMSCN

The unique reactivity of chiral salen-yttrium complexes prompted us to explore the ring opening of meso epoxides with cyanotrimethylsilane (TMSCN). A study of solvent effect shown in Table 26 revealed CH₂Cl₂ as the solvent of choice. Note that the reaction in THF afforded the product with different configuration of major enantiomer from other solvents (Table 26, entry 3). From this observation, the existence of the third coordination site on the yttrium of salen-yttrium complex 41' was implicated. In the reaction of TMSCN addition to cyclohexene oxide, all chiral yttrium complexes with salen-like ligands were found to be efficient catalysts (2 mol%) and the results are summarized in Table 27. As can be seen, chiral yttrium complex [(66)Y(N(dms)₂)THF] gave the best result with 41%ee (Table 27, entry 8). Interestingly, the chiral ligand 66, 70 with same axial chirality (R) on the binaphthyl backbone afforded different configuration of products (Table 27, entry 8 vs 12).
In addition, yttrium complex with sulfonamide-Schiff base ligand gave poor selectivity (Table 27, entry 6, 7). \[((^S)-Salen)Y(\mu-Cl)\text{THF}]_2 \text{ 42} \) with higher coordination number was still acidic enough to catalyze the reaction (Table 27, entry 14).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>time</th>
<th>conversion (%)</th>
<th>%ee</th>
<th>configuration of major enantiomer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>11 h 15 min</td>
<td>86</td>
<td>16.4</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>11 h 40 min</td>
<td>99⁺</td>
<td>12.9</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>10 h</td>
<td>99⁺</td>
<td>8.2</td>
<td>(1R, 2S)</td>
</tr>
<tr>
<td>4</td>
<td>Hexane</td>
<td>10 h 40 min</td>
<td>99⁺</td>
<td>6.7</td>
<td>(1S, 2R)</td>
</tr>
</tbody>
</table>

The reactions were carried out with cyclohexene oxide (1 mmol), TMSCN (1 mmol) in indicated solvent (1 mL) at ambient temperature.

*Configuration was determined by chiral GC elution order(tₚ).*¹

Table 26. Solvent Effect in Salen-Yttrium Complex (41')-Catalyzed Epoxide Opening with TMSCN
The reactions were carried out with epoxide (1 mmol) TMSCN (1 mmol) in CH₂Cl₂ (1 mL).

### Table 27. Chiral Yttrium Complex-Catalyzed TMSCN Addition to Cyclohexene Oxide

<table>
<thead>
<tr>
<th>entry</th>
<th>[L] (Y(N(dms)_2))THF</th>
<th>time</th>
<th>conversion (%)</th>
<th>%ee (configuration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29' (R,R)</td>
<td>11 h 15 min</td>
<td>86</td>
<td>16.4 (1S, 2R)</td>
</tr>
<tr>
<td>2</td>
<td>60 (R = 3,5'-Bu 29', R = 3-OMe 60)</td>
<td>9 h 5 min</td>
<td>99</td>
<td>5.7 (1R, 2S)</td>
</tr>
<tr>
<td>3</td>
<td>61 (S,S)</td>
<td>10 h 15 min</td>
<td>99'</td>
<td>16.3 (1R, 2S)</td>
</tr>
<tr>
<td>4</td>
<td>62 (S,S)</td>
<td>8 h 35 min</td>
<td>88</td>
<td>14.8 (1R, 2S)</td>
</tr>
<tr>
<td>5</td>
<td>63 (R = Bu 62', Br 63)</td>
<td>10 h 30 min</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>64 (R = 4-Me 64)</td>
<td>9 h 10 min</td>
<td>100</td>
<td>5.4 (1R, 2S)</td>
</tr>
<tr>
<td>7</td>
<td>65 (R = 2,4,6-Pr 65)</td>
<td>9 h 45 min</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

a. Configuration of major enantiomer was determined by chiral GC elution order (t<sub>R</sub>).

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The reactions were carried out with epoxide (1 mmol) TMSCN (1 mmol) in CH₂Cl₂ (1 mL).

<table>
<thead>
<tr>
<th>entry</th>
<th>L: [(L)Y(N(dms)₂)THF]</th>
<th>time</th>
<th>conversion (%)</th>
<th>%ee (configuration)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>(R)</td>
<td>8 h 40 min</td>
<td>100</td>
<td>41 (1R, 2S)</td>
</tr>
<tr>
<td>9</td>
<td>(R)</td>
<td>9 h 40 min</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>(R)</td>
<td>10 h 15 min</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>R = 3,5-tBu</td>
<td>9 h 20 min</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>R = 3-Bz, 5-tBu</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R = 3-OMe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R = 5-NO₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>(R)</td>
<td>10 h 45 min</td>
<td>100</td>
<td>11.2 (1S, 2R)</td>
</tr>
<tr>
<td>13</td>
<td>(S)</td>
<td>8 h 35 min</td>
<td>99</td>
<td>11.2 (1R, 2S)</td>
</tr>
<tr>
<td>14</td>
<td>(((S,S)-Salen)Y(μ-Cl)THF)₂</td>
<td>9 h 40 min</td>
<td>100</td>
<td>3</td>
</tr>
</tbody>
</table>

The reactions were carried out with epoxide (1 mmol) TMSCN (1 mmol) in CH₂Cl₂ (1 mL).

Table 27. (continued) Chiral Yttrium Complex-Catalyzed TMSCN Addition to Cyclohexene Oxide
The reactions were carried out with epoxide (1 mmol) TMSCN (1 mmol) in CH₂Cl₂ (1 mL).

The reactions were carried out with epoxide (1 mmol) TMSCN (1 mmol) in CH₂Cl₂ (1 mL).

Table 28. Chiral Yttrium Complex-Catalyzed TMSCN Addition to Cyclopentene Oxide

<table>
<thead>
<tr>
<th>entry</th>
<th>L: [(L)Y(N(dms)₂)THF]</th>
<th>time</th>
<th>conversion (%)</th>
<th>%ee (configuration)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[(R,R)N,N-benzyl]</td>
<td>29°</td>
<td>22 h 55 min</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>[(R,R)N,N-benzyl]</td>
<td>29°</td>
<td>47 h 40 min</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>[(R,R)N,N-benzyl]</td>
<td>29°</td>
<td>5 days</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>[(R,R)N,N-benzyl]</td>
<td>65°</td>
<td>24 h</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>[(S)P(O)(OPh)₂]</td>
<td>71°</td>
<td>41 h 40 min</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>[(S)P(O)(OPh)₂]</td>
<td>71°</td>
<td>1 week</td>
<td>86</td>
</tr>
</tbody>
</table>

¹ Configuration of major enantiomer was determined by chiral GC elution order (t<sub>R</sub>).
As can be seen from Table 28 cyclopentene oxide as substrate, the reactivity was dramatically decreased; furthermore, the configuration of major enantiomeric 5-membered-ring product was different from 6-membered-ring product (Table 27, entry 1 vs Table 28, entry 1; Table 27, entry 13 vs Table 28, entry 6). As expected, chiral yttrium complex [(66)Y(N(dms)2)THF] gave the best result with 45%ee (Table 28, entry 4). In the attempted low-temperature reactions shown in eq 44, the enantioselectivity was increased up to 66%ee.

5.3 SALEN-YTTRIUM COMPLEX-CATALYZED ASYMMETRIC RING OPENING OF MESO EPOXIDES WITH TMSN3

Salen-yttrium complex-catalyzed ring opening of epoxides with a heteroatom nucleophile (azide) was slower than the corresponding reaction with carbon nucleophile (cyanide).
The reactions were carried out with epoxide (1 mmol) TMSN₃ (1 mmol) in CH₂Cl₂ (1 mL).

a. %ee was determined by chiral GC (Cyclodex-β).

Table 29. Chiral Yttrium Complex-Catalyzed TMSN₃ Addition to Epoxides
As can be seen from Table 29, \([(66)\text{Y(N(dms)}_2\text{)}\text{THF}]\) was superior to other yttrium complexes in terms of reactivity and enantioselectivity.

5.4 FUTURE WORK

In conclusion, the preliminary results indicated that salen-yttrium complexes hold great promise to make advances in asymmetric ring opening of meso epoxides with carbon-based nucleophile (TMSCN). Up to 66% ee obtained at -10 °C with only 2 mol% loading of \([(66)\text{Y(N(dms)}_2\text{)}\text{THF}]\). Modification of the ligands could lead to improved selectivity in this as yet unsolved problem.
CHAPTER 6

EXPERIMENTAL SECTION

GENERAL

All catalyzed reactions were carried out under an inert atmosphere of nitrogen in a Vacuum Atmosphere drybox, or by Schlenk techniques. Solvents were distilled under nitrogen and stored over 4 Å molecular sieves prior to use. Analytical TLC was done on E. Merck precoated (0.25 mm) silica gel 60 F254 plates. Column chromatography was conducted by using silica gel 40 (Scientific Adsorbents Incorporated, Microns Flash). $^1$H/$^1$C NMR spectra were recorded on a Brucker AM-200, DPX-250, AC-300, and DPX 400 spectrometers in CDCl$_3$. Gas chromatographic analyses were performed on a Hewlett-Packard 5890 equipped with an HP-ultra-1 crosslinked methyl silicone capillary column (25 m length x 0.2 mm i.d.) and an FID detector connected to an HP 3396 integrator. As carrier gas helium was used. The retention times recorded are reported with programmed runs and are indicated under each experiments. In all cases base line separation of the relevant components was observed. GC separations of enantiomers of the amino acid esters were accomplished using Chirasil S-Val on WCOT fused silica (25 m x 0.25 mm, 0.12 mm film thickness) capillary GC column purchased from Chrompack.
GC separations of enantiomers of the product of TMSCN/TMSN₃ addition to meso epoxides and aromatic ketones accomplished using Cyclodex-β capillary GC column. HPLC separation of chiral alcohols was done on Daicel CHIRACEL OD column attached to a uv detection (254 nm) using 'PrOH/hexane solvent system. Baseline separation of isomers was observed under the optimum condition. All yttrium-catalyzed reactions were conducted under a nitrogen atmosphere. Reactions listed in the Table (or Scheme) were carried out with the conditions listed in the footnotes of the Table or indicated in the equations.

6.1 EXPERIMENTAL SECTION OF CHAPTER I

Typical experiment for Table 1

A mixture of alcohol (1 mmol), Y₅(O'Pr)₁₃O (24.1 mg; 0.02 mmol) and isopropenyl acetate (104.5 mg; 1 mmol) in benzene (2 mL) was stirred at room temperature. Reaction time was indicated in the Table. The reaction mixture was analyzed by gas chromatography.

Typical experiment for Table 2

A mixture of alcohol (1 mmol), Y₅(O'Pr)₁₃O (6.2 mg; 0.005 mmol) and enol acetate 3a or 3c (1 mL) was stirred at room temperature. Reaction time was indicated in the Table. The reaction mixture was analyzed by gas chromatography. When the reaction was complete, the reaction mixture was concentrated in vacuo to remove excess vinyl (or
isopropenyl) acetate, and subsequently distilled or filtered through a short column of silica gel. The crude product gave satisfactory $^1$H NMR data.

![Structure 1](image)

1,2-Diacetoxy-1-phenyl-ethane (Table 2, entry 9)

A mixture of 1-phenyl-1,2-ethanediol (138.4 mg; 1 mmol), $\text{Y}_3(\text{O}^{\text{Pr}})^{13}\text{O}$ (12.6 mg; 0.01 mmol) and isopropenyl acetate (1 mL) was stirred for 1.5 h at room temperature, and evaporated in vacuo to give di-acetylated product (99 % GC yield). Oil; $^1$H NMR (300 MHz, CDCl$_3$) δ 2.02 (s, 3 H, -OAc), 2.08 (s, 3 H, -OAc), 4.27 (dd, $J = 7.6, 8$ Hz, 1 H, PhCHCH$_2$), 4.33 (dd, $J = 4.2, 8$ Hz, 1 H, PhCHCH$_2$), 6.00 (dd, $J = 4.2, 7.6$ Hz, 1 H, PhCHCH$_2$), 7.27-7.35 (m, 5 H, Ph); GC (60°C/5min-20°C/min-250°C) $t_R = 12.617$. [MHL-122]

![Structure 2](image)

(E)-1,3-Diphenylallyl acetate (Table 2, entry 10)

A mixture of 1,3-diphenylallyl alcohol (2101.4 mg; 10 mmol), $\text{Y}_3(\text{O}^{\text{Pr}})^{13}\text{O}$ (123.4 mg; 0.1 mmol) and isopropenyl acetate (10 mL) was stirred for 1.5 h at room temperature. Removal of the solvent, followed by flash chromatography on silica gel with ethyl acetate-hexane (1:9) as the eluant, gave 2279 mg (90 % yield) of the allyl acetate. $^1$H NMR (300 MHz, CDCl$_3$) δ 2.15 (a, 3 H), 6.37 (dd, $J = 15.7$ Hz, 6.8 Hz, 1 H), 6.47 (d, $J = 6.7$ Hz, 1 H), 6.66 (d, $J = 15.7$ Hz, 1 H), 7.25-7.43 (m, aromatic); $^{13}$C NMR (75 MHz, [138] Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
Cinnamyl acetate (Table 2, entry 11, 12)

A mixture of cinnamyl alcohol (141.2 mg; 1 mmol), $Y_5(O'Pr)_{13}$O (6.4 mg; 0.005 mmol) and isopropenyl acetate (1 mL; 9.1 mmol) was stirred for 10 min at room temperature. Gas chromatographic analysis showed an exceptionally clean reaction, with nearly quantitative conversion of the starting material. The solvent was evaporated in vacuo to give acetate product as an oil. [MHL-266]

Preparative run using vinyl acetate with 1/2000 equivalents of the catalyst.

A mixture of cinnamyl alcohol (1370.1 mg; 10.2 mmol), $Y_5(O'Pr)_{13}$O (6.2 mg; 0.005 mmol) and vinyl acetate (4 mL; 4.3 equiv.) was stirred for 48 h at room temperature. Flash chromatography, with ethyl acetate-hexane (1:3) as eluant, gave 1287.0 mg (72% yield) of cinnamyl acetate isolated. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.09 (s, 3 H, -COCH$_3$), 4.73 (d, $J$ = 6.4 Hz, 2 H, -CH$_2$OAc), 6.29 (dt, $J$ = 15.9, 6.4 Hz, 1 H, PhCH=CH$^-$), 6.65 (d, $J$ = 15.9 Hz, 1 H, PhCH=CH$^-$), 7.25-7.41 (m, -Ph); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 20.7 (q), 64.8 (t), 123.1 (d), 126.4 (d), 127.9 (d), 128.4 (d), 134.0 (d), 136.1 (s), 170.5 (s); GC (60$^\circ$C/5 min-20$^\circ$C/min-250$^\circ$C) $t_R$ = 13.052. [MHL-267]
(2S,3S)-3-Methyl-3-(4-methylpent-3-enyl)oxiranemethanol acetate (Table 2, entry 13)
A mixture of (2S,3S)-epoxygeraniol (173.0 mg; 1 mmol), Y₅(0Pr)₁₃O (6.2 mg; 0.005 mmol), vinyl acetate (1 mL) was stirred for 5 min at room temperature, and evaporated in vacuo to give quantitative yield of acetate product. ¹H NMR (300 MHz, CDCl₃) δ 2.90 (dd, J = 6, 6 Hz, 1 H), 3.96 (dd, J = 12, 6 Hz, 1 H), 4.22 (dd, J = 12, 6 Hz, 1 H), 5.00 (m, 1 H, C=CH); ¹³C NMR (75 MHz, CDCl₃) δ 16.6 (q), 17.4 (q), 20.5 (q), 23.4 (t), 25.4 (q), 38.1 (t), 59.4 (d), 60.3 (s), 63.2 (t), 123.1 (d), 131.9 (s), 170.5 (s). [MHL-210]

Reactions listed in Scheme 3
A mixture of benzyl alcohol (122 mg; 1 mmol), α-methylbenzyl alcohol (128 mg; 1 mmol), Y₅(OPr)₁₃O (6.3 mg; 0.005 mmol) and vinyl acetate (1 mL; 10.8 mmol) was stirred at room temperature for 5 min. The reaction mixture was analyzed by gas chromatography. [MHL-103]
A mixture of benzyl alcohol (108.9 mg; 1 mmol), α-methylbenzyl alcohol (122.7 mg; 1 mmol), Y₅(OPr)₁₃O (24 mg; 0.02 mmol) and isopropenyl acetate (108.4 mg; 1 mmol) in benzene (2 mL) was stirred at room temperature for 24 h. The reaction mixture was analyzed by gas chromatography. [MHL-36]
A mixture of benzyl alcohol (109.4 mg; 1 mmol), α-methylbenzyl alcohol (122.2 mg; 1 mmol), [Y(thd)₂(OPr)] (10.2 mg; 0.02 mmol) and isopropenyl acetate (108.1 mg; 1
mmol) in benzene (2 mL) was stirred at room temperature for 24 h. The reaction mixture was analyzed by gas chromatography. [MHL-37]

A mixture of benzyl alcohol (109.3 mg; 1 mmol), α-methylbenzyl alcohol (122.1 mg; 1 mmol), Y$_5$(O'Pr)$_3$O (24 mg; 0.02 mmol) and isopropenyl benzoate (167.2 mg; 1 mmol) in benzene (2 mL) was stirred at room temperature for 24 h. The reaction mixture was analyzed by gas chromatography and $^1$H NMR. [MHL-35]

3-OAc 'Butyl cholate (eq 4)

A solution of 'butyl cholate (117.6 mg; 0.25 mmol), Y$_5$(O'Pr)$_3$O (9.3 mg; 0.0075 mmol) in toluene (1 mL), isopropenyl acetate (1 mL) was added. The reaction solution was stirred for 24 h at room temperature. Flash chromatography, with ethyl acetate-hexane (1:1) as eluant, gave 3-OAc 'butyl cholate (117.8 mg, 93% yield). White solid; TLC (EtOAc/hexane (2:3)) $R_f$ = 0.34; $^1$H NMR (300 MHz, CDCl$_3$) δ 3.85 (q, 1 H, HO-C(7)-H), 3.99 (t, 1 H, HO-C(12)-H), 4.57 (m, 1 H, AcO-C(3)-H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 68.3 (d), 72.9 (d), 74.3 (d), 79.9 (s), 170.7 (s), 173.6 (s). [MHL-139]

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3-Hydroxybenzyl acetate (eq 5)

A mixture of 3-hydroxybenzyl alcohol (621.2 mg; 5 mmol), Y5(O"Pr)13O (32.3 mg; 0.026 mmol) and vinyl acetate (5 mL) was stirred for 18 h at room temperature. Flash chromatography, with ethyl acetate-hexane (1:4) as eluant, gave 776.2 mg (93 % yield) of 3-hydroxybenzyl acetate isolated. White solid; TLC (EtOAc/hexane (1:4)) Rf = 0.23; 1H NMR (300 MHz, CDCl3) δ 2.12 (s, 3 H), 5.07 (s, 2 H), 6.18 (s, 1 H), 6.80-6.91 (m, 3 H), 7.22 (t, J = 7.8 Hz, 1 H); 13C NMR (75 MHz, CDCl3) δ 20.9 (q), 66.3 (t), 115.1 (t), 115.3 (d), 120.1 (d), 129.8 (d), 137.3 (s), 156.1 (s), 171.8 (s); GC (60°C/5min-20°C/min-250°C)
t = 13.30. [MHL-208]

(S)-PhCH2CHCO2Et
NHAc

(S)-N-Ac-Phenylalanine ethyl ester (eq 8)

(L)-Phenylalanine ethyl ester (192.3 mg; 1 mmol) and isopropenyl acetate (1 mL, 9.1 mmol) without any catalysts was stirred for 24 h at room temperature. The excess isopropenyl acetate was evaporated in vacuo to give a quantitative yield of the product. 1H NMR (300 MHz, CDCl3) δ 1.22 (t, J = 7 Hz, 3 H, -OCH2CH3), 1.96 (s, 3 H, -NAc), 2.99-3.12 (m, ABX, 2 H, PhCH2CHNHAc), 4.15 (q, J = 7 Hz, 2 H, -OCH2CH3), 4.85 (ddd, J = 7.4, 6, 5.8 Hz, 1 H, PhCH2CHNHAc), 6.04 (d, J = 7.4 Hz, 1 H, PhCH2CHNHAc), 7.10 (dd, J = 7.2, 2 Hz, 2 H, -Ph), 7.19-7.30 (m, 3 H, -Ph); GC (60°C/5min-20°C/min-250°C)
250°C) t_R = 14.35. The absence of any racemization was confirmed by GC analysis of the product on chirasil S-val column where base line separation of enantiomers have been observed on an authentic sample of the racemic product. [MHL-107]

**Reaction of (S)-Phenylalanine ethyl ester with isopropenyl acetate in the presence of Y_3(O^Pr)_{13}O.** A mixture of (L)-Phenylalanine ethyl ester (192.1 mg, 1 mmol), Y_3(O^Pr)_{13}O (6.1 mg, 0.005 mmol) and isopropenyl acetate (1 mL, 9.1 mmol) was stirred for 24 h at room temperature. The excess isopropenyl acetate was removed in vacuo and the product was analyzed by GC and NMR to reveal ~4% conversion into the amide. 1H NMR (300 MHz, CDCl_3) δ 1.21 (t, J = 7 Hz, 3 H, -OCH_2CH_3), 1.48 (s, -NH_2), 2.95 (ABX, v_A = 3.05, v_B = 2.84, J_{AB} = 13.5 Hz, J_{AX} = 5.4 Hz, J_{BX} = 7.8 Hz, 2 H, PhCH_2), 3.68 (dd, J = 5.4, 7.8 Hz, 1 H, PhCH_2CHNH_2), 4.14 (q, J = 7 Hz, 2 H, -OCH_2CH_3), 7.16-7.28 (m, 5 H, -Ph); GC (60°C/5min-20°C/min-250°C) t_R = 12.43. [MHL-106]

(R)-PhCHCO_2Me
\(\text{NHAc}\)

**(R)-N-Acetyl Phenylglycine methyl ester (eq 9)**

A mixture of (R)-Phenylglycine methyl ester (166.7 mg, 1 mmol) and isopropenyl acetate (1 mL, 9.1 mmol) was stirred for 24 h at room temperature without any catalysts, the low boiling components were removed on the pump and the product was analyzed by GC and NMR. 1H NMR (250 MHz, CDCl_3) δ 1.89 (s, 3 H, -NHAc), 3.59 (s, 3 H, -OMe), 5.46 (d, J = 6.6 Hz, 1 H, PhCH_2), 6.56 (d, J = 6.6 Hz, 1 H, -NHAc), 7.19-7.24 (m, 5 H, -Ph); GC (60°C/5min-20°C/min-250°C) t_R = 13.29. [MHL-156]
Reaction of (R)-Phenylglycine methyl ester with isopropenyl acetate in the presence of $Y_3(O'Pr)_{13}O$. A mixture of (R)-Phenylglycine methyl ester (165.4 mg; 1 mmol), $Y_3(O'Pr)_{13}O$ (6.2 mg; 0.005 mmol) and isopropenyl acetate (1 mL, 9.1 mmol) was stirred for 24 h at room temperature, and evaporated in vacuo. Analysis by GC and NMR showed mostly starting material. $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 1.80 (br, 2 H, $-\text{NH}_2$), 3.57 (s, 3 H, $-\text{OMe}$), 4.49 (s, 1 H, PhCH), 7.18-7.25 (m, 5 H, $-\text{Ph}$); GC (60°C/min-20°C/min-250°C) $t_R = 11.16$. [MHL-155]

Benzyl 2-amino-3-O-acetyl-4,6-$O$-benzylidene-2-deoxy-$\alpha$-$D$-glucopyranoside (eq 11)

A mixture of benzyl 2-amino-4,6-$O$-benzylidene-2-deoxy-$\alpha$-$D$-glucopyranoside (177.3 mg; 0.5 mmol), $Y_3(O'Pr)_{13}O$ (18.5 mg; 0.015 mmol), isopropenyl acetate (2 mL) and toluene (1 mL, 9.1 mmol) was stirred for 2 h at room temperature. Isolation of the product by evaporation of the solvent followed by flash chromatography on silica gel with ethyl acetate as eluant, gave 161 mg (82 % yield) of the acetoxy compound. Solid (mp $> 220 \degree$C); TLC (EtOAc) $R_f = 0.3$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.48 (br, NH$_2$), 2.13 (s, 3 H, $-\text{OAc}$), 2.95 (dd, $J = 10.0, 3.6$ Hz, 1 H, H$_2$), 3.56 (dd, $J = 9.5, 9.5$ Hz, 1 H, H$_4$), 3.74 (dd, $J = 10.2, 10.2$ Hz, 1 H, H$_{6\text{ex}}$), 3.96 (ddd, $J = 10.2, 9.5, 4.8$ Hz, 1 H, H$_3$), 4.24 (dd, $J = 10.2, 4.8$ Hz, 1 H, H$_{6\text{ex}}$), 4.66 (ABq, $J_{AB} = 11.7$ Hz, $\Delta v_{AB} = 60.9$ Hz, 2 H, PhCH$_2$O), 4.97 (d, $J = 3.6$ Hz, 1 H, H$_1$), 5.28 (dd, $J = 10.0, 9.5$ Hz, 1 H, H$_3$), 5.49 (s, 1 H, PhCH), 7.31-7.46 (m, aromatic, 2x Ph); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 21.0 (q), 55.5 (d), 144

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A mixture of 2-piperidinemethanol (230.3 mg; 2 mmol), Y$_5$(O'Pr)$_3$O (12.3 mg; 0.01 mmol) and isopropenyl acetate (1 mL; 4.5 equiv.) was stirred for 5 min at room temperature. Gas chromatographic analysis showed an exceptionally clean reaction, with nearly quantitative conversion of the starting material. The solvent was evaporated in vacuo to give O-acylation product as an oil. IR (neat): 1729.9 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) *inter alia* $\delta$ 3.69-3.96 (m, 2 H, ABX, -CH$_2$OAc), 2.96 (m, 1 H, H$_2$), 2.66 (m, 1 H, H$_6$), 2.51 (m, 1 H, H$_6$), 1.94 (s, 3 H, -COCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 20.6 (q), 24.0 (t), 26.0 (t), 28.5 (t), 46.3 (t), 54.9 (d), 68.6 (t), 170.6 (s); GC (60°C/5min-20°C/min-250°C) $t_R = 10.937$. [MHL-268]

Amine oxalate salt preparation: The crude product was dissolved in ethyl acetate and added to a ethyl acetate solution containing oxalic acid dihydrate (251.9 mg; 2 mmol) to form amine oxalate salt. The salt was recrystallized from EtOAc/CHCl$_3$ to give white fine crystals. Anal. Calcd for C$_{10}$H$_{17}$NO$_6$: C, 48.56; H, 6.93; N, 5.67. Found: C, 48.70; H, 6.98; N, 5.72.
Reaction of a 1:1 mixture of alcohol, amine and isopropenyl acetate in the presence of 1 mol% of Y₅(O'Pr)₁₃O (eq 14, Scheme 5)

A mixture of α-methylbenzyl alcohol (122.5 mg; 1 mmol), L-(-)-α-phenylethylamine (121.6 mg; 1 mmol), isopropenyl acetate (107.0 mg; 1 mmol), Y₅(O'Pr)₁₃O (12.2 mg; 0.01 mmol) and benzene (1 mL) was stirred for 4 h at rt. Analysis of the crude product by GC showed the product to be a mixture of amine (31%), the acetate ester (49%), acetone imine of α-phenylethylamine (18%) and <0.1% of the acetamide. ¹H and ¹³C NMR confirmed the structures of the major components. The benzylic proton absorption characteristic of the acetamide (δ 5.08) was absent in the ¹H NMR spectrum. Absence of the signals due to the CH₃C(O)-N in proton (δ 1.91) and carbon (δ 21.63, 169.09) NMR also confirmed the exclusive O-acylation. [MHL-265]

Diisopropenyl terephthalate (9)

A mixture of terephthalic acid (2.7 g), ZnCl₂ (0.5 g) in N-methyl-2-pyrrolidone (15 mL) was charged in a pressure vessel, and liquified propyne (ca 14 mL) was added into the vessel as soon as possible. When the solution temperature was warmed up to rt, the solution was heated at 156 °C. 267 psi for 20 h. The clear red brown solution was obtained after the reaction (no solid). To the solution ether was added, washed with water. The ether solution was concentrated to give pale yellow solid, and followed by Flash chromatography on Florisil with petroleum ether as eluant. The petroleum ether
solution was slowly evaporated to give nice square colorless solid (~0.8 g). Square colorless solid; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 2.06 (s, 6 H, -CH$_3$), 4.85 (s, 4 H, C=CH$_2$), 8.16 (s, 4 H, aromatic); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 19.5 (q, -CH$_3$), 102.5 (t, =CH$_2$), 129.9 (d, -CH), 133.9 (s), 153.0 (s), 163.8 (s, -COOR); GC (50°C/5min-10°C/min-250°C) $t_R$ = 22.63; IR (CHCl$_3$): 3018, 1729, 1215, 769, 669 cm$^{-1}$; HRMS 246.0872 (M$^+$ calcd. for C$_{14}$H$_{14}$O$_4$ 246.0892). [MHL-77]

![Divinyl adipate (10)](image)

**Divinyl adipate (10)**

A mixture of adipic acid (1.75 g; 11.97 mmol), Py$_2$Pd(OAc)$_2$ (0.12 g), TsOH (0.44 g), and vinyl acetate (32 g) was heated at 65 °C for 4.5 h and cooled to rt. To the mixture NaOAc (0.3 g) was added and evaporated (rotatory evaporation). To the mixture hexane (20 mL) was added, and washed with 2% NaOH aqueous solution (10 ml 2x), water (10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated to give 1.1358 g of product. TLC (KMnO$_4$ stain) (EtOAc/hexane (1:4)) $R_f$ = 0.42; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.65-1.70 (m, 4 H, -OC(O)CH$_2$CH$_2$-), 2.36-2.40 (m, 4 H, -OC(O)CH$_2$-), 4.53 (d, J = 6.3 Hz, 2 H), 4.84 (d, J = 13.8 Hz, 2 H), 7.24 (dd, J = 13.8, 6.3 Hz, 2 H, C=CHOCH(O)CH$_2$-); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 32.4 (t), 33.3 (t), 97.5 (t), 141.0 (d), 170.1 (s). [MHL-323]
3-Benzoyloxy-butene (12)

A mixture of benzoic acid (3.7 g; 30 mmol), 3-chlorobutene (2 mL; 19.8 mmol) and DBU (4.5 mL; 30 mmol) in toluene (40 mL) was heated under reflux for 19 h. The solution was cooled to room temperature, washed with water, and dried over MgSO₄. Removal of the solvent, followed by flash chromatography on silica gel with ethyl acetate-hexane (1:19) as eluant, gave the product (2.94 g; 84 % yield). TLC (EtOAc/hexane (1:19)) Rf = 0.23; ^1H NMR (250 MHz, CDCl₃) δ 1.45 (d, J = 6 Hz, 3 H), 5.19 (d, J = 11 Hz, 1 H), 5.34 (d, J = 17 Hz, 1 H), 5.61 (qd, J = 6, 6 Hz, 1 H), 5.97 (ddd, J = 17, 11, 6 Hz, 1 H), 7.43 (dd, J = 7, 7 Hz, 2 H), 7.54 (td, J = 7, 2.8 Hz, 1 H), 8.07 (dd, J = 7, 2.8 Hz, 2 H); ^13C NMR (62.5 MHz, CDCl₃) δ 19.9 (q), 71.4 (d), 115.7 (t), 128.2 (d), 129.4 (d), 130.5 (s), 132.7 (d), 137.6 (d), 165.6 (s); GC (50°C/5 min-100°C/min-250°C) tR = 15.355. [MHL-58]

Di-1-methylallyl terephthalate

A mixture of terephthalic acid (5.0 g; 30 mmol), 3-chlorobutene (8 mL; 70 mmol) and DBU (9 mL; 60 mmol) in toluene (40 mL) was heated under reflux for 17 h. The solution was cooled to room temperature, washed with water, and dried over MgSO₄.
Removal of the solvent, followed by flash chromatography on silica gel with ethyl acetate-hexane (1:19) as eluant, gave the product (6.9 g; 84 % yield). TLC (EtOAc/hexane (1:19)) \( R_f = 0.23 \); \(^1\)H NMR (250 MHz, CDCl\(_3\)) \( \delta 1.42 (d, J = 6 \text{ Hz}, 3 \text{ H}), 5.16 (d, J = 11 \text{ Hz}, 1 \text{ H}), 5.30 (d, J = 16.6 \text{ Hz}, 1 \text{ H}), 5.57 (qd, J = 6, 6 \text{ Hz}, 1 \text{ H}), 5.86-5.99 (m, 1 \text{ H}), 8.07 (s, 2 \text{ H}); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta 19.8 (q), 71.9 (d), 115.9 (t), 129.3 (d), 134.2 (s), 137.3 (d), 164.7 (s); \) GC (50°C/5min-10°C/min-250°C) \( t_R = 23.048 \). [MHL-61]
6.2 EXPERIMENTAL SECTION FOR CHAPTER 2

-2-Amino-1-phenylpropane-1,3-diol (4.0133 g) was added to a cooled rapidly stirred suspension of ethyl 3-amino-3-ethoxyprop-2-enimidate (2.1536 g) in DMF (22.5 mL) under nitrogen. The white suspension was almost completely solubilised before a new solid began to precipitate. The ice-bath was removed immediately, and the mixture was allowed to stir for 3 days at room temperature. The solid (NH₄Cl) was filtered off and the DMF distilled off below 50 °C. A small amount of the residue (6%, v/v) was purified by column chromatography (2-9% MeOH/CH₂Cl₂) and yielded a white crystalline solid which was recrystallized twice from hexane/EtOAc (1.5136 g).

\[ 22^{18} \]

\[ \text{Ph} - \text{O} - \text{N} - \text{N} - \text{Ph} - \text{O} - \text{CH}_2\text{OH} \]

\[ \text{TBSOCH}_2\text{C} - \text{N} - \text{N} - \text{Ph} - \text{CH}_2\text{OTBS} \]

\( ^{1}H \) NMR (300 MHz, CD₃CN) \( \delta \) 2.75 (br, -OH), 3.55 (d, \( J = 1.0 \text{ Hz} \), 2 H, -CH₂-), 3.56-3.74 (ABX, m, 4 H, -CH₂OH), 3.96-4.00 (m, 2 H, -CHN-), 5.44 (d, \( J = 6.5 \text{ Hz} \), 2 H, -OCHPh-), 7.31-7.36 (m, 10 H, aromatic); \( ^{13}C \) NMR (75 MHz, CD₃CN) \( \delta \) 29.1 (t), 64.0 (t), 77.1 (d), 84.5 (d), 126.8 (d), 129.4 (d), 129.9 (d), 141.8 (s), 164.3 (s). [MHL-274]

A mixture of bisoxazoline 22 (544 mg; 1.48 mmol), TBDMSCl (492 mg; 3.26 mmol), and imidazol (534 mg; 7.84 mmol) in DMF (20 mL) was heated to 66 °C for 29 h. Water was added into the mixture, and the product was extracted into ether (3x). The ether...
extracts were combined, washed with water (1x), dried over Na₂SO₄, filtered, and evaporated to give a yellow oil. Residual DMF was removed under vacuum at rt. Flash chromatography of the crude product with 1-3% MeOH/CH₂Cl₂ as eluant, gave a colorless oil¹⁸ (690.9 mg; 79%). TLC (MeOH/CH₂Cl₂ (2:98)) Rₓ = 0.21; ¹H NMR (300 MHz, CDCl₃) δ 0.08 (d, J = 2.5 Hz, 12 H, -SiMe₂'Bu), 0.90 (s, 18 H, -SiMe₂'Bu), 3.57 (s, 2 H, -CH₂-), 3.81 (ABX, Jₓₓ = 3.8 Hz, Jₓₓ = 6.9 Hz, Jₓₓ = 10.2 Hz, Δ νₓₓ = 69.2 Hz, 4 H, -CH₂OTBS), 3.98-4.15 (m, 2 H, -CHN), 5.46 (d, J = 6.4 Hz, 2 H, -OCHPh), 7.25-7.35 (m, 10 H, aromatic); ¹³C NMR (75 MHz, CDCl₃) δ -5.4 (q), 18.2 (s), 25.8 (q), 28.7 (t), 64.7 (t), 76.4 (d), 84.2 (d), 125.6 (d), 127.9 (d), 128.4 (d), 140.8 (s), 162.0 (s).

**Typical experiment for Table 5**

A mixture of Sn(OTf)₂ (10.6 mg; 0.025 mmol) and chiral ligand bisoxazoline 22 (10.1 mg; 0.027 mmol) in CH₂Cl₂ (0.7 mL) was stirred at rt for 50 min. To the solution alcohol (1 mmol) and isopropenyl acetate (121.4 mg; 1.2 mmol) was added, and 1 mL CH₂Cl₂ was used to rinse the vials containing alcohol and isopropenyl acetate. Reaction time was indicated in the Table. The reaction was conducted under nitrogen atmosphere. The solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

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Typical experiment for Table 6

A mixture of Cu(OTf)$_2$ (21.3 mg; 0.059 mmol) and chiral ligand bisoxazoline 22 (21.8 mg; 0.059 mmol) in CH$_2$Cl$_2$ (1.5 mL) was stirred at rt for 50 min. To the solution alcohol (1 mmol) and isopropenyl acetate (0.14 mL; 1.27 mmol) was added, and 0.5 mL CH$_2$Cl$_2$ was used to rinse the vials containing alcohol and isopropenyl acetate. Reaction time was indicated in the Table. The reaction was conducted under nitrogen atmosphere. The solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO$_4$, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

4-Acetoxy-4-phenyl-2-butanone (25) (eq 23)
A mixture of benzaldehyde (109.9 mg; 1 mmol), Cu(OTf)₂ (18.1 mg; 0.05 mmol) and isopropenyl acetate (0.2 mL; 1.8 mmol) in CH₂Cl₂ (1 mL) was stirred at ambient temperature for 2.5 h. The mixture was poured into water (20 mL) and extracted with CH₂Cl₂. The CH₂Cl₂ solution was washed with water, saturated NaHCO₃(aq), saturated NaCl(aq) and dried over MgSO₄. Removal of the solvent, followed by flash chromatography on silica gel with ethyl acetate-hexane (1:3) as the eluant, gave 129.9 mg (63% yield). TLC (EtOAc/hexane (3:7)) Rₜ = 0.28; ¹H NMR (300 MHz, CDCl₃) δ 2.01 (s, 3 H, -Me), 2.12 (s, 3 H, -Me), 2.95 (ABX, Jₓₓ = 8.7 Hz, Jₓₓ = 4.9 Hz, Jₓₓ = 16.7 Hz, ΔJₓₓ = 88.5 Hz, 2 H, PhCHCH₂), 6.17 (dd, J = 8.7, 4.9 Hz, 1 H, PhCHCH₂), 7.28-7.34 (m, 5 H, aromatic); ¹³C NMR (75 MHz, CDCl₃) δ 20.9 (q), 30.3 (q), 49.6 (t), 71.4 (d), 126.3 (d), 128.1 (d), 128.5 (d), 139.6 (s), 169.6 (s), 204.5 (s). [MHL-327]

4-Benzoyl-4-phenyl-2-butanone (26)(eq 24)

A mixture of benzaldehyde (213.1 mg; 2 mmol), Cu(OTf)₂ (9.4 mg; 0.026 mmol) and isopropenyl benzoate (329.2 mg; 2 mmol) in CH₂Cl₂ (1 mL) was stirred at ambient temperature for 2 h. The mixture was poured into water (20 mL) and extracted with CH₂Cl₂. The CH₂Cl₂ solution was washed with water, saturated NaHCO₃(aq), saturated NaCl(aq) and dried over MgSO₄. Removal of the solvent, followed by flash chromatography on silica gel with ethyl acetate-hexane (1:4) as the eluant, gave 226.9 mg (42% yield). TLC (EtOAc/hexane (1:4)) Rₜ = 0.23; ¹H NMR (300 MHz, CDCl₃) δ 2.18

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(S, 3 H, -C(O)Me), 3.13 (ABX, J_{AX} = 5.1 Hz, J_{BX} = 8.4 Hz, J_{AB} = 16.6 Hz, \Delta \nu_{AB} = 94.9 Hz, 2 H, PhCH(OBz)CH_2-), 6.47 (dd, J = 8.4, 5.1 Hz, 1 H, PhCH(OBz)CH_2-), 7.29-7.55 (m, 8 H, aromatic), 8.03-8.07 (m, 2 H, aromatic); \textsuperscript{13}C NMR (75 MHz, CDCl_3) \delta 30.3 (q), 49.9 (t), 72.2 (d), 126.3 (d), 128.1 (d), 128.2 (d), 128.5 (d), 129.5 (d), 129.8 (s), 132.9 (d), 139.6 (s), 165.2 (s), 204.5 (s); Anal. Calcd for C_{17}H_{16}O_3: C, 76.10; H, 6.01. Found: C, 76.63; H, 6.00. [MHL-346]

![Methyl-4-oxo-2-phenyl-1,3-dioxin](image)

6-Methyl-4-oxo-2-phenyl-1,3-dioxin (27)(eq 25)

A mixture of benzaldehyde (112.4 mg, 1.06 mmol), Cu(OTf)_2 (18.2 mg, 0.05 mmol) and diketene (0.1 mL, 1.30 mmol) in CH_2Cl_2 (1 mL) was stirred at ambient temperature for 2 h. The mixture was poured into water (20 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with water, saturated NaHCO_3(aq), saturated NaCl(aq) and dried over MgSO_4. Removal of the solvent, followed by flash chromatography on silica gel with ethyl acetate-hexane (1:4) as the eluant, gave 48.4 mg (25.5% yield). TLC (EtOAc/hexane (1:4)) R_f = 0.18; \textsuperscript{1}H NMR (300 MHz, CDCl_3) \delta 2.09 (s, 3 H, -Me), 5.41 (s, 1 H, HC=C-), 6.38 (s, 1 H, PhCH-), 7.43-7.46 (m, 3 H, aromatic), 7.55-7.59 (m, 2 H, aromatic); \textsuperscript{13}C NMR (75 MHz, CDCl_3) \delta 19.4 (q), 96.3 (d), 99.9 (d), 126.4 (d), 128.5 (d), 130.3 (d), 133.5 (s), 162.1 (s), 172.0 (s). [MHL-338]
Typical experiment for Table 7

A mixture of Ti(OPr)$_4$ (7.4 mg; 0.026 mmol) and chiral ligand bisoxazoline 23 (15.5 mg; 0.026 mmol) in toluene (0.5 mL) was stirred at rt for 30 min. To the solution alcohol (1 mmol) and isopropenyl acetate (0.14 mL; 1.27 mmol) was added, and 1 mL toluene was used to rinse the vials containing alcohol and isopropenyl acetate. Reaction time was indicated in the Table. The reaction was conducted under nitrogen atmosphere. The solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO$_4$, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):

- α-Methylbenzyl alcohol: PrOH/hexanes (3/97), flow rate 1 mL min$^{-1}$
- α-Methylnaphthalene methanol: PrOH/hexanes (10/90), flow rate 1 mL min$^{-1}$
- 4-Phenyl but-3-en-2-ol: PrOH/hexanes (10/90), flow rate 0.6 mL min$^{-1}$

![Chemical Structure Image]

$\text{[(S,S)-Salen]Cr(Cl)]}^{24b}$ (35)
A mixture of CrCl₂ (185.5 mg; 1.5 mmol) and (S,S)-salen ligand (547.2 mg; 1 mmol) in THF (10 mL) was stirred at room temperature for 6 h under a nitrogen atmosphere, and saturated NH₄Cl(aq) (10 mL) was added. The resulting solution was exposed to air, stirred for another 6 h, and tert-butyl methyl ether (25 mL) was added. The solution was separated and the organic layer was washed with saturated NH₄Cl(aq) (25 mL 4x), saturated NaCl(aq) (25 mL 2x), dried over Na₂SO₄, and concentrated in vacuo to give [(salen)Cr(Cl)] complex as brown powder²⁴b (512.8 mg). [MHL-532]

(R)-SALBinaphtAlOCH₃²⁵a (36)

AlEt₃ (1.9 M in toluene, 0.24 mL, 0.456 mmol) was added dropwise to a solution of (R)-(+) -Schiff base 30 (247.1 mg, 0.5 mmol) in toluene (2.5 mL). The mixture was stirred for 14 h at room temperature and concentrated in vacuo to dryness. MeOH (distilled from CaH₂ and kept in 4Å MS, 2.5 mL) was added to the solid and the resulting pale yellow suspension was stirred for 6 h at room temperature, filtered, and washed with MeOH. The pale yellow solid²⁵a was dried in vacuo to give 155.3 mg (62% yield). [MHL-508]

![Diagram](image-url)

1,3-Bis(1,2,2,3-tetramethylcyclopentyl)-1,3-propanedione (38)

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To a ice-cold solution of Eu(dcm)$_3$ (23 mg) in ether (10 mL), 5 mL of ice-cold 10% H$_2$SO$_4$ was added. The mixture was stirred for 10 min at -10~0 °C, and the organic solution was separated. The aqueous layer was extracted with ether (10 mL 2x). The combined ether solution was washed with water (10 mL), saturated NaHCO$_3$(aq) (10 mL), saturated NaCl(aq) (10 mL), dried over MgSO$_4$, and concentrated to give the 1,3-dicarbonyl chiral ligand 38 (19.6 mg; >98%). $^1$H NMR (300 MHz, CDCl$_3$) δ 0.63 (s, 6 H, -Me), 0.85 (d, $J$ = 6.6 Hz, 6 H, -CHCH$_3$), 1.03 (s, 6 H, -Me), 1.17 (s, 6 H, -Me), 1.21-1.37 (m, 4 H, -CH$_2$), 1.81-2.00 (m, 4 H, -CH$_2$), 2.32-2.43 (m, 2 H, -CHCH$_3$), 5.68 (s, 1 H, C=CH), 11.44 (s, 1 H, C=C-OH); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 14.5 (q), 18.8 (q), 22.0 (q), 22.3 (q), 28.7 (t), 31.6 (t), 41.7 (d), 45.8 (s), 56.3 (s), 95.9 (d), 199.3 (s). [MHL-295]

A mixture of 1,3-dicarbonyl chiral ligand 38 (95.1 mg; 297.6 μmol) and Y$_5$(O$^t$Pr)$_{13}$O (35.6 mg; 29 μmol) in toluene (0.7 mL) was heated to reflux for 10 min, cooled to ambient temperature, concentrated in vacuo to remove the solvent, and ether was added.
The ether solution was slowly evaporated and completely dried in vacuo to give white foam solid 39. [MHL-296]

Reactions listed in Table 8

A mixture of α-methylbenzyl alcohol (1 mmol), Mn 34 (or Cr 35, Al 36) (0.02 mmol) and isopropenyl acetate (1.27 mmol) in toluene (1.5 mL) was stirred at room temperature.

A mixture of α-methylbenzyl alcohol (1 mmol), Eu(dcm)₃ (0.01 mmol) and isopropenyl (or vinyl) acetate (1 mL) in benzene (2 mL) was stirred at room temperature.

A mixture of α-methylbenzyl alcohol (1 mmol), [(dcm)(O'Pr)] (39) (16 mg or 31.6 mg) and isopropenyl acetate (1.27 mmol) in toluene (1.5 mL) was stirred at room temperature.

The solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):

α-Methylbenzyl alcohol: 'PrOH/hexanes (3/97), flow rate 1 mL min⁻¹

Typical experiment for Table 9

To a mixture of alcohol (1 mmol) and "in-situ prepared" Y-salen complex from Y₅(O'Pr)₁₃O in toluene (1.5 mL) cooled to the indicated temperature, isopropenyl acetate
(0.14 mL; 1.27 mmol) was added. The reaction was conducted under nitrogen atmosphere. The (cooled) solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

Preparation of "in-situ prepared" $Y$-salen complex from $Y_3(O'Pr)_{13}O$: A mixture of $Y_3(O'Pr)_{13}O$ (0.01 mmol) and salen ligand 29 or 30 (0.05 mmol) in toluene (0.7 mL) was heated to reflux for 10 min, cooled to room temperature and concentrated to dryness to get yellow solids to be directly used for transacylation.

Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):

$\alpha$-Methylbenzyl alcohol: 'PrOH/hexanes (3/97), flow rate 1 mL min⁻¹

$\alpha$-Tetralol: 'PrOH/hexanes (1/99), flow rate 0.6 mL min⁻¹

[YCl₃-3THF]

YCl₃ (4109.7 mg, 21.0 mmol) in THF (120 mL) was charged in a 250-mL two-necked flask under an inert atmosphere, and heated to reflux for 1.5 h. The mixture was cooled to room temperature, evaporated to dryness to give white powder (8877.2 mg). By weight difference between YCl₃ and the white THF adduct, the product should be [YCl₃-3THF]. [MHL-388]

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Bis(dimethylsilyl)amido lithium Li\(\text{N(SiHM}_{\text{e}}\text{e})_{\text{2}}\)

1,1,3,3-Tetramethyl disilazane (4.0 g; 30 mmol) in hexane (30 mL) was charged in a 100-mL two-necked flask which was connected with a addition funnel charged with \(^{n}\text{BuLi} (1.6 \text{ M in hexane, 18.0 mL; 28.8 mmol}) under a inert atmosphere. The flask was cooled to -78 °C, and \(^{n}\text{BuLi} was added dropwise over a period of 30 min under vigorous stirring. After complete addition, the white suspension was allowed to warm up to room temperature, stirred for another 2 h, and evaporated to dryness to give a voluminous white powder (4118.4 mg; quantitative yield). \(^{1}\text{H NMR (300 MHz, C}_{6}\text{D}_{6}) \delta 0.21 \text{ (d, } J = 2.9 \text{ Hz, 12 H, -SiHM}_{\text{e}}\text{e}), 4.65 \text{ (m, 2 H, -SiHM}_{\text{e}}\text{e}), \text{ }^{13}\text{C NMR (75 MHz, C}_{6}\text{D}_{6}) \delta 4.6. [MHL-386]

\[\text{[Y(N(SiHM}_{\text{e}}\text{e})_{\text{2}}]_{\text{2}}-2\text{THF} (40)}\]

\(\text{LiN(SiHM}_{\text{e}}\text{e})_{\text{2}}\) (859.3 mg; 6.2 mmol) was added slowly to a suspension of \([\text{YCl}_{3}-3\text{THF}]\) (970.7 mg, 2.4 mmol) in hexane (17 mL). The mixture was stirred for 12 h at room temperature and filtered. The white residue was washed with hexane (10 mL). The hexane solution was concentrated in vacuo to give white solid and crystallized from pentane (1101.4 mg, 74% yield). \(^{1}\text{H NMR (300 MHz, C}_{6}\text{D}_{6}) \delta 0.39 \text{ (d, 36 H, -SiHM}_{\text{e}}\text{e}), 1.36 \text{ (m, 8 H, THF), 3.90 \text{ (m, 8 H, THF), 5.00 \text{ (sept, 6 H, -SiHM}_{\text{e}}\text{e}), \text{ }^{13}\text{C NMR (75 MHz, C}_{6}\text{D}_{6}) \delta 3.8 \text{ (q), 25.7 \text{ (d), 71.2 \text{ (d). [MHL-392]}}\]

\[\text{[(29)Y(N(SiHM}_{\text{e}}\text{e})_{\text{2}}]THF} (41)\]

A mixture of salen ligand 29 (545.7 mg; 1 mmol) and \([\text{Y(N(SiHM}_{\text{e}}\text{e})_{\text{2}}]_{\text{2}}-2\text{THF}] (630.0 mg; 1 mmol) in hexanes (5 mL) and THF (5 mL) was stirred for 5 days at room temperature.
temperature, and concentrated in vacuo to give salen-yttrium complex as solid. The solid was recrystallized from pentane. Anal. Calcd for C_{44}H_{74}N_{3}O_{3}Si_{2}Y: C, 63.05; H, 8.90; N, 5.01. Found (I): C, 61.79; H, 8.63; N, 4.88. Found (II): C, 62.00; H, 8.72; N, 4.33. [MHL-401]

Typical experiment for Table 10

To a mixture of alcohol (1 mmol) and Y catalyst (0.01 mmol) in toluene (1.5 mL) cooled to the indicated temperature, isopropenyl acetate (0.14 mL; 1.27 mmol) was added. The reaction was conducted under nitrogen atmosphere. The (cooled) solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO_{4}, assayed by GC to determine the conversion.

\[([\text{(S,S)-Salen})\text{Y(\text{\textmu-Cl})THF}]_2\] (42)

To a solution of (S,S)-salen ligand (648.3 mg; 1.2 mmol) in THF (17.5 mL), KH (95.4 mg; 2.4 mmol) was added. Bubbling (H_{2(\text{g})}) was observed and the solution color changed from pale yellow to dark golden. After 30 min, YCl_{3} was added into the solution, and the solution turned cloudy pale yellow. The mixture was stirred for 6 h at room temperature, filtered and evaporated to give pale yellow solid (714.7 mg; 81% yield). [MHL-474]

\[(\text{\textsuperscript{t}Bu-Box})\text{Y(N(SiHMMe_{2})_{2})_{2}}\] (43)

To a stirred solution of [Y(N(dms)_{2})_{2}2THF] (315.5 mg; 0.5 mmol) in toluene (5 mL), \textsuperscript{t}Bu-Box (133.8 mg; 0.5 mmol) was added. The mixture was stirred for 12 h at room temperature.

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temperature and evaporated in vacuo. The resulting solids dissolved in 2.5 mL of hexane
and crystallized at -35 °C. ¹H NMR (400 MHz, CD₂J) δ 0.30 (d, J = 3 Hz, 24 H, -
SiHMe₂), 0.82 (s, 18 H, 'Bu), 3.70-3.80 (m, 4 H), 3.88 (dd, J = 8.6, 5.1 Hz, 2 H), 4.64 (s,
1 H), 5.06 (sept, J = 3 Hz, 4 H, -SiHMe₂); ¹³C NMR (100 MHz, CD₂J) δ 3.1, 3.2, 6.0,
34.6, 58.5, 68.2, 74.6, 174.2; Anal. Calcd for C₂₁H₃₇N₂O₂Si₂Y: C, 44.63; H, 8.63; N,
9.05. Found: C, 43.83; H, 8.33; N, 8.27. [MHL-475]

Typical experiment for Table 11

To a mixture of alcohol (1 mmol), [((S,S)-Salen)Y(μ-Cl) THF]₂ (42) (0.01 mmol) and
additive (0.02 mmol) in toluene (1.5 mL), isopropenyl acetate (0.14 mL; 1.27 mmol) was
added. The reaction was conducted under nitrogen atmosphere. The solution was poured
into water (20 mL) and extracted with ether. The ether solution was washed with
saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the
conversion.

To a mixture of alcohol (1 mmol) and [(tBu-Box)Y(N(SiHMe₂)₂)₂] (43) (1 mmol) in
toluene (1.5 mL) cooled to -27 °C, isopropenyl acetate (0.14 mL; 1.27 mmol) was added.
The reaction was conducted under nitrogen atmosphere and stirred for 12 h. The (cooled)
solution was poured into water (20 mL) and extracted with ether. The ether solution was
washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to
determine the conversion, and concentrated in vacuo to remove the solvent. The residue
was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to
give recovered alcohol for further ee(%) determination.

Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):

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1-Indanol: 'PrOH/hexanes (2/98), flow rate 1.1 mL min⁻¹

\[ \text{[Y(OSiPh}_3)_2\text{-THF}_4] \quad (44) \]

To a solution of \([Y(N(dms)_2)_2\cdot2\text{THF}] \) (202.6 mg; 0.32 mmol) in toluene (20 mL), triphenylsilanol (272.6 mg; 0.98 mmol) was added in small portions. The mixture was stirred at rt for 4 days and evaporated to dryness. The residue was washed with pentane and dried in vacuo to give \([Y(OSiPh}_3)_2\text{-THF}_4\] white solid (313.3 mg). [MHL-813]

\[ \text{[Y(OSiPh}_3)_2\text{-THF}_4\] (44)-catalyzed acylation of 1-indanol (eq 34) \]

A mixture of 1-indanol (1 mmol), \([Y(OSiPh}_3)_2\text{-THF}_4\] (44) (22.2 mg) and isopropenyl acetate (1.27 mmol) in toluene (1.5 mL) was stirred at room temperature. The reaction mixture was analyzed by gas chromatography.
6.3 EXPERIMENTAL SECTION OF CHAPTER 3

Typical procedure for kinetic resolution studies (Table 12, eq 35, Table 14, 15, 16):

To a mixture of alcohol (1 mmol) and Y catalyst in toluene (1.5 mL) cooled to the indicated temperature, isopropenyl acetate (0.14 mL; 1.27 mmol) or modified acylating agent (1~1.2 mmol) was added. The reaction was conducted under nitrogen atmosphere. The (cooled) solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):

α-Methylbenzyl alcohol: PrOH/hexanes (3/97), flow rate 1 mL min⁻¹

2-Methyl-1-phenyl-1-propanol: PrOH/hexanes (3/97), flow rate 1 mL min⁻¹

2,2-Dimethyl-1-phenyl-1-propanol: PrOH/hexanes (3/97), flow rate 1 mL min⁻¹

α-Methylnaphthalene methanol: PrOH/hexanes (10/90), flow rate 1 mL min⁻¹

4-Phenyl but-3-en-2-ol: PrOH/hexanes (10/90), flow rate 0.6 mL min⁻¹

α-Tetralol: PrOH/hexanes (1/99), flow rate 0.6 mL min⁻¹

1-Indanol: PrOH/hexanes (2/98), flow rate 1.1 mL min⁻¹

1-(2-Methoxy-phenyl)-ethanol (48): PrOH/hexanes (1/99), flow rate 1 mL min⁻¹

Chiral analysis by GC:

5-Fluoro-2-methyl-indan-1-ol (46): Chiral GC (Chirsil-val-L) (90°C/30min-5°C/min-190°C): tᵣ = 25.132, 25.549; tᵣ = 27.275, 28.162 (cis/trans two sets of enantiomers)
1-(2-Furyl)ethanol (49): Chiral GC (Cyclodex-β) (80°C/20min-1°C/min-180°C): $t_R = 16.923$; $t_R = 17.746$ (two enantiomers).

**Typical experiment for Table 13:**

To a mixture of α-Methylnaphthalene methanol (1 mmol) and Y-salen complex 41 (0.01 mmol) in solvent (listed in the Table) cooled to -3 °C, isopropenyl acetate (1.27 mmol) was added. The reaction was conducted under nitrogen atmosphere and stirred for 7.5 h. The reaction mixture was analyzed by gas chromatography.

**Typical procedure for preparation of enol esters 52, 53, 54, 56:**

A mixture of ketone (pinacolone for 52; acetophenone for 53; 4'-methylacetophenone for 54; cyclohexanone for 56) (0.1 mol), isopropenyl acetate (0.2 mol) and $p$-toluenesulfonic acid (151.3 mg) was heated at 60–90 °C overnight, and then low boiling components were separated by fractional distillation. The residual liquid was cooled and poured into a cold (0-5 °C) mixture of saturated aqueous sodium bicarbonate and pentane. The resulting cold mixture was stirred for 30 min, during which time portions of solid sodium bicarbonate were added periodically until carbon dioxide evolution ceased. The pentane layer was dried, concentrated and distilled to isolate enol acetate. Several distillations (spin distillation) might be required to obtain high purity of enol acetate. The purity of enol acetate was determined by GC.
2-Acetoxy-3, 3-dimethyl-but-1-ene (52): \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.02 (s, 9 H, \(^\text{Bu}\)), 2.09 (s, 3 H, -OAc), 4.55 (d, \( J = 2 \) Hz, 1 H), 4.79 (d, \( J = 2 \) Hz, 1 H); \(^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 20.8 (q), 27.5 (q), 35.8 (s), 98.9 (t), 162.3 (s), 168.9 (s). [lit. 129-130 or 140-141 °C]; [MHL-590]

\( \alpha \)-Acetoxy-styrene (53): \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 2.27 (s, 3 H, -OAc), 5.06 (d, \( J = 2.2 \) Hz, 1 H), 5.51 (d, \( J = 2.2 \) Hz, 1 H), 7.30-7.40 (m, 3 H, aromatic), 7.48-7.52(m, 2 H, aromatic); \(^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 20.7 (q), 101.9 (t), 124.6 (d), 128.3 (d), 128.7 (d), 134.0 (s), 152.7 (s), 168.9 (s). [lit. 80-110 °C, 29 torr]; GC (60°C/5 min-20°C/min-250°C) \( t_R = 10.354 \) [MHL-559]

4'-Methylacetophenon enol acetate (54): The crude mixture was distilled under reduced pressure, and 84-85.5 °C distillate was collected. GC (60°C/5 min-20°C/min-250°C) \( t_R = 11.325 \); \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 2.28 (s, 3 H, 2.36 (s, 3 H), 4.99 (d, \( J = 2.1 \) Hz, 1 H), 5.45 (d, \( J = 2.1 \) Hz, 1 H), 7.17 (d, \( J = 8.2 \) Hz, 2 H), 7.38 (d, \( J = 8.2 \) Hz, 2 H); \(^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 20.9 (q), 21.1 (q), 101.1 (t), 124.7 (d), 129.1 (d), 131.3 (s), 138.9 (s), 152.9 (s), 169.0 (s). [MHL-639]

1-Acetoxy-cyclohexene (56): The crude mixture was distilled under house vacuum, and 96-100.6 °C distillate was collected. GC (60°C/5 min-20°C/min-250°C) \( t_R = 8.220 \); \( ^1H \) NMR (300 MHz, CDCl\(_3\)) \( \delta \) 1.56-1.62 (m, 2 H), 1.70-1.74 (m, 2 H), 2.07-2.14 (m, 4 H), 2.10 (s, 3 H), 5.34-5.37 (m, 1 H); \(^{13}C \) NMR (75 MHz, CDCl\(_3\)) \( \delta \) 21.1 (q), 21.6 (t), 22.6 (t), 23.6 (t), 26.8 (t), 114.0 (d), 148.3 (s), 169.5 (s). [MHL-627]

1-Acetoxy-2-methyl-propene (55): Isobutyraldehyde (36 g; 0.5 mol) was dissolved in Ac\(_2\)O (76.5 g; 0.75 mol) and anhydrous K\(_2\)CO\(_3\) (6 g; 0.063 mol) was added. The mixture
was heated under reflux for 2 h, and cooled to rt. The mixture was washed with water and 5% aqueous NaHCO₃, and dried over MgSO₄. The crude oil was distilled twice. Most low boiling components were distilled off, and the residue was distilled under house vacuum by spin distillation, and 44-45 °C distillate was collected. [lit. 124 °C, 760 mm]

$^1$H NMR (300 MHz, CDCl₃) δ 1.62 (d, $J = 1.6$ Hz, 3 H), 1.66 (d, $J = 1.1$ Hz, 3 H), 2.11 (s, 3 H, -OAc), 6.80-6.83 (m, 1 H); $^{13}$C NMR (75 MHz, CDCl₃) δ 15.5 (q), 19.5 (q), 20.7 (q), 118.1 (s), 129.8 (d), 168.3 (s). [MHL-593]

(1S)-2-Acetoxy-bornene (57): To a solution of (+)-camphor (5.4 g) in THF (50 mL), $^n$BuLi (1.6 M in hex, 25 mL) was added at rt. The solution was stirred at rt for 15 min and cooled to -78 °C and Ac₂O (4.2 mL) was added. The solution was warmed to 0 °C, pentane was added, and saturated aqueous NaHCO₃ was added. The mixture was stirred at 0 °C and clear layer separation was observed. The pentane layer was washed with saturated aqueous NaHCO₃ solution, brine, and dried over MgSO₄. The crude mixture was distilled under reduced pressure, and 48.2-49.3 °C distillate was collected. GC (60°C/5 min-20°C/min-250°C) $t_R = 10.355$; $^1$H NMR (300 MHz, CDCl₃) δ 0.73 (s, 3 H), 0.91 (s, 2x 3 H), 1.06-1.14 (m, 1 H), 1.22-1.30 (m, 1 H), 1.49-1.57 (m, 1 H), 1.79-1.87 (m, 1 H), 2.11 (s, 3 H, -OAc), 2.31 (dd, $J = 3.6, 3.6$ Hz, 1 H), 5.54 (d, $J = 3.6$ Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl₃) δ 9.9 (q), 19.4 (q), 19.8 (q), 21.0 (q), 25.9 (t), 31.1 (t), 49.8 (d), 53.2 (s), 55.9 (s), 114.3 (d), 155.8 (s), 168.6 (s). [MHL-701]

(-)-2-Menthen-2-yloxytrimethylsilane

(3R,6S)-(6-isopropyl-3-methyl-cyclohex-1-enyloxy)-trimethyl-silane

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To a solution of BuLi (1.6 M in hex, 31.25 mL; 0.05 mol) in dry THF (50 mL) at 0 °C
diisopropylamine (7.0 mL; 0.05 mol) was added under nitrogen. The solution was stirred
for 10 min at 0 °C and then cooled to -78 °C. (-)-Menthone (6 g; 0.039 mol) was added
dropwise to the LDA solution. The mixture was stirred for 30 min at -78 °C and then the
temperature was raised to 0 °C. TMSCl (6.35 mL; 0.05 mol) was then added, and the
reaction mixture was stirred for 1 h. The reaction mixture was diluted with pentane and
extracted with ice-cold saturated aqueous NaHCO₃ solution. The organic layer was dried
over MgSO₄ and concentrated to give crude product as a yellow oil. The crude product
was distilled under reduced pressure twice and 51 °C distillate was collected as a
colorless oil. GC (60°C/5 min-20°C/min-250°C) tᵣ = 10.571; ¹H NMR (300 MHz,
CDCl₃) δ 0.18 (s, 9 H, -OTMS), 0.76 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 7 Hz, 3 H), 0.92
(d, J = 6.9 Hz, 3 H), 0.84-1.02 (m, 1 H), 1.27-1.33 (m, 1 H), 1.62-1.75 (m, 2 H), 2.01-
2.04 (m, 1 H), 2.12-2.20 (m, 2 H), 4.68-4.69 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 0.3
(q), 16.8 (q), 20.2 (q), 22.5 (t), 22.9 (q), 27.3 (d), 30.1 (d), 31.6 (t), 44.3 (d), 112.1 (d),
152.1 (s). [MHL-643]

(3R,6S)-6-Isopropyl-3-methylcyclohexen-1-yl acetate (58)
To a solution of (-)-menthone silyl enol ether (2272.8 mg; 10.04 mmol) in DME (10 mL)
and 0 °C, MeLi (1.4 M in Et₂O, 7.6 mL; 10.64 mmol) was added dropwise. The mixture
was stirred for 20 min at 0 °C and Ac₂O (1.1 mL; 11.66 mmol) was added. To the
reaction mixture pentane was added and washed with cold saturated aqueous NaHCO₃
solution. The organic layer was dried over MgSO₄, and evaporated to remove the
solvent. The crude product was distilled under reduced pressure, and 56.5-57.9 °C

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distillate was collected as a colorless oil. GC (60°C/5 min–20°C/min–250°C) \( t_R = 10.804 \); 
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 0.76 (d, \( J = 7 \) Hz, 3 H), 0.87 (d, \( J = 7 \) Hz, 3 H), 0.96 (d, \( J = 7 \) Hz, 3 H), 1.12–1.20 (m, 1 H), 1.32–1.36 (m, 1 H), 1.70–1.88 (m, 3 H), 2.08 (s, 3 H, -OAc), 2.20–2.27 (m, 1 H), 2.41–2.45 (m, 1 H), 5.21–5.23 (m, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 16.8 (q), 19.9 (q), 20.9 (q), 21.7 (q), 22.4 (t), 27.5 (d), 30.0 (d), 30.6 (t), 41.5 (d), 121.9 (d), 150.0 (s), 169.1 (s); Anal. Calcd for C\(_{12}\)H\(_{20}\)O\(_2\): C, 73.43; H, 10.27. Found: C, 71.95; H, 10.29. [MHL-653]

(+)−2-Menthen-2-ylxytrimethylsilane

(3S,6R)-(6-isopropyl-3-methyl-cyclohex-1-enylxy)-trimethyl-silane

GC (60°C/5 min–20°C/min–250°C) \( t_R = 10.565 \); 
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \textit{inter alia} \( \delta \) 0.18 (s, 9 H, -OTMS), 4.68–4.69 (m, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 0.3 (q), 16.8 (q), 20.2 (q), 22.5 (t), 22.9 (q), 27.3 (d), 30.1 (d), 31.6 (t), 44.3 (d), 112.1 (d), 152.1 (s). [MHL-681]

(3S,6R)-6-Isopropyl-3-methylcyclohexen-1-yI acetate (59)

GC (60°C/5 min–20°C/min–250°C) \( t_R = 10.808 \); 
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \textit{inter alia} \( \delta \) 0.78 (d, \( J = 6.8 \) Hz, 3 H), 0.88 (d, \( J = 7.0 \) Hz, 3 H), 0.98 (d, \( J = 7.0 \) Hz, 3 H), 2.09 (s, 3 H, -OAc), 5.21–5.23 (m, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 16.8 (q), 20.0 (q), 20.9 (q), 21.7 (q), 22.4 (t), 27.5 (d), 30.0 (d), 30.6 (t), 41.5 (d), 121.9 (d), 150.0 (s), 169.2 (s). [MHL-694]
(eq 38) A mixture of 1-indanol (1 mmol), (+)-menthone enol acetate (100.5 mg; 0.51 mmol), (-)-menthone enol acetate (100.1 mg; 0.51 mmol) and Y-salen complex 41 (21.1 mg; 0.025 mmol) in toluene (1.5 mL) was stirred for 12 h at -15 °C. The (cooled) solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion.

(eq 39) A mixture of 1-indanol (1 mmol), (-)-menthone enol acetate (1 mmol) and Y-salen complex 41 or Y₅(O'Pr)₁₃O (0.01 mmol) in toluene (1.5 mL) was stirred at room temperature. The solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

*Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):*

1-Indanol: 'PrOH/hexanes (2/98), flow rate 1.1 mL min⁻¹

*Reaction listed in Scheme 18.*

A mixture of 1-indanol (1 mmol), (-)-menthone enol acetate (1 mmol) and Y-salen complex (0.025 mmol) in toluene (1.5 mL) was stirred for 12 h at -15 °C. The (cooled) solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue...
was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

*Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):*

1-Indanol: 'PrOH/hexanes (2/98), flow rate 1.1 mL min⁻¹

*Typical experiment in Table 17*

A mixture of 1-indanol (1 mmol), isopropenyl acetate (1.27 mmol) and Y-salen complex (0.01 mmol) in toluene (1.5 mL) was stirred for 12 h at -25 °C. The (cooled) solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

*Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):*

1-Indanol: 'PrOH/hexanes (2/98), flow rate 1.1 mL min⁻¹
A mixture of \((R,R)-1,2\)-diammonium cyclohexane mono-\((+)-\)tartrate salt (11.2 mmol), \(K_2CO_3\) (22.5 mmol), and distilled water (15 mL) was stirred until dissolution was achieved, and then ethanol (60 mL) was added. The resulting cloudy mixture was heated to reflux, and a solution of \(\text{o-vallin}\) (22.5 mmol) in ethanol (25 mL) was added over 30 min, and the yellow solution was stirred at reflux for 2 h. Water (15 mL) was added and the stirred mixture was cooled to \(\leq 5^\circ\)C over 2 h and maintained at that temperature for 1 additional hour. The crude product was filtered via vacuum filtration, but not many solids were collected. The solid did not dissolve well in \(\text{EtOH}\) and \(\text{CH}_2\text{Cl}_2\). The dark green filtrate was extracted with \(\text{CH}_2\text{Cl}_2\) (3x). The \(\text{CH}_2\text{Cl}_2\) solution was washed with water (2x), brine and dried over \(\text{Na}_2\text{SO}_4\). Removal of the solvent, followed by flash chromatography on silica gel with ethyl acetate-hexane (2:3) as the eluant, gave yellow solids. TLC (EtOAc/hexane (2:3)) \(R_f = 0.23\); \(^1\)H NMR (300 MHz, \(\text{CDCl}_3\)) \textit{inter alia} \(\delta\) 3.28-3.32 (m, 1 H), 3.85 (s, 3 H, OMe), 6.68-6.86 (m, 3 H), 8.23 (s, 1 H), 13.79 (s, 1 H); \(^{13}\)C NMR (75 MHz, \(\text{CDCl}_3\)) \(\delta\) 24.0 (t), 32.9 (t), 56.0 (q), 72.3 (d), 113.9 (d), 117.8 (d), 118.4 (s), 123.1 (d), 148.2 (s), 151.6 (s), 164.7 (d); Anal. Calcd for \(\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4\): C, 69.09; H, 6.85; N, 7.32. Found: C, 69.01; H, 6.94; N, 7.19. [MHL-866]
(61) A mixture of (1S,2S)-(−)-1,2-diphenyl-1,2-diphenyl-1,2-ethanediamine (2 mmol) and 3,5-di-tert-butylsalicylaldehyde (4 mmol) in MeOH (20 mL) was heated to reflux for 2 days and cooled to room temperature, and filtered to give pale yellow solids. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.24 (s, 9 H, tBu), 1.44 (s, 9 H, tBu), 4.74 (s, 1 H), 7.00 (d, $J$ = 2.4 Hz, 1 H), 7.19-7.21 (m, 5 H), 7.32 (d, $J$ = 2.4 Hz, 1 H), 8.42 (s, 1 H), 13.62 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 29.4 (q), 31.4 (q), 34.0 (s), 35.0 (s), 80.1 (d), 117.8 (s), 126.3 (d), 127.1 (d), 127.4 (d), 128.0 (d), 128.2 (d), 136.3 (s), 139.8 (s), 140.0 (s), 157.9 (s), 167.2 (d); Anal. Calcd for C$_{44}$H$_{56}$N$_2$O$_4$: C, 81.94; H, 8.75; N, 4.34. Found: C, 81.80; H, 8.79; N, 4.47. [MHL-636]

(62) A mixture of chiral diamine (0.82 mmol) and 3,5-di-tert-butylsalicylaldehyde (1.65 mmol) in MeOH (20 mL) was heated to reflux for 2 days and cooled to room temperature, and filtered to give yellow solids. Flash chromatography on silica gel with ethyl acetate-hexane (1:19) as the eluant gave yellow solids. TLC (EtOAc/hexane (9:1)) $R_f$ = 0.24; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.25 (s, 18 H, 2tBu), 1.44 (s, 9 H, tBu), 1.48
(s, 9 H, 'Bu), 3.78-3.91 (m, 3 H, H₂/H₃/H₄), 4.09 (dd, J = 10, 9.2 Hz, 1 H, H₆ₓₓ), 4.21-4.29 (m, 1 H, H₃), 4.40 (dd, J = 10, 4.8 Hz, 1 H, H₆ᵧᵧ), 4.76 (ABq, J_ABC = 12.0 Hz, Δν_AB = 67.4 Hz, 2 H, PhCH₂), 4.98 (d, J = 3.6 Hz, 1 H, H₁), 5.59 (s, 1 H, PhCH), 6.99-7.00 (m, 1 H, aromatic), 7.29-7.48 (m, 13 H, aromatic), 8.33 (s, 1 H), 8.37 (s, 1 H), 13.39 (s, 1 H), 13.76 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 29.4 (q, 2 C), 31.4 (q, 2 C), 34.0 (s, 2 C), 35.0 (s, 2 C), 63.3 (d), 67.7 (d), 69.2 (t), 69.7 (t), 71.7 (d), 79.7 (d), 98.1 (d), 101.6 (d), 117.6 (s), 117.8 (s), 126.1 (d), 126.3 (d), 126.6 (d), 127.3 (d), 127.4 (d), 127.9 (d), 128.1 (d), 128.2 (d), 128.4 (d), 128.9 (d), 136.4 (s), 136.7 (s), 136.9 (s), 137.3 (s), 139.9 (s), 140.2 (s), 158.0 (s), 158.4 (s), 168.7 (d), 169.9 (d). [MHL-787]

![Chemical structure](image)

(63) A mixture of chiral diamine (0.8 mmol) and 3-bromo-5-tert-butylsalicylaldehyde (1.6 mmol) in MeOH (8 mL) was heated to reflux for 2 days and cooled to room temperature, and filtered to give yellow solids. ¹H NMR (300 MHz, CDCl₃) δ 1.23 (s, 9 H, 'Bu), 1.25 (s, 9 H, 'Bu), 3.73-3.87 (m, 3 H, H₂/H₃/H₄), 4.08-4.21 (m, 2 H, H₆ₓₓ), 4.34 (m, 1 H, H₆ᵧᵧ), 4.73 (ABq, J_ABC = 12.1 Hz, Δν_AB = 56.9 Hz, 2 H, PhCH₂), 4.93 (d, J = 3.6 Hz, 1 H, H₁), 5.54 (s, 1 H, PhCH), 7.10-7.11 (m, 2 H), 7.26-7.42 (m, 10 H), 7.57 (dd, J = 11.2, 2.3 Hz, 2 H), 8.22 (s, 1 H), 8.24 (s, 1 H), 13.68 (s, 1 H), 13.84 (s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 31.2 (q, 2 C), 34.1 (s, 2 C), 63.3 (d), 68.3 (d), 69.1 (i), 70.0 (t).
71.8 (d), 79.6 (d), 97.9 (d), 101.8 (d), 110.2 (s), 110.6 (s), 118.4 (s), 118.5 (s), 126.1 (d),
127.9 (d), 128.0 (d, 2 C), 128.1 (d), 128.2 (d), 128.5 (d), 129.0 (d), 133.3 (d), 133.6 (d),
136.7 (s), 137.0 (s), 142.6 (s), 143.0 (s), 155.3 (s), 155.9 (s), 167.4 (d), 168.5 (d); Anal.
Calcd for $C_{42}H_{46}Br_2N_2O_5$: C, 60.44; H, 5.56; N, 3.36. Found: C, 60.48; H, 5.59; N, 3.49.

[MLH-871]

(64) Prepared according to the procedure described in the literature$^{14 b}$ without any
changes. $^1$H NMR (300 MHz, CDCl$_3$) inter alia $\delta$ 2.98 (m, 1 H), 3.19 (m, 1 H), 4.56 (d,
$J = 5.9$ Hz, 1 H), 6.98 (d, $J = 2.4$ Hz, 1 H), 7.10 (d, $J = 7.3$ Hz, 2 H), 7.38 (d, $J = 2.4$
Hz, 1 H), 7.63 (d, $J = 7.3$ Hz, 2 H), 8.25 (s, 1 H), 13.02 (s, 1 H); $^{13}$C NMR (75 MHz,
CDCl$_3$) $\delta$ 21.5 (q), 23.7 (t), 24.2 (t), 29.4 (q), 31.5 (q), 32.6 (t), 33.6 (t), 34.1 (s), 35.0 (s),
57.6 (d), 71.8 (d), 117.5 (s), 126.2 (d), 126.9 (d), 127.2 (d), 129.6 (d), 136.4 (s), 137.1 (s),
140.1 (s), 143.0 (s), 157.7 (s), 166.7 (d); Anal. Calcd for $C_{28}H_{40}N_2O_3$: C, 69.38; H, 8.32;
N, 5.78. Found: C, 69.53; H, 8.38; N, 5.75. [MLH-607]
(65) Prepared according to the procedure described in the literature\textsuperscript{14b} without any changes. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \textit{inter alia} \(\delta\) 2.87 (sept, \(J = 6.9\) Hz, 1 H), 3.19 (m, 1 H), 3.45 (m, 1 H), 4.11 (sept, \(J = 6.8\) Hz, 2 H), 4.36 (d, \(J = 5.3\) Hz, 1 H), 7.07 (d, \(J = 2.4\) Hz, 1 H), 7.11 (s, 2 H), 7.38 (d, \(J = 2.4\) Hz, 1 H), 8.37 (s, 1 H), 13.20 (s, 1 H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 23.3 (t), 23.5 (q), 23.7 (t), 24.8 (q), 29.4 (q), 29.7 (d), 30.6 (t), 31.5 (q), 33.0 (t), 34.1 (d), 35.0 (s, 2 C), 56.9 (d), 71.6 (d), 117.7 (d), 123.7 (d), 126.1 (d), 127.2 (d), 133.6 (s), 136.6 (s), 140.1 (s), 149.9 (s), 152.6 (s), 157.9 (s), 166.7 (d). [MHL-606]

![Chemical Structure](image)

(66) A mixture of (\textit{R})-(-)-1,1'-binaphthyl-2,2'-diamine (1 mmol) and 3,5-di-\textit{tert}-butylsalicylaldehyde (2 mmol) in MeOH (10 mL) was heated to reflux for 2 days and cooled to room temperature, and filtered to give solids. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 1.24 (s, 18 H, 2 \textit{tBu}), 7.06 (d, \(J = 2.4\) Hz, 1 H), 7.26-7.36 (m, 3 H), 7.42-7.47 (m, 1 H), 7.59 (d, \(J = 8.8\) Hz, 1 H), 7.95 (d, \(J = 8.2\) Hz, 1 H), 8.05 (d, \(J = 8.8\) Hz, 1 H), 8.67 (s, 1 H), 12.73 (s, 1 H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 29.2 (q), 31.4 (q), 34.0 (s), 34.9 (s), 117.3 (d), 118.2 (s), 125.5 (d), 126.5 (d, 2 C), 126.8 (d), 127.5 (d), 128.1 (d), 129.3 (s), 129.6 (d), 132.5 (s), 133.4 (s), 136.6 (s), 139.8 (s), 144.0 (s), 158.2 (s), 162.7 (d). [MHL-855]
(67) A mixture of (R)-(+)−1,1′-binaphthyl-2,2′-diamine (1 mmol) and 3-bromo-5-tert-
butylsalicylaldehyde (2 mmol) in MeOH (10 mL) was heated to reflux for 2 days and
cooled to room temperature, and filtered to give solids. ¹H NMR (300 MHz, CDCl₃)
δ 1.23 (s, 9 H, 'Bu), 7.17-7.29 (m, 4 H), 7.42-7.49 (m, 2 H), 7.57 (d, J = 8.8 Hz, 1 H),
7.95 (d, J = 8.1 Hz, 1 H), 8.07 (d, J = 8.8 Hz, 1 H), 8.60 (s, 1 H), 12.61 (s, 1 H); ¹³C
NMR (75 MHz, CDCl₃) δ 31.2 (q), 34.0 (s), 110.3 (s), 117.6 (d), 119.4 (s), 125.9 (d),
126.5 (d), 127.0 (d), 128.2 (d), 128.3 (d), 128.8 (s), 130.2 (d), 132.6 (s), 133.3 (s), 133.5
(d), 142.5 (s), 143.9 (s), 155.2 (s), 162.4 (d); Anal. Calcd for C₄₂H₃₈Br₂N₂O₂: C, 66.15;
H, 5.02; N, 3.67. Found: C, 66.07; H, 5.09; N, 3.66. [MHL-865]

(68) A mixture of (R)-(+)−1,1′-binaphthyl-2,2′-diamine (1 mmol) and o-vanillin (2 mmol)
in MeOH (10 mL) was heated to reflux for 2 days and cooled to room temperature, and
filtered to give yellow solids. ¹H NMR (300 MHz, CDCl₃) δ 3.76 (s, 3 H, OMe), 6.69-
6.83 (m, 3 H), 7.16-7.26 (m, 2 H), 7.38-7.44 (m, 1 H), 7.55 (d, J = 8.8 Hz, 1 H), 7.92 (d,
\[ J = 8.2 \text{ Hz, } 1 \text{ H} \), 8.04 \text{ (d, } J = 8.8 \text{ Hz, } 1 \text{ H} \), 8.59 \text{ (s, } 1 \text{ H} \), 12.29 \text{ (s, } 1 \text{ H}) \]; \[^{13}\text{C NMR (75 MHz, CDCl}_3\) \delta 56.0 \text{ (q), 114.5 \text{ (d), 117.7 \text{ (d), 118.1 \text{ (d), 119.3 \text{ (s), 123.9 \text{ (d), 125.7 \text{ (d), 126.4 \text{ (d), 126.8 \text{ (d), 128.3 \text{ (d), 128.6 \text{ (s), 130.1 \text{ (d), 132.5 \text{ (s), 133.2 \text{ (s), 144.4 \text{ (s), 148.0 \text{ (s), 150.9 \text{ (s), 162.9 \text{ (d); Anal. Calcd for C}_{36}\text{H}_{28}\text{N}_{2}\text{O}_6: C, 78.24; H, 5.11; N, 5.07. Found: C, 78.07; H, 5.22; N, 5.19. [MHL-858]}

\[ \text{[MHL-858]} \]

A mixture of \((R)-(+)\)-1,1'-binaphthyl-2,2'-diamine (1 mmol) and 5-nitrosalicylaldehyde (2 mmol) in MeOH (10 mL) was heated to reflux for 2 days and cooled to room temperature, and filtered to give yellow solids. \[^1\text{H NMR (300 MHz, CDCl}_3\) \delta 6.74 \text{ (d, } J = 9.2 \text{ Hz, } 1 \text{ H} \), 7.22-7.36 \text{ (m, } 2 \text{ H) , 7.49-7.55 \text{ (m, } 1 \text{ H) , 7.73 \text{ (d, } J = 8.9 \text{ Hz, } 1 \text{ H) , 8.00-8.09 \text{ (m, } 2 \text{ H) , 8.17-8.23 \text{ (m, } 2 \text{ H) , 8.80 \text{ (s, } 1 \text{ H) , 13.14 \text{ (s, } 1 \text{ H}) ;^{13}\text{C NMR (75 MHz, CDCl}_3\) \delta 116.0 \text{ (d), 118.1 \text{ (d), 118.2 \text{ (s), 126.4 \text{ (d), 126.8 \text{ (d), 127.6 \text{ (d), 128.0 \text{ (d), 128.1 \text{ (d), 128.5 \text{ (d), 130.3 \text{ (s), 130.7 \text{ (d), 133.1 \text{ (s, } 2 \text{ C), 139.8 \text{ (s), 141.9 \text{ (s), 159.6 \text{ (d), 166.3 \text{ (s); Anal. Calcd for C}_{34}\text{H}_{22}\text{N}_{4}\text{O}_6: C, 70.10; H, 3.81; N, 9.62. Found: C, 69.99; H, 3.81; N, 9.50. [MHL-868]}

\[ \text{[MHL-868]} \]

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(70) Prepared according to the procedure described in the literature\textsuperscript{15c} without any changes. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 1.30 (t, \(J = 7.1\) Hz, 12 H, -CH\textsubscript{2}CH\textsubscript{3}), 3.50-3.66 (m, 8 H, -CH\textsubscript{2}CH\textsubscript{3}), 7.16 (d, \(J = 8.1\) Hz, 2 H, aromatic), 7.26-7.37 (m, 4 H, aromatic), 7.85 (d, \(J = 8.1\) Hz, 2 H, aromatic), 7.94 (s, 2 H, aromatic), 8.24 (s, 2 H, -OH); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 13.4 (q), 42.0 (t), 115.9 (s), 122.6 (s), 124.0 (d), 124.7 (d), 127.5 (s), 128.0 (d), 128.2 (d), 128.7 (d), 134.5 (s), 151.1 (s), 170.2 (s). [MHL-918]

(71) Prepared according to the procedure described in the literature\textsuperscript{15d} without any changes. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 3.97 (dd, \(J = 14, 14\) Hz, 2 H), 4.10 (dd, \(J = 14, 14\) Hz, 2 H), 6.93 (d, \(J = 8.4\) Hz, 2 H, aromatic), 7.19 (t, \(J = 7.5\) Hz, 2 H, aromatic), 7.26-7.30 (m, 2 H, aromatic), 7.45-7.57 (m, 12 H, aromatic), 7.71-7.85 (m, 12 H, aromatic), 7.92 (br, 2 H, -OH); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 34.0 (d, \(J = 66.4\) Hz), 117.1, 121.5, 121.6, 123.6, 124.7, 126.4, 127.7, 128.6 (d, \(J = 2.2\) Hz), 128.7 (d, \(J = 2.2\) Hz), 129.0 (d, \(J = 2.2\) Hz), 130.8, 131.0 (d, \(J = 5.9\) Hz), 131.1 (d, \(J = 5.9\) Hz), 131.4 (2 C), 131.8, 132.0,
132.1 (d, J = 2.5 Hz), 132.1 (d, J = 2.4 Hz), 133.2, 151.3, 151.4; $^{31}$P NMR (100 MHz, CDCl$_3$) δ 35.9. [MHL-947]

**General procedure for preparation of Salen-Yttrium complex** [(L)Y(N(SiHMe$_2$)$_2$)THF]

A mixture of chiral ligand L (1 mmol) and [Y(N(SiHMe$_2$)$_2$)$_2$;2THF] (1 mmol) in hexanes (5 mL) and THF (5 mL) was stirred for 5 days at room temperature, and concentrated in vacuo to give salen-yttrium complex as solids. If syrup was obtained after concentration, pentane was added and triturated to give solids.

**Typical experiment in Table 18**

A mixture of 1-indanol (1 mmol), and Y-salen complex [(L)Y(N(SiHMe$_2$)$_2$)THF] in toluene (1.5 mL) was cooled to indicated temperature, and isopropenyl acetate (1.27 mmol) was added. The (cooled) solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO$_4$, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

**Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):**

1-Indanol: 'PrOH/hexanes (2/98), flow rate 1.1 mL min$^{-1}$. 

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Typical experiment in Table 19

A mixture of α-Methylnaphthalene methanol (1 mmol), and Y-salen complex [(L)Y(N(SiHMe₂)₂)THF] in toluene (1.5 mL) was cooled to indicated temperature, and isopropenyl acetate (1.27 mmol) was added. The (cooled) solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):
α-Methylnaphthalene methanol: ‘PrOH/hexanes (10/90), flow rate 1 mL min⁻¹

Typical experiment in Table 20

A mixture of 1-indanol (1 mmol), additive and Y-salen complex [(29')Y(N(SiHMe₂)₂)THF] in toluene (1.5 mL) was cooled to indicated temperature, and isopropenyl acetate (1.27 mmol) was added. The (cooled) solution was poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):
1-Indanol: ‘PrOH/hexanes (2/98), flow rate 1.1 mL min⁻¹
Reactions listed in Scheme 25

1,3-Diisopropylimidazolium chloride

To a suspension of paraformaldehyde (3 g; 0.1 mol) in toluene (17 mL) isopropylamine (5.91 g; 0.1 mol) was added at such a rate that temperature did not exceed 40 °C. When the addition was complete, the mixture was stirred for additional 10 min. The mixture was cooled to 0 °C, and isopropylamine (5.91 g; 0.1 mol) was added dropwise to the cooled mixture. When the second isopropylamine addition was complete, 6N HCl (16.7 mL) was added dropwise over 30 min to the reaction mixture, and the reaction temperature was held below 20 °C. When the HCl addition was complete, the ice bath was removed and the solution was warmed to room temperature. At this temperature, 40% aqueous glyoxal (14.51 g) was added. When the glyoxal addition was complete, the reaction mixture was stirred for an additional 1 h. To the reaction mixture toluene (15 mL) was added, and water was removed by azeotropic distillation (Dean Stark trap). The residue was dried in vacuo to give very hygroscopic 1,3-diisopropylimidazolium chloride as brown solids (quantitative yield). $^1$H NMR (400 MHz, CD$_3$CN) δ 1.56 (d, J = 6.7 Hz, 12 H, -CHMe), 4.75 (sept, J = 6.7 Hz, 2 H, -CHMe$_2$), 7.70 (s, 2 H), 10.03 (s, 1 H); $^{13}$C NMR (100 MHz, CD$_3$CN) δ 23.1, 53.9, 121.4, 135.6. [MHL-1027]
1,3-Diisopropylimidazol-2-ylidene

To a suspension of 1,3-diisopropylimidazolium chloride (6.18 g, 32.7 mmol) in THF (15 mL), oil-free NaH (881 mg) was added. The suspension was stirred for 3 min, and KO'Bu (189 mg) in THF (5 mL) was added as a single portion. The mixture was stirred for 4 h at room temperature and filtered through Celite. The filter cake was washed with THF (25 mL 2x). The filtrate and washes were combined and concentrated in vacuo to give carbene. $^1$H NMR (400 MHz, $d_8$-THF) δ -0.33 (d, $J = 6.8$ Hz, 12 H, -CHMe), 2.71 (sept, $J = 6.8$ Hz, 2 H, -CHMe), 5.22 (s, 2 H). [MHL-1029]

$([(R,R)-Salen]Y(\text{Carbene})\ N(\text{SiHMe}_2)_2]$ (72)

To a solution of $([(R,R)-Salen]Y(\text{N(\text{SiHMe}_2)_2})\text{THF}$ (167.8 mg, 0.2 mmol) in hexane (6 mL), 1,3-diisopropylimidazol-2-ylidene (31.8 mg, 0.2 mmol) in THF (0.7 mL) was added. The mixture was stirred for 24 h at room temperature, and concentrated in vacuo to give 183.6 mg (quantitative yield). [MHL-1035]
[(R,R)-Salen]Y(Carbene) N(SiHMe₂)₂ (72)-catalyzed acylation of 1-indanol: A mixture of 1-indanol (1 mmol) and [(R,R)-Salen]Y(Carbene) N(SiHMe₂)₂ (0.01 mmol) in toluene (1.5 mL) was cooled to -16 °C, and isopropenyl acetate (1.27 mmol) was added. The mixture was stirred for 12 h, poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

*Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):*

1-Indanol: PrOH/hexanes (2/98), flow rate 1.1 mL min⁻¹

*Reactions listed in Scheme 26*

[ScCl₃·THFₓ]₂

To a mixture of ScCl₃·6H₂O (0.8 g) in THF (10 mL), SOCl₂ (5 mL) was added dropwise (an exothermic reaction). The resulting solution was heated under reflux for 8 h and cooled to -20 °C overnight. The white crystals of [ScCl₃·THFₓ] was isolated by decanting, washed with cold (-20 °C) THF (10 mL 3x), concentrated to dryness and taken into a glove box. The white solid was washed with ether (10 mL 3x) and dried in vacuo to give 1310.5 mg. By weight difference between ScCl₃ and the white THF adduct, the product should be [ScCl₃·2.3THF]. [MHL-1015]
[Sc(N(SiHMe₂)₂)₃]THF (73)

To a mixture of [ScCl₃·THF₂₃] (1032.7 mg; 3.3 mmol) in hexane (25 mL), LiN(SiHMe₂)₂ (1228.8 mg, 8.8 mmol) was added in small portions. The resulting mixture was stirred for 12 h at room temperature and filtered. The residue was washed with hexane (15 mL). The hexane solution was concentrated in vacuo and crystallized from pentane to give white solid (1455.3 mg, 87% yield). ¹H NMR (300 MHz, C₆D₆) δ 0.23 (d, J = 3 Hz, 36 H, -SiHMe₂), 1.42 (m, 4 H, THF), 3.97 (m, 4 H, THF), 4.89-4.91 (m, 6 H, -SiHMe₂); ¹³C NMR (75 MHz, C₆D₆) δ 3.4, 25.7, 73.2. [MHL-1016]

[((S,S)-Salen)Sc(N(SiHMe₂)₂)] (74)

A mixture of (S,S)-Salen ligand (274.1 mg; 0.5 mmol) and [Sc(N(SiHMe₂)₂)₃]THF (257.2 mg, 0.5 mmol) in toluene (15 mL) was stirred for 36 h at room temperature, and concentrated in vacuo to give 354.3 mg (98% yield). [MHL-1019]

[[(S,S)-Salen]Sc(N(SiHMe₂)₂)] (74)-catalyzed acylation of 1-indanol: A mixture of 1-indanol (1 mmol) and [((S,S)-Salen)Sc(N(SiHMe₂)₂)] (0.02 mmol) in toluene (1.5 mL) was cooled to -1 °C, and isopropenyl acetate (1.27 mmol) was added. The mixture was

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stirred for 17 h, poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

**Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):**

1-Indanol: 'PrOH/hexanes (2/98), flow rate 1.1 mL min⁻¹

**Typical experiment in Table 21**

A mixture of 1-indanol (1 mmol), additive and Y-salen complex 41 in toluene (1.5 mL) was cooled to -25 °C, and isopropenyl acetate (1.27 mmol) was added. The mixture was stirred for 12 h, poured into water (20 mL) and extracted with ether. The ether solution was washed with saturated NaCl aqueous solution, dried over MgSO₄, assayed by GC to determine the conversion, and concentrated in vacuo to remove the solvent. The residue was purified by column chromatography using hexane/ethyl acetate (4:1) as the eluant to give recovered alcohol for further ee(%) determination.

**Chiral analysis by HPLC (Daicel CHIRALCEL OD, 254 nm):**

1-Indanol: 'PrOH/hexanes (2/98), flow rate 1.1 mL min⁻¹
6.4 EXPERIMENTAL SECTION OF CHAPTER 4

Typical experiment for (eq 42): A mixture of acetophenone (1 mmol), TMSCN (1 mmol), and Y catalyst in toluene (1.5 mL) was stirred at room temperature. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.

Typical experiment for Table 22: A mixture of acetophenone (1 mmol), TMSCN (1 mmol), and Y-salen complex 41 in solvent (1.5 mL) was stirred at room temperature. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.

Typical experiment for (eq 43): A mixture of acetophenone or propiophenone (1 mmol), TMSCN (1 mmol), and Y-salen complex 41 (0.05 mmol) in toluene (1.5 mL) was stirred at -25 °C. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.

Typical experiment for Table 23: A mixture of acetophenone (1 mmol), TMSCN (1 mmol), and Y-salen complex in toluene (1.5 mL) was stirred at room temperature. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.
**Typical experiment for Table 24:** A mixture of ketone (1 mmol), TMSCN (1 mmol), and Y-salen complex in toluene (1.5 mL) was stirred at room temperature. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.

**Typical experiment for Table 25:** A mixture of ketone (1 mmol), TMSCN (1 mmol), and [(71)Y(N(dms)2)THF] (0.02 mmol) in CH₂Cl₂ (1 mL) was stirred at room temperature. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.

\[
\begin{align*}
\text{OTMS} & \quad \text{Ph} & \quad \text{CN} \\
\end{align*}
\]

2-Phenyl-2-trimethylsilanyloxy-acetonitrile

\( ^1H \text{ NMR (300 MHz, CDCl}_3 \) \( \delta \) 0.27 (s, 9 H, -OTMS), 5.54 (s, 1 H), 7.41-7.53 (m, 5 H, aromatic); Chiral GC (Cyclodex B) (90°C/2min-0.1°C/min-190 °C): \( t_R = 133.583; t_R = 134.832 \) (two enantiomers). [MHL-526]

\[
\begin{align*}
\text{OTMS} & \quad \text{Ph} & \quad \text{Me} & \quad \text{CN} \\
\end{align*}
\]

2-Phenyl-2-trimethylsilanyloxy-propionitrile

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$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.22 (s, 9 H, -OTMS), 1.88 (s, 3 H, Me), 7.30-7.45 (m, 3 H, aromatic), 7.57-7.60 (m, 2 H, aromatic); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 1.0 (q), 33.5 (q), 71.5 (s), 121.5 (s), 124.5 (d), 128.6 (d, 2 C), 141.9 (s); Chiral GC (Cyclodex B) (90°C/2min-0.1°C/min-190°C): $t_R = 77.737$; $t_R = 79.210$ (two enantiomers). [MHL-527]

![OTMS](OTMS)

2-Phenyl-2-trimethylsilyloxy-butyronitrile

$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.16 (s, 9 H, -OTMS), 1.00 (t, $J = 7.3$ Hz, 3 H, -CH$_2$CH$_3$), 1.91-2.11 (m, ABX, 2 H, -CH$_2$CH$_3$), 7.30-7.54 (m, 5 H, aromatic); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 0.8 (q), 8.6 (q), 39.1 (t), 76.1 (s), 120.6 (s), 125.0 (d), 128.4 (d), 128.5 (d), 140.8 (s); Chiral GC (Cyclodex B) (110°C/2min-0.1°C/min-190°C): $t_R = 44.847$; $t_R = 45.933$ (two enantiomers). [MHL-560]

![OTMS](OTMS)

3-Methyl-2-phenyl-2-trimethylsilyloxy-butyronitrile

$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.12 (s, 9 H, -OTMS), 0.84 (d, $J = 6.7$ Hz, 3 H), 1.11 (d, $J = 6.7$ Hz, 3 H), 2.13 (sept, $J = 6.7$ Hz, 1 H), 7.35-7.39 (m, 3 H, aromatic), 7.49-7.52 (m, 2 H, aromatic); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 0.7 (q), 17.1 (q), 17.2 (q), 41.4 (d), 80.0 (s),

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119.8 (s), 125.6 (d), 128.2 (d), 128.5 (d), 140.1 (s); Chiral GC (Cyclodex B) (100°C/2min-0.1°C/min-190°C): $t_R = 76.313$, $t_R = 77.682$ (two enantiomers). [MHL-562]

![TMSQ-CN](image)

1-Trimethylsilylxyloxy-indan-1-carbonitrile

$^1$H NMR (300 MHz, CDCl$_3$) δ 0.22 (s, 9 H, -OTMS), 2.42-2.51 (m, 1 H), 2.68-2.77 (m, 1 H), 2.95-3.19 (m, 2 H), 7.27-7.39 (m, 3 H, aromatic), 7.55-7.58 (m, 1 H, aromatic); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 1.1 (q), 29.3 (t), 42.7 (t), 76.4 (s), 120.9 (s), 124.0 (d), 125.1 (d), 127.2 (d), 129.9 (d), 142.0 (s), 142.5 (s). [MHL-563]

![TMSQ-CN](image)

1-Trimethylsilyloxy-1,2,3,4-tetrahydro-naphthalene-1-carbonitrile

$^1$H NMR (300 MHz, CDCl$_3$) δ 0.26 (s, 9 H, -OTMS), 2.01-2.09 (m, 2 H), 2.20-2.27 (m, 1 H), 2.33-2.40 (m, 1 H), 2.83-2.88 (m, 2 H), 7.12-7.15 (m, 1 H, aromatic), 7.27-7.32 (m, 2 H, aromatic), 7.68-7.71 (m, 1 H, aromatic); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 1.2 (q), 18.6 (t), 28.2 (t), 37.6 (t), 69.7 (s), 122.0 (s), 126.5 (d), 127.9 (d), 129.0 (d), 129.2 (d), 135.5 (s), 136.0 (s). [MHL-575]
3-Chloro-2-phenyl-2-trimethylsilylanyloxy-propionitrile

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.19 (s, 9 H, -OTMS), 3.72 (ABq, $J_{AB}$ = 11.3 Hz, $\Delta\nu_{AB}$ = 27 Hz, 2 H, -CH$_2$Cl), 7.41-7.46 (m, 3 H, aromatic), 7.55-7.59 (m, 2 H, aromatic); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 0.8 (q), 52.6 (t), 75.9 (s), 118.8 (s), 125.5 (d), 128.8 (d), 129.7 (d), 137.9 (s); Anal. Calcd for C$_{12}$H$_{16}$NOClSi: C, 56.79; H, 6.35; N, 5.52. Found: C, 57.06; H, 6.21; N, 5.42. [MHL-]

![3-Chloro-2-phenyl-2-trimethylsilylanyloxy-propionitrile](image)

2-(4-Nitro-phenyl)-2-trimethylsilylanyloxy-propionitrile

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.23 (s, 9 H, -OTMS), 1.87 (s, 3 H), 7.71-7.75 (m, 2 H, aromatic), 8.23-8.28 (m, 2 H, aromatic); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 1.0 (q), 33.4 (q), 70.9 (s), 120.6 (s), 123.9 (d), 125.7 (d), 148.0 (s), 148.9 (s); Chiral GC (Cyclodex B) (126°C/2min-0.1°C/min-190°C): $t_R$ = 185.013; $t_R$ = 187.121 (two enantiomers). [MHL-1054]

![2-(4-Nitro-phenyl)-2-trimethylsilylanyloxy-propionitrile](image)

2-(4-Bromo-phenyl)-2-trimethylsilylanyloxy-propionitrile

![2-(4-Bromo-phenyl)-2-trimethylsilylanyloxy-propionitrile](image)
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.20 (s, 9 H, -OTMS), 1.83 (s, 3 H), 7.40-7.44 (m, 2 H, aromatic), 7.50-7.54 (m, 2 H, aromatic); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 1.0 (q), 33.4 (q), 71.0 (s), 121.1 (s), 122.7 (s), 126.3 (d), 131.8 (d), 141.2 (s); Chiral GC (Cyclodex B) (100°C/2min-0.1°C/min-190°C): $t_R = 195.224$; $t_R = 197.550$ (two enantiomers). [MHL-1053]

4-tert-Butyl-1-trimethylsilylloxy-cyclohexanecarbonitrile

$^1$H NMR (300 MHz, CDCl$_3$) inter alia $\delta$ 0.22 (s, 9 H, -OTMS), 0.86 (s, 9 H, 'Bu); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 1.5 (q), 24.3 (t), 27.5 (q), 32.1 (s), 39.8 (t), 46.6 (d), 71.7 (s), 121.5 (s). [MHL-577]

1,7,7-Trimethyl-2-trimethylsilylloxy-bicyclo[2.2.1]heptane-2-carbonitrile

(Two diastereomers): $^1$H NMR (300 MHz, CDCl$_3$) inter alia $\delta$ 0.22 (s, 9 H, -OTMS), 0.24 (s, 9 H, -OTMS); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 1.0 (q, -OSi(CH$_3$)$_3$), 1.2 (q, -OSi(CH$_3$)$_3$), 122.1 (s, -CN), 123.0 (s, -CN). [MHL-1056]
6.5 EXPERIMENTAL SECTION OF CHAPTER 5

*Typical experiment for Table 26:* A mixture of cyclohexene oxide (1 mmol), TMSCN (1 mmol), and Y-salen complex 41 (0.02 mmol) in solvent (1 mL) was stirred at room temperature. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.

*Typical experiment for Table 27:* A mixture of cyclohexene oxide (1 mmol), TMSCN (1 mmol), and [(L)Y(N(dms)2)THF] (0.02 mmol) in CH₂Cl₂ (1 mL) was stirred at room temperature. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.

*Typical experiment for Table 28:* A mixture of cyclopentene oxide (1 mmol), TMSCN (1 mmol), and [(L)Y(N(dms)2)THF] (0.02 mmol) in CH₂Cl₂ (1 mL) was stirred at room temperature. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.

*Reactions listed in eq 44:* A mixture of cyclopentene oxide (1 mmol), TMSCN (1 mmol), and [(66)Y(N(dms)2)THF] (0.03 mmol) in CH₂Cl₂ (1 mL) was stirred at -10 °C for 14 days. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.
A mixture of cyclohexene oxide (1 mmol), TMS CN (1 mmol), and
\([\text{L}6\text{Y}(\text{dms})_2\text{THF}]\) (0.02 mmol) in \(\text{CH}_2\text{Cl}_2\) (1 mL) was stirred at -10 °C for 6 days. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.

**Typical experiment for Table 29:** A mixture of cyclopentene oxide or cyclohexene oxide (1 mmol), TMSN\(_3\) (1 mmol), and \([\text{L}6\text{Y}(\text{dms})_2\text{THF}]\) (0.02 mmol) in \(\text{CH}_2\text{Cl}_2\) (1 mL) was stirred at room temperature. The reaction mixture was passed through a pipet plugged with silica gel and analyzed by gas chromatography.

![Chemical Structure](image)

**2-Trimethylsilyloxy-cyclohexane-1-carbonitrile**

\(^1\text{H NMR (300 MHz, CDCl}_3\) \(\delta\) 0.12 (s, 9 H, -OTMS), 1.12-1.29 (m, 3 H), 1.46-1.71 (m, 3 H), 1.83-1.88 (m, 1 H), 2.02-2.07 (m, 1 H), 2.32-2.40 (m, 1 H), 3.59-3.66 (m, 1 H); \(^{13}\text{C NMR (75 MHz, CDCl}_3\) \(\delta\) -0.0 (q), 23.1 (t), 23.7 (t), 28.0 (t), 34.5 (t), 37.5 (d), 71.0 (d), 121.4 (s); Chiral GC (Cyclodex B) (100°C/30min-1°C/min-180°C): \(t_R = 47.816; t_S = 48.751\) (two enantiomers). [MHL-972]
2-Trimethylsilyloxy-cyclopentane-1-carbonitrile

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.13 (s, 9 H, -OTMS), 1.52-1.97 (m, 5 H), 2.08-2.18 (m, 1 H), 2.57-2.64 (m, 1 H), 4.33 (ddd, $J = 11.7, 5.7, 5.6$ Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ -0.2 (q), 22.1 (t), 28.4 (t), 34.6 (t), 37.5 (d), 77.2 (d), 121.8 (s); Chiral GC (Cyclodex B) (90°C/25min-1°C/min-180°C): $t_R = 38.614$; $t_R = 39.487$ (two enantiomers).

[MLH-1051]

\[
\text{OSiMe}_3
\]

2-Azido-1-(trimethylsiloxy)cyclohexane

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.15 (s, 9 H, -OTMS), 1.15-1.35 (m, 4 H), 1.64-1.70 (m, 2 H), 1.83-1.93 (m, 2 H), 3.13-3.21 (m, 1 H), 3.38-3.46 (m, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 0.1 (q), 23.9 (t), 24.1 (t), 30.5 (t), 34.6 (t), 66.8 (d), 75.2 (d); Chiral GC (Cyclodex B) (100°C/5min-1°C/min-180°C): $t_R = 24.767$; $t_R = 25.567$ (two enantiomers).

[MLH-1058]

\[
\text{OSiMe}_3
\]

2-Azido-1-(trimethylsiloxy)cyclopentane

195

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$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.13 (s, 9 H, -OTMS), 1.50-2.03 (m, 6 H), 3.62 (ddd, $J = 11.9, 6.8, 6.6$ Hz, 1 H), 3.98 (ddd, $J = 11.9, 6.0, 5.4$ Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ -0.1 (q), 20.1 (t), 28.2 (t), 32.5 (t), 68.7 (d), 77.9 (d); Chiral GC (Cyclodex B) (90°C/10min-1°C/min-180°C): t$_R$ = 21.470; t$_R$ = 22.089 (two enantiomers). [MHL-1049]
REFERENCES OF CHAPTER 1:


4. The blank reaction was carried out with benzyl alcohol (108.7 mg; 1 mmol) and vinyl acetate (1 mL) without any catalysts for 24 h at ambient temperature, and no reaction was observed.

14. Acetaldehyde might decrease the enzyme activity in ester interchange of vinyl ester where the side-reaction (aldolization) was observed. (a) Degueil-Castaing, M.; De Jeso, B.; Drouillard, S.; Maillard, B. Tetrahedron Lett. 1987, 28, 953. Aldehyde-trapping agents such as n-butylamine, hydrogen sulphite and 5,5-dimethylcyclohexane-1,3-dione were attempted to reactivate the enzyme. (b) Berger, B.; Faber, K. J. Chem. Soc., Chem. Commun. 1991, 1198.


REFERENCES OF CHAPTER 2:


2. (a) For a leading reference to asymmetric hydrogenation of ketones, see: Noyori, R.;
Hashiguchi, S. Acc. Chem. Res. 1997, 30, 97. (b) Asymmetric hydrogenation of cyclic
enol acetates to chiral acetates: Jiang, Q.; Xiao, D.; Zhang, Z.; Cao, P.; Zhang, X.


19. If vinyl acetate was employed instead of isopropenyl acetate under the same condition in eq 23 (CH$_2$Cl$_2$ as the solvent), slow reaction was observed (19% conversion, 52 h) and complicated mixture was found in 2 weeks.


24. \(((S,S)-\text{Salen})\text{Mn(Cl)}\): (a) available commercially (Aldrich) or prepared according the procedure described in the literature, see: Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. J Org. Chem. 1994, 59, 1939. \(((S,S)-\text{Salen})\text{Cr(Cl)}\):


\[ s = \frac{k_{\text{rel}}}{k_{\text{slow}}} = \frac{\ln [(1-c/100)(1-\text{ee}/100)]}{\ln [(1-c/100)(1+\text{ee}/100)]} \]

\(c\): conversion; \(\text{ee}\): enantiomeric excess of the recovered substrate


29. \([\text{YCl}_{3}\text{THF}_{3}]\) synthesis: (a) Rossmannith, K.; Auer-Welsbach, C. Monatch. Chem. 1965, 96, 602. \(\text{LiN(SiHMe}_{2})_{2}\) synthesis: (b) Eppinger, J.; Herdtweck, E.; Anwander, R. Polyhedron 1998, 17, 1195. \([\text{Y(N(SiHMe}_{2})_{2})_{2}\text{THF}]\) synthesis: (c) Herrmann, W. A.; Münck, F. C.; Artus, G. R. J.; Runte, O.; Anwander, R. Organometallics 1997, 16, 682. \([\text{Salen}]\text{Y(N(SiHMe}_{2})_{2}\text{THF}]\) synthesis: (d) Runte, O.; Priemeier, T.;

30. Structure factors are included in the Appendix.


REFERENCES OF CHAPTER 3:


5. Meanwhile, it will provide a novel efficient method to find out the active chiral complex via probing the extent of asymmetric agostic interaction by computation instead of traditional trial and error method.


9. Enolesters 52, 53, 54, 56: Prepared from ketones (pinacolone, acetophenone, 4'-methylacetophenone, cyclohexanone) according to the procedure described in the


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REFERENCES OF CHAPTER 4:


REFERENCES OF CHAPTER 5:


GC condition: initial temp 60 °C; initial time 5 min; rate 20 °C/min; final temp 250 °C

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**BOL FACTOR=1.000000**

214
GC condition: initial temp 60 °C; initial time 5 min; rate 20 °C/min; final temp 250 °C

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CH₃ | CH₃
---|---
| | 

CH₃OH + CO₂ → 2 mol% Y₂(O₂)₃O₇ benzene, rt; 17.5 h → CH₃OPh + CH₃OPh

21:1

GC condition: initial temp 60 °C; initial time 5 min; rate 10 °C/min; final temp 250 °C

[Table and diagram]

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\[
\text{OAc} + (\text{I}-\text{PhCH}_2\text{CHCO}_2\text{Et}) \xrightarrow{\text{No catalyst}} (\text{I}-\text{PhCH}_2\text{CHCO}_2\text{Et})_{\text{NHAc}}
\]

GC conditions: initial temp 60 °C; initial time 5 min; rate 20 °C/min; final temp 250 °C

*RUN 0109 JAN 22, 1981 23:45:35*

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\text{OAc} + \text{\(\text{H}_{2}\)} \text{\(\text{PhCH}_2\text{CO}_2\text{Et}\)}} \rightarrow \text{\(\text{H}_{2}\)} \text{\(\text{PhCH}_2\text{CO}_2\text{Et}\)}} \\
\text{No catalyst} \longrightarrow \text{\(\text{H}_{2}\)} \text{\(\text{PhCH}_2\text{CO}_2\text{Et}\)}} \text{\(\text{NMe}_2\)} \text{, 24 h, 99.5%} \]

Chiral GC condition: initial temp 160°C; initial time 20 min; rate 5°C/min; final temp 189°C

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Chiral GC data for the mixture of the product and Sigma authentic compound

9.758

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FILE TABLE STOP

Sigma chemical (authentic compound)

9.768 (I)-PhCH=CHCO₂Et

NHaC

FILE TABLE STOP

225
\[
\text{\textnormal{PAC}} + (\text{L})-\text{PhCH}_2\text{CHOO}_2\text{Et} \xrightarrow{0.5 \text{ mol\% } \text{Yb(OAc)}_3\text{MeO}} (\text{L})-\text{PhCH}_2\text{CHOO}_2\text{Et} \xrightarrow{\text{t, 24 h, 9\%}} \text{NHAc}
\]

GC condition: initial temp 60 °C; initial time 5 min; rate 20 °C/min; final temp 250 °C

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SIGNAL FILE: \text{\texttt{MSIGNAL .BMC}}

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&\text{No catalyst} \\
&r, 24\text{h}, 99\% \\
&\Rightarrow (\text{R}-\text{PhCHCOMe})\text{NHAc}
\end{align*}
\]

GC condition: initial temp 60 °C; initial time 5 min; rate 20 °C/min; final temp 250 °C

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&\text{CH}_3 \\
&0.5\text{ mol}\% \text{Yb(OAc)}_2 \\
&r, 25\text{h}, 4\% \\
&\Rightarrow (\text{R}-\text{PhCHCOMe})\text{NHAc}
\end{align*}
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**NUL FACTOR=1.0000E+00**
A two-step reaction is shown with the following reactions:

CH$_3$OH + CH$_3$NBS + CH$_3$CO$_2$H $\rightarrow$ 1 mmol Y$_2$(O$_3$P)$_3$O

in benzene, rt, 4 h

The GC conditions are: initial temp 60 °C; initial time 5 min; rate 20 °C/min; final temp 250 °C

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**TOTAL AREA=3955358 **

**REL FACTOR=1.00000+00 **

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OH
CH₃

OH
CH₃

OD, 3% PrOH/hexanes; 1 mL min⁻¹
23%ee (S)

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</table>

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\[
\begin{align*}
\text{H}_2\text{C}_2\text{OH} + \text{AcO} & \xrightarrow{1 \text{ mol}\% \ Y} \text{H}_2\text{C}_2\text{OAc} \\
\text{CH}_2 & \text{CH} \xrightarrow{-3^\circ \text{C}, 7.5 \text{ h}, 61\%} \text{CH}_2\text{CH}_2\text{CH} = \text{C} = \text{CH}_2 \\
\text{H}_2\text{C}_2\text{OH} & \text{OD, 10\% PrOH/hexanes; 1 mL min}^{-1} \text{36\%ee (S)}
\end{align*}
\]

\[
\begin{align*}
\text{PH} & 1 \text{ AZ} 1 \\
& 3, 4, 4 \text{.1} 4, 4 \text{.5} 6, 6 \text{.4} 11, 1.87
\end{align*}
\]

DATA SAVED TO BIN 37

**FILE** 1  METHOD 0  **RUN** 165  **INDEX** 165  **BIN** 37

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<td>10</td>
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TOTAL 188 183Q0153

**35.81\% ee**
H₂C·OH + \( \text{CH}_3 \) \noop{1.5 \text{ mol}\%} Y\noop{1.0 \text{ \%}} \rightarrow H₂C·OAc

\[ -3^\circ \text{C}, 9 \text{ h}, 88\% \]

OO, 10\% PrOH/hexanes; 1 mL min\(^{-1}\)

60\% ee


FILE 1. METHOD 8. RUN 137 INDEX 116

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TOTAL 100% 38579218

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1. **METHOD**

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**TOTAL**: 1656524
```

**OD, 10% PrOH/hexanes; 1 mL min⁻¹, 15% ee**
OH

\[
\text{Ph} + \text{Ac} \rightarrow \text{PhAc}
\]

1 mol% \( V' \)

-25°C, 12 h, 77%

91% ee (R)

OH

OD, 2% 4PrOH/hexanes; 1.1 mL min\(^{-1}\)

91% ee (R)

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</tbody>
</table>

TOTAL 100. 3963247

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OH \rightarrow Q A c \text{ImoficY^*}

CH\text{\textregistered} \rightarrow 2

$\text{S} \rightarrow \text{12h.40\%}$

OH \rightarrow OH \text{2\% PtOH/hexanes; 1.1 mL min}^{-1}

25\% ee (R)

\text{H1 AZ1}

3.34
4.72
9.44
13.46
12.15

ER 0

FILE 1. METHOD 0. RUN 126 INDEX 105

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TOTAL 100.

9025471

253
OH
\[ \text{HOAc} \]

OD, 2% PrOH/hexanes; 1.1 mL min\(^{-1}\)
85% ee(S)

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TOTAL: 100 ...

84.6% ee (S)

254
OH

\[ \text{OD, 1\% PrOH/hexanes; 0.6 mL min}^{-1} \]
14\% ee

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TOTAL 198, 11304222
OH
-2

RCR*OAc
<3% -OAc

OH

OD, 10% 3PrOH/hexanes; 0.6 mL min⁻¹
13% ee

DATA SAVED TO FILE 81

PEAKS AREA% RT AREA BC
1 8.826 5 56271 02
2 8.869 5.64 129476 02
3 8.476 6.2 965777 02
4 7.193 6.19 668592 02
5 6.32 6.85 387399 02
6 6.019 8.44 5616 02
7 6.003 8.84 5292 02
8 6.004 9.72 7286 03
9 43.736 12.61 67729526 02
10 8.917 14.33 34003 03
11 55.622 18.121 12371361 01

TOTAL 282943565


FILE METH0D RUN INDEX BIN 81

1

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A reaction is shown: \[
\text{Cyclohexylamine} + \text{TMSCHN} \xrightarrow{2 \text{ mol}\% \{\text{KCNdiam} \}_2 \text{THF}} \xrightarrow{\text{CH}_2\text{Cl}_2, -10^\circ\text{C}, 6 \text{ days}} \text{TMSQ} \xrightarrow{25^\circ\text{C}} \text{99\% conversion, 66\% ee (1R, 2S)}
\]

Chiral GC (Cyclodex-β) (100 °C 30 min-1 °C/min-180 °C)

A table shows:

<table>
<thead>
<tr>
<th>RT</th>
<th>AREA</th>
<th>TYPE</th>
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<td>17.98391</td>
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<tr>
<td>48.751</td>
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<td>88</td>
<td>.239</td>
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</table>

**TOTAL AREA= 100760**

**HNR FACTOR=1.0000E+00**

Closing signal file M:SIGNAL BNA

RUN# 075  DEC 31, 1981  10:38:49

SIGNAL FILE: M:SIGNAL.BNA

ARENA

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<td>48.751</td>
<td>83654</td>
<td>88</td>
<td>.239</td>
<td>82.99659</td>
</tr>
</tbody>
</table>

**TOTAL AREA= 100760**

**HNR FACTOR=1.0000E+00**

291
\[ \text{6 + TMSQ} \xrightarrow{3 \text{ mol} \% \text{[6]} 	ext{Y[N(cod)]THF]} \xrightarrow{\text{CH}_2\text{Cl}_2, -10 \degree \text{C}, 14 \text{ days}} \text{TMSQ} \xrightarrow{\text{CN}} 72\% \text{ conversion} \]

Chiral GC (Cyclohex-f) (90 \degree \text{C}/25 \text{ min}^{-1} \degree \text{C/min}^{-1} \degree \text{Cmin}^{-1} \degree \text{C})

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Chiral GC (Cyclodex-f) (100 °C/5 min-1 °C/min-180 °C)
\[
\begin{align*}
\text{CH}_3\text{Cl}_2, \text{rt, 3 days} & \quad \text{TMOS} \quad \text{TMSO} \quad N_3 \\
\begin{array}{c}
\text{2 mol\% [Ru(dms)\text{THF}]} \\
\end{array}
\end{align*}
\]

Chiral GC (Cyclohex-) (60 °C/10 min−1°C/min−180 °C)

Closing signal file M:SIGNAL.BMC

RUN# 988 JAN 13, 1992 10:33:29

SIGNAL FILE: M:SIGNAL.BMC
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TOTAL AREA- 83424
MULT FACTOR-1.88866E+06

11.927% ee
### Crystallographic details for RajanBabu 895

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<td><strong>Wavelength</strong></td>
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<td>c</td>
<td>26.3369(2) Å</td>
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<td><strong>Density (calculated)</strong></td>
<td>1.147 Mg/m³</td>
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<td><strong>Absorption coefficient</strong></td>
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<td><strong>F(000)</strong></td>
<td>1800</td>
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<tr>
<td><strong>Crystal size</strong></td>
<td>0.19 x 0.31 x 0.35 mm</td>
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<td><strong>Theta range for data collection</strong></td>
<td>2.29 to 27.49 deg.</td>
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<td><strong>Index ranges</strong></td>
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<td><strong>Data / restraints / parameters</strong></td>
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<td><strong>R indices (all data)</strong></td>
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<td><strong>Largest diff. peak and hole</strong></td>
<td>0.529 and -0.305 e/Å³</td>
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<td>Bond lengths [Å] and angles [deg] for RajanBabu 895</td>
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Refined isotropically with occupancy factor of 0.63(1).
**Refined isotropically with occupancy factor of 0.37.
*Refined isotropically with occupancy factor of 0.29(1).
*Refined isotropically with occupancy factor of 0.71.

$U_{eq}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.
Anisotropic displacement parameters ($A^2 \times 10^{-3}$) for RajanRabu 895.
The anisotropic displacement factor exponent takes the form:

\[-2 \pi^2 \{ a^{*2} a^{*2} U_{11} + \ldots + 2 b^* a^* b^* U_{12} \}\]

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*Refined isotropically"
The following are responses to the error messages generated by checkcif.

1. Absorption was handled by the Scalepack procedure. See the description in the "_exptl_special_details" section of the cif.

2. The Hirshfeld test for the Y-Si(2) bond appears to fail, as the checkcif procedure is assuming that this is a normal sigma bond. But the Y-Si(2) distance is long and this should not be interpreted as a normal sigma bond.

3. There is some disorder in this structure, as described in the "_refine_special_details" section of the cif. This results in most of the warnings and comments by the checkcif program.

4. The standard uncertainties on the unit cell axes are small, but these are the reported values from the Scalepack program.