CHAPTER-IV

STUDIES ON CHIRAL CATALYSIS EMPLOYING (2S,3S) AND (2S,3R)- TETRAHYDRO-3-HYDROXY-5-OXO-2,3- FURAN DICARBOXYLIC ACIDS

IV.01 Introduction

Enantioselective reduction of prochiral ketones is carried out mostly using aluminium and boron based reagents. A large number of asymmetric catalysts have been prepared based on aluminium and boron hydrides. The chiral (acyloxy) borane (CAB) obtained from optically active hydroxy acid namely tartaric acid and sodium borohydride has been recognized as exceptionally efficient catalysts in the reduction of prochiral ketones. Due to the extreme sensitivity to moisture, these catalysts are normally generated in situ.

IV.02 Asymmetric catalytic reduction

The reduction of prochiral ketones have been accomplished with great success by using metal hydrides modified with chiral compounds such as diol\textsuperscript{121}, amines,\textsuperscript{122} aminoalcohols\textsuperscript{123} and \(\alpha\)-pinene\textsuperscript{124,125} which promises to be a useful tool for the synthesis of enantiomerically pure compounds of biological interest. The molecules which have been employed as chiral modifiers along with sodiumborohydride are presented in Figure.- IV.01. [120-125].
Enormous progress has been made in recent years in the design and development of homogenous transition metal catalysis, organocatalysis and enzyme-catalysed reactions. However various advantages like high chemical yields, simple reaction conditions, short reaction time and easy recoverability of the catalyst precursor make asymmetric reduction of prochiral ketones one of the most attractive research fields. Among other asymmetric heterogeneous catalysts the most successful one is the catalysts modified with naturally occurring optically active compounds. The judiciously selected modifiers influence the selectivity and activity of the catalyst. The most effective heterogeneous catalytic hydrogenating systems are the Ni-tartaric acid, Pt-cinchona alkaloids, Pd-cinchona alkaloids and vinca alkaloids (Scheme IV.01).
IV.02(i). The asymmetric borane Reductions

Many chiral boron reagents\(^{131}\), both trigonal and tetrahedral, have been developed for the synthesis of optically pure compounds. The development emerged in the area of organo-borane\(^{132}\) intermediates provide ready access towards the synthesis of chiral molecules with maximum optical purity. The electrophilic nature and the tendency to form complex compound with the electron rich center of the functional groups makes the reduction with borane very selective and specific. Optically active oxazaborolidine is often used as a chiral catalyst in the enantioselective reduction of prochiral ketones using an air-stable borane\(^{133}\) (Scheme-IV. 02).
This process, pioneered by Itsuno\textsuperscript{134}, was subsequently improved by Corey \textit{et al}\textsuperscript{135} leading to the development of Corey-Bakshi-Shibata (CBS) catalyst. This proline based catalyst finds many uses in organic reactions such as asymmetric reductions, Diels-Alder reactions and [3+2] reactions. The selectivity of this catalyst is due to steric strain in the transition state which develops for one enantiomer but doesn’t for the other.

Diborane may be transformed into various borane agents for special need in terms of reactivity and selectivity. Several reviews on various boron based reducing agents for selective reduction of carbonyl compounds are available. Table- IV.01 presents some of the widely used chiral borane reagents [126-133].

\begin{table}
\centering
\caption{Chiral borane reagents for selective reduction}
\begin{tabular}{|c|c|}
\hline
Name / Structure & Name / structure \\
\hline
\includegraphics[width=2cm]{126} & 126 (-) D PC \\
& (-)-Diisopinocampheylchloroborane \\
\hline
\includegraphics[width=2cm]{127} & 127 (+)-DPC \\
& (+)Diisopinocampheylchloroborane \\
\hline
\includegraphics[width=2cm]{128} & 128 CBS \\
& (S)-Methyl Oxazaborolidine \\
\hline
\includegraphics[width=2cm]{129} & 129 R- MeCBS \\
& \textit{R}-Methyl Oxazaborolidine \\
\hline
\includegraphics[width=2cm]{130} & 130 Borazolidine \\
\hline
\includegraphics[width=2cm]{131} & 131 Borathiazolidine \\
\hline
\end{tabular}
\end{table}
The Diisopinocampheychloroborane (DPC) [126] and Methylazoxaborolidines (MeCBS) [128 and 129] are excellent choices for the enantioselective reduction of prochiral ketones. While DPC is a stoichiometric reducing agent, MeCBS (“Corey catalyst”) is typically used in conjunction with a borane source such as Borane-tetrahydrofuran (BTHF), Dimethylsulfide borane (DMSB), or Diethylaniline borane (DEANB). 136 Both products have proven their advantages over alternative technologies in commercial applications and are available in both enantiomeric forms.
The chiral oxazaborolidine-catalyzed reduction (CBS)\textsuperscript{135} is yet another important method for the preparation of secondary chiral alcohol. Jiang\textsuperscript{137} has shown that, (S)-\(\alpha\), \(\alpha\)-diphenylpyrrolidinemethanol catalyzed the NaBH\(_4\) reduction of achiral ketone afford the chiral alcohol with excellent enantiomeric excess. A similar chiral auxiliary has been employed in the reduction of the carbonyl group of \(\alpha\),\(\beta\)-unsaturated ketones. At the chiral interface of amphiphilic block copolymers with dendrimer structures, alcohols were obtained in high ee by the reduction of the corresponding prochiral ketones\textsuperscript{138} (Scheme-IV.03).

\[
\text{NaBH}_4 + \text{Me}_3\text{SiCl} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{OH}
\end{array} \\
\text{Scheme-IV.03}
\]

\textbf{IV.02(ii). The Acyloxyborohydrides}

Acyloxyborohydrides are unsurpassed in their versatility as reagents in organic synthesis. In addition to their superior ability in effecting reductive amination of aldehydes and ketones, acyloxyborohydrides can reduce a vast number of species selectively like nitrogen heterocycles (indoles, quinolines, isoquinolines), imines, enamines, oximes, amides, nitriles, benzylic alcohols, aryl ketones, aldehydes, acetals and \(\beta\)-hydroxyketones. The ability to control chemoselectivity, regioselectivity, and stereoselectivity by adjusting the carboxylic acid - borohydride reagent stoichiometry and temperature has no parallel in the repertoire of organic chemists (Scheme-IV.04).

\[
\begin{array}{c}
\text{Beeta hydroxy keteone reduction} \\
\text{Oxime reduction alkylation} \\
\text{Acetals, ketal reductive cleavage} \\
\text{Amine alkylation} \\
\text{Quinoline,isoquinoline reduction}
\end{array} \rightarrow \\
\text{NaBH(OCOR)}_3 \rightarrow \\
\begin{array}{c}
\text{Indole reduction} \\
\text{Aryl carbinol reduction} \\
\text{Indole reduction} \\
\text{Arene alkylation} \\
\text{Amide and nitrile reduction} \\
\text{Selective aldehyde reduction}
\end{array}
\]

\textbf{Scheme-IV.04}
An acyloxyborane is an initial intermediate obtained during the rapid reaction between carboxylic acid and borane. The carbonyl group in this molecule, which is essentially a mixed anhydride, is activated by the electronegative nature of the trivalent boron atom. Chiral acyloxyboranes such as 140 and 141 derived from tartaric acid are found to be one of the best chiral catalysts in the synthesis of secondary alcohols (Figure- IV.02).

During the course of the study on asymmetric reduction using NaBH₄, it has been found that modification of NaBH₄ with an optically active acid leads to the formation of a chiral sodium (acyloxy) borohydride (CAB) that often acts as potential asymmetric reducing agent. Carboxylic acids are not normally reduced with NaBH₄ in both protic and aprotic solvents. However under specific conditions, NaBH₄ may simply react with an optically active hydroxy acid represented as R*(COOH)ₙ according to the following equation.

\[
R^* (COOH)_n + NaBH_4 \rightarrow NaBH_4 - n[R^*(COO)_n] + nH_2
\]

\[n = 1 \text{ or } 2\]

In fact, there is rapid evolution of approximately one or two molar equivalents of hydrogen on addition of R*(COOH)ₙ to a suspension of NaBH₄ in tetrahydrofuran (THF) at 0~5°C leading the formation of sodium (acyloxy) borohydride intermediate. This chiral intermediate is known to catalyze various asymmetric reactions like Diels-Alder reactions of unsaturated aldehydes, asymmetric aldol reactions etc. A characteristic feature of CAB is the chiral involvement of an α-hydroxycarboxylic acid ligand which dictates the chemistry of boron reagent. The five membered ring system seems to be the major structural feature for the active catalyst [142] (Scheme- IV.05).
The CAB has a remarkable property to induce very high enantioselectivity in various asymmetric reactions like asymmetric Diels-Alder reactions, catalytic asymmetric Aldol reactions and asymmetric $S_{E1}$ addition reactions\textsuperscript{139} (Scheme- IV.06).

\[ \text{L-Tartaric acid} \rightarrow \text{BH}_3\text{-THF} \rightarrow 0^\circ\text{C, THF} \]

Chiral (Acyloxy) borane complex

(CAB)

Active Ligand

Inactive Ligand

Scheme- IV.05
Reports are available on new catalysts derived from readily available sulfonamide of amino acids. Catalysts 143 and 144 are found to catalyze Diels-Alder reactions whereas 145 catalyzes aldol reactions\textsuperscript{140} (Figure.IV.03). The exposure of an amino acid to a sulfonyl chloride in the presence of sodium hydroxide affords the desired products as white crystals. The sulfonamide obtained was subsequently treated with an equimolar amount of borane-THF complex to affect the catalyst.

\textbf{Figure- IV.03:} Structures of borane-sulfonamide based complexes.
It is known that chiral agents based on NaBH₄ and tartaric acid can involve itself as a chiral factor for the asymmetric reduction of α- or β- functionalized ketones like acetophenone and α-chloro acetophenone. The asymmetric reduction of propiophenone using NaBH₄- (D)- tartaric acid system in dioxane give only a low optical yield. However reports are available on a successful asymmetric reduction of functionalized ketones with NaBH₄- (L)- tartaric acid system with high optical yield.¹⁴¹

**IV.03. Results and Discussion**

In the context of the above discussion, efforts have been made to develop a chiral system for the reduction of prochiral ketones employing 1 and 2 based on sodium borohydride. The substrates selected for the present study are acetophenone, α-chloroacetophenone, ethyl acetoacetate and methyl acetoacetate.

In general, the reduction of acetophenone and its derivatives follow Prelog’s rule (the hydrogen transfer is taking place through pseudo re-faces, assuming the fact that aryl group is larger than methyl group) (Figure- IV.04).

**Figure - IV.04:** Prelog’s rule and its application

The addition of sodium borohydride (30.0 mmol) to the title acid 1 (30.0 mmol) in THF (100 ml.) at 0°C, is expected to result in the formation of chiral acyloxyborane intermediate [1c] (scheme-IV.07).
**IV.03(i) Asymmetric reduction of ketones using (2S,3S) and (2S,3R)-Tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarboxylic acids.**

The results of chiral reduction of acetophenone [146], α-Chloroacetophenone [148] and methylacetoacetate [152] using (2S,3S) and (2S,3R)-Tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarboxylic acids – NaBH₄ systems are summarized in Tables –IV.02 and IV.03 respectively.
**Table-IV.02**  Asymmetric reduction of ketones / ketoesters using NaBH₄-(2S,3S)-Tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarboxylic acid system

<table>
<thead>
<tr>
<th>Run</th>
<th>Ketone/ Ketoester</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>*% Yield</th>
<th>[α]₂₀°</th>
<th>**% ee</th>
<th>[α]₂₀° values Reported for Corresponding alcohols</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetophenone</td>
<td>R.t.</td>
<td>60</td>
<td>27</td>
<td>-0.551</td>
<td>1.2</td>
<td>1-Phenyl ethanol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-20</td>
<td>22</td>
<td>78</td>
<td>-2.120</td>
<td>4.7</td>
<td>[α]₂₀° = -45°, C = 5 in Methanol</td>
</tr>
<tr>
<td>3</td>
<td>α-Chloroacetophenone</td>
<td>0</td>
<td>20</td>
<td>57</td>
<td>-2.421</td>
<td>5.1</td>
<td>2-Chloro-1-phenyl ethanol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-20</td>
<td>15</td>
<td>82</td>
<td>-9.680</td>
<td>21.5</td>
<td>[α]₂₀° = -48°, C = 2.8 in hexane</td>
</tr>
<tr>
<td>5</td>
<td>Methylacetoacetate</td>
<td>R.t.</td>
<td>24</td>
<td>76</td>
<td>-2.501</td>
<td>12.63</td>
<td>Methyl-3-hydroxy-butyrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-20</td>
<td>18</td>
<td>85</td>
<td>-8.09</td>
<td>40.85</td>
<td>[α]₂₀° = +19.8°, neat</td>
</tr>
</tbody>
</table>

The mixture of NaBH₄ and 1 in THF was aged for 4h under reflux.

* Yield : Isolated yield.

**% ee : Determined by comparing the maximum specific rotation values reported for the respective alcohols at the same concentration.
Table-IV.03 Asymmetric reduction of ketones / ketoesters using NaBH₄-(2S,3R)-Tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid system

<table>
<thead>
<tr>
<th>Run</th>
<th>Ketone/ Ketaoester</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>*Yield (%)</th>
<th>[α]D²⁰</th>
<th>** % e.e.</th>
<th>[α]D²⁰ values Reported for Corresponding alcohols</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Acetophenone</td>
<td>R.t.</td>
<td>55</td>
<td>29</td>
<td>-1.377</td>
<td>2.9</td>
<td>1-Phenyl ethanol [α]D²⁰ = - 45°, C = 5 in Methanol</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>-20</td>
<td>18</td>
<td>82</td>
<td>-5.836</td>
<td>12.15</td>
<td>2-Chloro-1-phenyl ethanol [α]D²⁰ = - 48°, C = 2.8 in hexane</td>
</tr>
<tr>
<td>9</td>
<td>α-Chloroacetophenone</td>
<td>0</td>
<td>20</td>
<td>63</td>
<td>-5.181</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>-20</td>
<td>12</td>
<td>85</td>
<td>-17.615</td>
<td>36.77</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Methylacetoacetate</td>
<td>R.t.</td>
<td>22</td>
<td>80</td>
<td>-5.09</td>
<td>25.70</td>
<td>Methyl-3-hydroxy-butyrate [α]D²⁰ = + 19.8 °, neat</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>-20</td>
<td>15</td>
<td>87</td>
<td>-16.28</td>
<td>82.</td>
<td></td>
</tr>
</tbody>
</table>

The mixture of NaBH₄ and 2 in THF was aged for 4 h under reflux.

* Yield : Isolated yield.
** % e.e : Determined by comparing the maximum specific rotation values reported for the respective alcohols at the same concentration.

As given in the Table- IV.02, NaBH₄ - (2S,3S)- Tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid [1] system appeared to show poor enantioselectivity to simple ketone (Run 1) especially at room temperature and the product (S)-1-phenyl ethanol[147b] is formed only with low optical yield (1.2% ee). On the other hand, at low temperature (-20°C), it shows comparatively high enantioslectivity (4.7%.ee) (Run
2), obviously due to the re-face selectivity leading to the formation of (S)-1-phenyl ethanol (Scheme-IV.09). The S-configuration is justified on the basis of proposed structures of the intermediates. In the case of NaBH₄ - (2S,3R)- Tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarboxylic acid system as catalyst, it was observed that both the optical as well as chemical yields (isolated) have been increased. Thus the optical purity of 1-phenyl ethanol was increased to 2.9% ee at room temperature (Run 7) and 12.15% ee at -20°C (Run 8) respectively (Table –IV.03). It is obviously due to the si-face selectivity leading to the formation of (R)-1-phenyl ethanol [147a] (Scheme- IV.12). The enantioface selectivity of the product is justified based on the proposed structures of intermediates.

The reduction of α-chloroacetophenone [148] using NaBH₄-(2S,3S)and(2S,3R)-Tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acids systems, lead to the formation of 2-Chloro-1-phenyl ethanol with promising increase in the optical yield (Table-IV.02, run 3&4 and Table-IV.03, run 9 &10). The increased enantioselectivity may be explained on the basis of the fact that the affinity of lone pairs around the oxygen and chlorine atoms towards sodium ion or boron facilitate the enantioselective face selection.

The reduction of Methylacetoacetate [152] using NaBH₄-1 system, (Table –IV.02), leads to the formation of methyl 3-hydroxy butanoate in 12.63% ee at room temperature (Run 5) and 40.85 % ee at -20 °C (Run 6), where as the reduction of ketoester using NaBH₄ –2 system furnished the hydroxy ester with 25.70 % ee at room temperature (Run 11) and 82% ee at -20 °C (Run 12) respectively. Thus it may be concluded that the NaBH₄ - (2S,3S)-and (2S,3R)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acids systems can also act as effective chiral reducing agents for the asymmetric reduction of prochiral ketones and keto esters.

The ageing of the reagent, even though used routinely to ensure complete removal of naked NaBH₄, is expected to give an improvement in the asymmetric reduction. The formation of 1-Phenyl ethanol [147] and 2-Chloro-1-phenyl ethanol [149] have been confirmed on the basis of IR, ¹H and ¹³C NMR spectral data [Figures- IV.05 a-c and IV.06a-b]. The ¹³C NMR spectrum of 149 consists of more number of signals than expected due to impurities. Attempts to purify the product failed. However the structure was tentatively ascertained on the basis of the NMR spectrum which shows all the signals expected for the molecule.
Figure IV.05 a

$^1$H NMR

Figure IV.05 b

$^{13}$C NMR

Figure IV.05 c
$^1$H NMR

Figure-IV.06a

IR

Figure-IV.7 a
IV.03(ii). Mechanistic aspects of the reduction

It may be noted that in the available report on the enantioselective reduction of ketones using tartaric acid – sodiumborohydride borane system no clear mechanism is suggested. However reports are available on the formation of Chiral (acyloxy)borane (CAB) from mono acyl derivative of tartaric acid and aryloboric acid. These catalysts have been used in Hetero Diels –Alder reactions. Report pertaining to the use of several kinds of tartaric acid derivatives reveals that the boron atom might form a five-membered ring structure with α-hydroxy acid moiety of tartaric acid. The remaining carboxyl group may not be involved in bond formation with the boron atom. The involvement of the aforementioned five membered ring structure leads to the formation of chiral (acyloxy borane) complex.

In conjunction with this, the following plausible mechanisms have been suggested for the reduction of prochiral ketones and keto esters using chiral acyloxy boranes derived from 1 and 2.

The difference in selectivity of the catalysts derived from 1 and 2 towards the asymmetric reduction can be explained on the basis of the intermediates (154–165) proposed (Schemes- IV.09,10, IV.11 and IV.12). The initial formation of the oxyborane intermediates 1a and 1b are equally probable and which eventually end up in the formation of acyloxy borane complex (1c) by extending the coordination of boron atom to both of the carboxylic and hydroxy groups(Scheme-IV.08).

[Diagram of mechanistic aspects of the reduction]
The formation of the intermediate, 1c, is favored due to the fact that C-2 and C-3 carboxylic acids are on the same plane. The coexistence of five and six-membered ring structure with in the molecule is possible (1c). This structure could effectively block the si-face and hence an effective hydride shift is taking place through the re-face leading to the formation of chiral alcohol with (S)-configuration (Scheme- IV.09). The 1-phenyl ethanol [146] isolated showed an optical rotation of ([α]_D^{20} = - 5.836 (C = 5 in methanol)).

The structures 154, 155 and 156 represent various possible intermediates involved in the reduction process leading to the formation of (S)-1-phenyl ethanol [147b] as the major product.

A similar mechanism is suggested for the reduction of α-chloro-acetophenone [148]. The affinity of boron atom towards chlorine atom in 148 stabilizes the five-membered cyclic ring structures [157 &158] (Scheme-IV.10). This may facilitate a re-face hydride shift to the carbonyl group of the ketone leading to the formation of excess chiral alcohol namely 2-chloro-1-phenyl-1-ethanol [149b] with (S)-configuration and which showed an optical rotation of ([α]_D^{20} = -9.680° (C = 2..8 in hexane)).
In the case of reduction using \((2S, 3R)\)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid (2)-\(\text{NaBH}_4\) system, a cyclic structure [2c] is involved. As the –COOH groups are trans to each other a five membered cyclic structure, 2c, may be involved. This marked differences in the intermediates (1c and 2c ) make \((2S,3R)\)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acid [2] a better chiral catalyst in the asymmetric reduction over the on other enantiomer, 1 (Figure-IV.8).

Based on these, separate mechanisms have been suggested for the enantioselective reductions of acetophenone [146] and \(\alpha\)-chloroacetphenone [148] using \(\text{NaBH}_4\)- 2 systems. As shown in (scheme-IV.11), the ketone may take an orientation around the CAB complex [159] in the intermediate in such a way that it is susceptible for a si-face attack stronger than the attack in the opposite mode, leading to
the formation of 147a with predominantly (R)-configuration. The various structures possible for the intermediates are also shown.

Similarly a tentative mechanism is proposed for the enantioselective reduction of α-chloroacetophenone [148] using sodium borohydride - 2 system. The (S)-2-chloro-1-phenyl ethanol [149b] has been isolated as the major product (scheme-IV.12).
IV.03(iii). Supporting Factors for the proposed mechanism

The mechanism proposed could be justified in view of the fact that when dialkyl derivatives namely dimethyl [108] or diisopropyl [110] esters of (2S,3S) tetrahydro-3-hydroxy-5-oxo-2,3-furan dicarbxylic acid, were used in place of 1, the reaction failed to give any enantioselectivity (Scheme- IV.13). Similar was the case with the esters of acid lactone 2 also.

Another support for the suggested mechanism is that when the molecule obtained, by the regioselective protection of C-3 carboxyl group of 1 or 2 using trichloroacetaldehyde \( [\text{CH}_2\text{Cl}_3\text{CHO}] \) -4, 8-dioxo-2-(trichloromethyl) \( 1, 3, 7 \) trioxaspiro[4,4]nonane-6-carboxylicacid,166] is used along with sodiumborohydride for reduction, no enantioselectivity was observed (Scheme –IV.14). The formation of 166 has been confirmed on the basis of NMR and mass spectral data (Figure- IV.9a-d).

The observation also suggest that the hydroxyl groups of acids such as 1 and 2 is responsible for the enantioselectivity observed in asymmetric reduction. The difference in structural features of chiral (acyloxy) borane complexes and the involvement of these intermediates in the enantioselectivity is depicted in Scheme-IV-15
The new CAB catalysts generated from 1 and 2 reveal the following characteristic features: (i) The extent of asymmetric induction is largely depends on the diastereomeric nature of 1 and 2. The Hibiscus acid [2], imparts a better asymmetric induction (Table-IV.3, entries 8, 10 and 12.) than its diastereomer 1. (ii) A substitution in the α-carbon atom of ketone is also crucial for obtaining high enantio-selectivity. (iii) Judging from the absolute configuration of the alcohol, CAB catalyst generated from the title acids and sodium borohydride should effectively cover the si-face of carbonyl group of the ketone when coordinated, and selective transfer of the hydride through the re-face leads to the formation of (S)-alcohols in excess, matching with the experimental observation.

An earlier report on the asymmetric reduction of propiophenone using sodium borohydride and (S)-(-)-2,2-dimethyl (2'-chlorophenyl)-1,3 – propanediol (S)-(-)-2,3a and 2-chlorobenzoic acid, (Figure.-IV.10), also justified the proposed mechanism.
IV.04. Conclusion

A practical, simple, less expensive chiral catalysts have been developed for the enantioselective reduction of ketones to secondary alcohols from diastereomeric $(2S,3S)$ and $(2S,3R)$-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acids and sodium borohydride. It is found that high enantioselectivity was obtained when the acetophenone bears a suitable substitution in the $\alpha$-carbon atom. The chiral (acyloxy) borane formed between the title acids and sodium borohydride have been found to be a possible intermediate in the reduction process.

The two diastereomers gave varying chiral inductions obviously due to the involvement of two different intermediates. The experimental results gained in this work are expected to stimulate further advances in the study of the chiral boron reagents. Though the mechanism of asymmetric induction is not clear, it may tentatively be argued that $\alpha$-hydroxy acid and borane make the rigid cyclic structure to form an effective asymmetric field. Further work in this direction is in progress to confirm the proposed hypothesis.
IV.05. Experimental

IV.05(i). Preparation of (S)-1-phenyl ethanol (146)

NaBH₄ (1.26 g, 90 % purity, 30 mmol.) and 1 (5.7 g, 30.00 mmol.) were suspended in THF (100 ml) and the resulting suspension was heated to 70 °C for 4h. The suspension cooled to -20 °C was added drop wise acetophenone (2.42 g, 20 mmol.) in 10 ml of THF over 5 min. After the addition the reaction mixture was stirred at -20 °C for 20-22 h. The mixture was added 50 ml of AcOEt and 25 ml of 1M HCl at the same temperature. The organic layer was separated, washed (sat. NaHCO₃), dried (MgSO₄), filtered and concentrated in vacuo and purified by the column chromatography (Hexane - chloroform, 3:7)
Yield : 78 %

$[\alpha]_D^{20}$ : -5.836 (C = 5 in methanol)

Optical purity : 12.15 % ee

$^1$H NMR (CDCl$_3$) : δ 7.383- 7.318 (m, 5H), 4.925-4.860 (q, $J$ = 6.6 Hz, 1H), 1.50(d, $J$ = 6.0 Hz, 3H) ppm

$^{13}$C NMR (CDCl$_3$) : δ 147,128,127,125,69,25 ppm.

### IV.05(ii). Preparation of (1S) - 2- chloro-1-phenyl-1-ethanol [147]

NaBH$_4$ (1.26 g, 90 % purity, 30.00 mmol.) and 1(5.7 g, 30.00 mmol.) were suspended in THF (100 ml) and the resulting suspension was heated to 70 °C for 4h. The suspension cooled to -20 °C was added drop wise α- chloro acetophenone (3.11 g, 20 mmol.) in 10 ml of THF over 5 min. After the addition the reaction mixture was stirred at -20 °C for 12 h. The mixture was added 50 ml of AcOEt and 25 ml of 1M HCl at the same temperature. The organic layer was separated, washed (sat. NaHCO$_3$), dried (MgSO$_4$), filtered and concentrated in vacuo and purified by column chromatography (Chloroform – acetone, 9:1)

Yield : 85 %

$[\alpha]_D^{20}$ : -17.615 (C = 2.8 in hexane)

$^1$H NMR (CDCl$_3$) : δ 7.353- 7.310 (m, 5H), 4.854-4.825 (t, $J$ = 4.45 Hz, 1H), 3.724-3.712(d, $J$ =3.6Hz,2 H), 2.813(br.1H) ppm

$^{13}$C NMR (CDCl$_3$) : δ 139,128,126,76,51ppm.