Chapter 3

Studies on the asymmetric Michael addition reaction
3.1 Introduction

Since its discovery, in the mid 1880’s, Michael reaction has been extensively explored and used in organic chemistry. In the past two decades, much progress has been made in the development of asymmetric variants of this reaction, allowing the elaboration of Michael adducts of high enantiomeric purity. In recent years, catalysis of asymmetric Michael reaction by chiral metal complexes has been recognized as an efficient method for the enantioselective construction of carbon-carbon bonds. We have undertaken studies on the use of chiral borate derivatives for such applications. Accordingly, it may be of interest to briefly review the recent advances in the asymmetric Michael reaction promoted by various chiral ligands.

Barbas and coworkers reported the catalytic enantioselective direct Michael additions of ketone enolates to alkylidene malonates. Michael adducts were obtained in up to 91% ee (Scheme 1).

Scheme 1
Recently, Barbas and Beatancort\(^8\) reported the direct catalytic enantio and diastereoselective Michael additions of unmodified aldehydes using \(\text{(S)-2-(morpholinomethyl)pyrrolidine}\) 2 as a catalyst (Scheme 2). The reaction proceeded in good yields in a highly \emph{syn}-selective manner (up to 98:2) with enantioselectivity approaching 80%. The resulting \(\gamma\)-formyl nitro compounds are readily converted to chiral 3,4-disubstituted pyrrolidines.

\textbf{Scheme 2}

\[
\begin{align*}
\text{RCHO} + \text{R}^\prime\text{NO}_2 \xrightarrow{\text{THF, rt}} \text{OHC} \text{R}^\prime\text{NO}_2 \\
\text{96\% (78\% ee)}
\end{align*}
\]

List \textit{et al}\(^9\) reported the chiral proline 3 catalysed Michael reaction of unmodified ketones with nitro olefins (Scheme 3). The \(\gamma\)-nitro ketones are obtained with modest enantioselectivity and in excellent yields.

\textbf{Scheme 3}

\[
\begin{align*}
\text{Ketone} + \text{Ph} = \text{NO}_2 \xrightarrow{\text{DMSO, 16 h}} \text{Product} \\
\text{94\% (23\% ee)}
\end{align*}
\]
Recently, Corey et al.\textsuperscript{11} reported the enantioselective Michael addition of nitromethane to an $\alpha,\beta$-enone using chiral quarternary ammonium salt as chiral catalyst which is a key step in the synthesis of $(R)$-bacolfen $6$ (Scheme 4).

**Scheme 4**

A solid-liquid phase transfer catalyst, efficiently promotes asymmetric Michael reaction without added solvent (Scheme 5). For example, in the reaction of chalcone with acetylamino malonate in the presence of quaternary salt derived from TV-methyl ephedrine, the corresponding adduct was obtained in 68% ee (Scheme 5).\textsuperscript{10}
Kim et al. reported the catalytic asymmetric Michael addition, promoted by quaternary ammonium salt derived from cinconidine (Scheme 6). Treatment of nitroalkanes with chalcone derivatives under mild conditions afforded the corresponding Michael adducts in moderate to good enantiomeric excess (Scheme 6).\textsuperscript{12}

Mukaiyama and coworkers\textsuperscript{13} reported the catalytic asymmetric Michael reaction of enethiolates, employing catalytic amount of stannous triflate and a chiral diamine (Scheme 7).
A cobalt catalyst, prepared from Co(acac)$_2$ and (+) or (-)-1,2-diphenylethane-1,2-diamine, is useful in the enantioselective Michael addition of β-keto ester to methyl vinyl ketone (Scheme 8). Asymmetric induction of 66% ee was realized in the reaction of methyl indane-1-one-2-carboxylate.$^{14}$

Catalytic asymmetric Michael reaction of (3-keto esters and methyl vinyl ketone was reported by Suzuki et al.$^{15}$ using a chiral diamine based Ru complex to obtain Michael adducts in up to 75% ee (Scheme 9).
Yamaguchi et al.\textsuperscript{16} found that the (S)-proline rubidium salt catalyses the asymmetric Michael reaction of malonate anions (Scheme 10). High enantiomeric excess was obtained when di(t-butyl)malonate was reacted with (E)-enones in the presence of CsF.

Koga et al.\textsuperscript{17} prepared the chiral amino alcohol lithium alkoxides for use in the enantioselective Michael reaction of methyl phenylacetate and methyl acrylate. The corresponding adduct was obtained in 84% ee (Scheme 11).
Benzene based tripodal oxazolines are found to be novel chiral ligands for the catalytic enantioselective Michael addition via potassium enolates (Scheme 12). Methyl phenylacetate undergoes 1,4-addition to methyl acrylate using a catalytic amount of a KOBu'-oxazoline complex in toluene at -78 °C to give the corresponding adduct in 84% yield (82% ee).\(^{18}\)

Sundararajan and Manickam\(^{19-21}\) synthesised the \(C_2\)-symmetric chiral amino diol derived polymer anchored catalyst 15 for applications in asymmetric Michael addition reaction (Scheme 13).
Narasimhan and coworkers\textsuperscript{23} developed a chiral amino diol catalyst 16, which promotes certain asymmetric Michael additions (Scheme 14).

Scheme 14

Choudary and coworkers\textsuperscript{24} prepared a heterobimetallic catalyst by the reaction of LiAlH\textsubscript{4} with an aminodiol derived from natural (+)-tartaric acid that promotes asymmetric Michael addition of malonic esters, thiophenols and nitro
alkanes with acyclic enones in excellent yields, but with low enantiomeric excesses (Scheme 15).

**Scheme 15**

![Scheme 15](image)

Joshi et al.\(^{25}\) reported that the heterobimetallic complex 18, prepared from a chiral SALEN ligand and RED-Al catalyses the Michael reaction between various dialkyl malonates and cycloalkenones to give adducts in high yields with up to 58% ee (Scheme 16).

**Scheme 16**

![Scheme 16](image)
Recently, Kumarasamy et al.\textsuperscript{26} reported a new calcium-binol catalyst 19 for asymmetric Michael addition of enones (Scheme 17). In the reaction between cyclopentenone and dimethyl malonate an asymmetric induction of 88\% ee was realized (Scheme 17) using this catalyst.

Scheme 17

A spectacular achievement in the asymmetric Michael reaction is the discovery of heterobimetallic multifunctional asymmetric catalysis by Shibasaki and coworkers.\textsuperscript{57} In a series of reports, these authors elaborated the ability of such heterobimetallic complexes of binol-aluminium 20 or binol-lanthanide alkali metal complexes to bring about highly enantioselective Michael addition reactions (Scheme 18).
Recently, Sasai et al.\textsuperscript{34} reported that the polymer anchored heterobimetallic binol-aluminium complex promote the asymmetric Michael addition reaction. The immobilised poly-ALBs 21 are readily prepared from polymeric BINOL derivatives and LiAlH\textsubscript{4}. The combined use of 9 mol\% of \textit{n}-BuLi with 10 mol\% of 6,6'-aryl-tethered poly-ALB gave the Michael adducts in up to 93\% ee. After completion of the reaction, the insoluble catalyst was recovered and reused.
Previously, it was found in this laboratory\textsuperscript{55} that the ammonium borate complex, prepared using the chiral 1,1’-bi-2-naphthol, B(OH)\textsubscript{3} and (\textit{R},\textit{R})-\textalpha,\textalpha’-dimethylidibenzylamine, promotes the asymmetric Michael addition reaction of diethyl malonate to cyclohexenone in the presence of KO\textsubscript{Bu}\textsuperscript{t} to give the corresponding Michael adducts in up to 45\% ee.
In continuation of these efforts, we have examined the application of the borate complexes prepared using chiral 1,1’-bi-2-naphthol, α,α-diphenyl-2-pyrrolidine methanol and boric acid. We have also examined the application of oxazaborolidine derived from α,α-diphenyl-2-pyrrolidinemethanol for application in asymmetric Michael additions. The results are described in this chapter.
3. 2 Results and Discussion

3. 2. 1 Asymmetric Michael reaction promoted by chiral α,α-diphenyl-2-pyrrolidinemethanol derived ammonium borate complex 22

As discussed in chapter 1, the ammonium borate complex 22 can be readily prepared using chiral 1,1'-bi-2-naphthol, α,α-diphenyl-2-pyrrolidinemethanol and boric acid. The reaction between diethyl malonate and cyclohexenone in THF solvent in the presence of the borate complex 22 (10 mol%) and KOBu₁ (20 mol%) gave the corresponding Michael adduct in 80% yield and 20% ee (Scheme 21). Since the complex is capable of catalyzing the Michael reactions, we undertook efforts to study the reaction under various conditions, so as to optimize the results.

Scheme 21
Table 1: Asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by chiral ammonium complex 22: Effect of various solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>THF</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>2.</td>
<td>Toluene</td>
<td>13</td>
<td>79</td>
</tr>
<tr>
<td>3.</td>
<td>DCM</td>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>4.</td>
<td>CHCl₃</td>
<td>6</td>
<td>72</td>
</tr>
</tbody>
</table>

a. All the reactions were performed by dissolving ammonium borate complex 22 (0.5 mmol), KOBu<sup>f</sup> (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in various solvents and the contents were stirred at rt for 12h.

b. The ee values are calculated on the basis of reported [α]<sub>D</sub>values.<sup>5</sup>

Generally, lowering the temperature leads to improvement in the enantioselectivity. To examine this, we carried out the reactions at lower temperatures. Unfortunately, there was no significant increase in the ee of the product even when the reactions were carried out at -78 °C. Moreover, the chemical yields were very poor under these conditions. Reactions were also carried out in various solvents such as DCM, toluene and THF. The results were better in THF solvent (Table 1).

A tentative mechanism may be considered for the formation of the Michael adducts, where the donor is deprotonated and coordinated to the boron atom. The enone, would then accept the enolate as shown in the Scheme 22. After the 1,4-addition, the ketone is released abstracting a proton from the complex to afford the corresponding Michael adduct (Scheme 22).
3.2.2 Asymmetric Michael reaction promoted by the chiral oxazaborolidine derivatives

The chiral ammonium borate complex 22 (Scheme 21) provided only poor asymmetric induction. Accordingly, we have decided to examine the applications of the oxazaborolidine derivative 24 that can be readily prepared from (S)-(−)-α,α-diphenyl-2-pyrrolidinemethanol and trimethyl borate (Scheme 23).\(^{37}\)

Scheme 22

![Diagram of the Asymmetric Michael reaction](image)

Scheme 23

![Diagram showing the synthesis of 24](image)
We found that the Michael reaction of diethyl malonate and cyclohexenone using this reagent, did not take place even after 7 days. Presumably, the complex is not basic enough to promote the Michael reaction. As discussed in the introductory section, sodium or potassium alkoxides (NaOR or KOR) are generally used for the preparation of bimetallic catalysts capable of catalyzing Michael reaction. Accordingly, we examined the use of oxazaborolidine catalyst 24 in the presence of KOBu\textsuperscript{1}. Indeed, it was observed that the use of KOBu\textsuperscript{1} was effective in the catalysis of Michael reaction. For example, the reaction between diethyl malonate and cyclohexenone in the presence of the oxazaborolidine catalyst 24 and KOBu\textsuperscript{1} in THF solvent gave the Michael adduct in 16\% ee (80 \% yield) (Scheme 24).

Scheme 24

Since, the complex 24 is capable of catalyzing the Michael reaction, we undertook efforts to study the reaction under various conditions. The reaction was carried out in different solvents like toluene and dichloromethane (DCM). It was observed that the enantiomeric excess increased from 16\% ee to 25\% ee when toluene was used as solvent (Table 2)-
Table 2: Effect of solvents on the asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by the catalyst 24.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>THF</td>
<td>16</td>
<td>80</td>
</tr>
<tr>
<td>2.</td>
<td>Toluene</td>
<td>25</td>
<td>78</td>
</tr>
<tr>
<td>3.</td>
<td>DCM</td>
<td>15</td>
<td>75</td>
</tr>
<tr>
<td>4.</td>
<td>CHCl₃</td>
<td>12</td>
<td>72</td>
</tr>
</tbody>
</table>

a. The oxazaborolidine complex 24 (5 mmol), KOBu¹ (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) were taken in various solvents and stirred at rt for 12 h.

Table 3: Effect of temperature on the asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by the catalyst 24.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>12h</td>
<td>25</td>
<td>25</td>
<td>80</td>
</tr>
<tr>
<td>2.</td>
<td>20h</td>
<td>0</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>24h</td>
<td>-10</td>
<td>62</td>
<td>70</td>
</tr>
</tbody>
</table>

a. All the reactions were performed by dissolving oxazaborolidine complex 24 (5 mmol), KOBu¹ (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in toluene and the contents were stirred at various temperature.

The reactions were also carried out at lower temperatures. Fortunately, there was significant increase in the ee of product when the reactions were carried out at 0 °C. The ee increased from 25% to 50% in toluene at 0 °C (Table 3). Unfortunately, the chemical yields were very poor when the reactions were carried out below −10 °C.
Table 4: Effect of different bases on the asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by the catalyst 24.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additives</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>NaOBu</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>2.</td>
<td>n-BuLi</td>
<td>35</td>
<td>74</td>
</tr>
<tr>
<td>3.</td>
<td>NaH</td>
<td>0</td>
<td>77</td>
</tr>
</tbody>
</table>

a. All the reactions were performed by dissolving oxazaborolidine complex 24 (5 mmol), base (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in toluene and the contents were stirred at 0°C for 20 h.

Since carrying out reactions at lower temperature did not give fruitful results, we investigated the effect of the base used in the reaction. As outlined in the introductory section, Yamaguchi et al. reported that (S)-proline salts of ions such as Li, Na, K, Rb and Cs were effective catalyst for Michael addition. They noted that the sodium and potassium ions were more effective than the lithium ions. Hence, we have examined the reactions using various bases. However, there was no significant increase in the ee when compared to the use of KOBu\(^1\) (Table 4).

It is known that the addition of molecular sieves to the reaction mixture facilitates the removal of traces of water present, leading to better results in certain reactions. To examine this effect, reactions were carried out in the presence of molecular sieves (MS 4A\(^\circ\)). Unfortunately, there was no significant difference in the ee under these conditions.
Table 5: Effect of concentration of the chiral oxazaborolidine catalyst 24 on the asymmetric Michael reaction between cyclohexenone and diethyl malonate.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>24 (eq.)</th>
<th>KOBu(^i)</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>0.1</td>
<td>0.2</td>
<td>11</td>
<td>72</td>
</tr>
<tr>
<td>2.</td>
<td>0.5</td>
<td>0.2</td>
<td>25</td>
<td>73</td>
</tr>
<tr>
<td>3.</td>
<td>1.0</td>
<td>0.2</td>
<td>50</td>
<td>75</td>
</tr>
</tbody>
</table>

\(^a\) All the reactions were performed by dissolving oxazaborolidine complex 24 (1-5 mmol), KOBu\(^i\) (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in toluene and the contents were stirred at 0 °C for 20 h.

As expected, increase in the concentration of the oxazaborolidine catalyst 24 led to increase in the enantioselectivity. The results are summarised in Table 5.

The effect of different R group in the (B-OR) moiety (R = n-Bu) was also studied (Scheme 25). It was observed that there is slight increase in the enantioselectivity under these conditions (Table 6).

Scheme 25
Table 6: Effect of different solvents and temperature on the asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by the catalyst 25.<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additives</th>
<th>Time (h)</th>
<th>ee(%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>THF</td>
<td>25 °C, 12 h</td>
<td>25</td>
<td>80</td>
</tr>
<tr>
<td>2.</td>
<td>THF</td>
<td>0 °C, 20 h</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>3.</td>
<td>Toluene</td>
<td>25 °C, 12 h</td>
<td>30</td>
<td>78</td>
</tr>
<tr>
<td>4.</td>
<td>Toluene</td>
<td>0 °C, 20 h</td>
<td>58</td>
<td>74</td>
</tr>
</tbody>
</table>

<sup>a</sup> The oxazaborolidine complex 25 (5 mmol), KOBu<sup>1</sup> (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) were taken in THF and the contents were stirred at rt and 0 °C.

<sup>b</sup> The oxazaborolidine complex 25 (5 mmol), KOBu<sup>1</sup> (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) were taken in Toluene and the contents were stirred at rt and 0 °C.

Table 7: Effect of Lewis acids on the asymmetric Michael reaction between cyclohexenone and diethyl malonate promoted by the catalyst 24.<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metalcomplex</th>
<th>ee(%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ti(OPr&lt;sup&gt;r&lt;/sup&gt;)</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>2.</td>
<td>TiCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>15</td>
<td>75</td>
</tr>
<tr>
<td>3.</td>
<td>Al(OPr&lt;sup&gt;r&lt;/sup&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>30</td>
<td>78</td>
</tr>
<tr>
<td>4.</td>
<td>LiAlH&lt;sub&gt;4&lt;/sub&gt;</td>
<td>50</td>
<td>74</td>
</tr>
</tbody>
</table>

<sup>a</sup> All the reactions were performed by dissolving oxazaborolidine complex 24 (5 mmol), KOBu<sup>1</sup> (1 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in toluene and the contents were stirred at 0 °C for 20 h.

Since the boron centre is relatively less Lewis acidic, we have examined the use of more acidic aluminium and titanium derivatives. The metal complexes were prepared by reaction of the (S)-(−)-α,α-diphenyl-2-pyrrolidinemethanol
with Ti(OPr\(^i\))\(_4\), TiCl\(_4\), Al(OPr\(^i\))\(_4\) and LiAlH\(_4\). The results of Michael reactions are summarised in the Table 7.

As discussed in chapter 1 and chapter 2, we have developed convenient methods of preparation of enantiopure 1,2-amino alcohols like phenylglycinol, phenylalaninol, valinol and 2-amino butanol. Accordingly, we have also carried out studies on the Michael reaction using various oxazaborolidine derivatives 26-29 that can be readily prepared from the above mentioned amino alcohols and trimethyl borate (Scheme 26).

Scheme 26

For example, the reaction between diethyl malonate and cyclohexenone in the presence of the oxazaborolidine catalyst 26-29 and KOBu\(^1\) in toluene solvent gave the Michael adduct in 25-32% ee (68-71% yield) (Scheme 27).
Scheme 27

It is evident from these studies that the (S)-(−)-α,α-diphenyl-2-pyrrolidinemethanol derived oxazaborolidines 24 and 25 in the presence of KOBu\(^\dagger\) gave better results. We have also examined the reactions using various malonate derivatives, such as dimethyl malonate, diethyl malonate, dibenzyl malonate and di-\(\alpha\)-butyl malonate. The results are summarized in Scheme 28.

Scheme 28
A tentative mechanism can be considered for the formation of the Michael adducts, where the dialkyl malonate is deprotonated and coordinated to the central boron atom via exchange of the alkoxy group (Scheme 30). The enone then accepts the enolate through coordination with the boron atom (Scheme 30).
We have also briefly extended the studies to acyclic enones like trans-chalcone and enolate derived from methyl phenylacetate. In these cases, the Michael addition was smooth but the enantioselectivity realized was very poor. This may be due to the loss of rigidity in the acyclic system. For example, chalcone reacts with dimethyl malonate in the presence of oxazaborolidine catalyst 24 and KOBu¹ to give the product in 64% yield with only 10% ee (Scheme 31).
Methyl phenylacetate reacts with methacrylate in the presence of chiral oxazaborolidine 24 and KOBu$^1$ to give the product in 65% yield in only 5% ee (Scheme 32).

Scheme 32

3. 2. 3 Asymmetric Michael reactions promoted by chiral $\alpha,\alpha$-diphenyl-2-pyrrolidinemethanol derived lithium alkoxide

As mentioned in the introductory section, Koga et al.$^{17}$ reported that the simple amino alcohol derived lithium alkoxide were effective catalyst for asymmetric Michael addition reaction. It was noted that the lithium alkoxide was more effective than the sodium and potassium alkoxides.

Therefore, we have examined the $\alpha,\alpha$-diphenyl-2-pyrrolidinemethanol derived lithium alkoxide prepared in situ as shown in the Scheme 33. It was found that this catalyst was also effective for promoting the Michael addition reactions.

Scheme 33
Table 8: Effect of temperatures on the asymmetric Michael reaction between cyclohexenone and dimethyl malonate using the chiral lithium alkoxide catalyst 37.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Condition</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Hexane</td>
<td>25 °C, 12 h</td>
<td>21</td>
<td>90</td>
</tr>
<tr>
<td>2.</td>
<td>Hexane</td>
<td>0°C, 12 h</td>
<td>45</td>
<td>85</td>
</tr>
<tr>
<td>3.</td>
<td>Hexane</td>
<td>-78 °C, 12 h</td>
<td>70</td>
<td>80</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All the reactions were performed by dissolving chiral lithium alkoxide catalyst 37 (5 mmol), n-BuLi (5 mmol), diethyl malonate (6 mmol) and cyclohexenone (5 mmol) in hexane.

The enantioselectivity realized was better when reactions were carried out at -78 °C as shown in the Table 8. It was found that only poor results were obtained (5-10% ee) in the reactions using α,α-diphenyl-2-pyrrolidinemethanol derived potassium and sodium alkoxides.

3. 2. 4 HPLC Analysis of the Michael adducts

The enantiomeric excesses of the adducts formed in the Michael reactions using the chiral ammonium borate complex 22 and oxazaborolidine 24 were calculated from the $[\alpha]_D$ values reported by Shibasaki and coworkers for these samples.\textsuperscript{5} However, the $[\alpha]_n$ values exhibited by these derivatives are low and hence prone to have higher experimental errors. Therefore, we have carried out HPLC analysis of these samples. The adducts formed in the Michael reaction
could not be analysed using chiral columns accessible to us (chiral cell OD, chiral pak OP and chirex (S)-valine).

We have then made attempts to prepare the diastereomeric ketal derivatives for HPLC analysis. The ketal derivatives of \((S, S)-(-)-1,2\text{-diphenyl-}1,2\text{-ethane diol}\) could be readily prepared (Scheme 34). The \((\pm)-1,2\text{-diphenyl-}1,2\text{-ethane diol}\) has been resolved readily using \((S)\)-proline to obtain \((S, S)-(-)-1,2\text{-diphenyl-}1,2\text{-ethane diol}\) in > 99% ee following the procedure developed in this laboratory.\(^{36}\)

![Scheme 34](image)

The \(\text{H}\) and \(^3\text{C}\) NMR data of the diastereomeric ketals were not helpful to estimate the ee of these isomers. The HPLC analysis of the diastereomeric ketals of racemic adducts and the optically active adducts were carried out on chiralcell OD column (hexane/2-propanol (96:4) mixture as eluent). Unfortunately, accurate values of the ee could not be estimated as the column efficiency was poor and the values of ee could not be confirmed by \(^1\text{H}\) NMR analysis or HPLC data.
It is of interest to note that the \([\alpha]_{D}^{25}\) values (lit\(^{25}\) for 100% ee, \([\alpha]_{D}^{25} = (+) 69.0\) (C3.93, CHCl\(_3\))) of the Michael adduct 34 obtained from cyclopentenone and dimethyl malonate are higher than that of the corresponding cyclohexyl adduct (lit\(^{29}\) for 75% ee, \([\alpha]_{D}^{25} = (+) 3.01\) (C 2.1, CHCl\(_3\))). Although, the cyclopentenone is relatively expensive, it is desirable to use the cyclopentyl derivatives in further studies so as to minimize the error in ee values.
3.3 Conclusions

Catalytic asymmetric Michael reaction of various malonate derivatives with different Michael acceptor using chiral ammonium borate complexes prepared from chiral 1,1'-bi-2-naphthol, B(OH)$_3$, (S)-$\alpha,\alpha$-diphenylpyrrolidine methanol was investigated. The chiral ammonium borate complex catalyses the Michael addition of diethyl malonate to cyclohexenone in the presence of KOBu$_t$ to give the corresponding adducts in < 20% ee. Asymmetric Michael addition reaction using chiral oxazaborolidines derived from (S)-$\alpha,\alpha$-diphenylpyrrolidinemethanol and B(OMe)$_3$ catalyses the Michael reaction of diethyl malonate to cyclohexenone in the presence of KOBu$_t$ to give the corresponding adducts in < 62% ee. Plausible mechanism were considered. The asymmetric Michael addition reaction using chiral lithium alkoxide prepared from (S)-$\alpha,\alpha$-diphenylpyrrolidine methanol was also studied. The chiral lithium alkoxide complex in the presence of KOBu$_t$ catalyses the Michael reaction of diethyl malonate to cyclohexenone to give the corresponding adducts in < 70% ee.
3. 4 Experimental Section

3. 4. 1 General Information

Several of the general experimental details given in Chapter 1 and Chapter 2 are also applicable here. Cyclohexenone, cyclopentenone, dibenzyl malonate, diethyl malonate, di(t-butyl)malonate were purchased from Lancaster, U.K. (S)-α,α-Diphenyl-2-pyrrolidinemethanol (DPPM) was synthesized as described in chapter 1.

3. 4. 2 Preparation of chiral 1,1'-bi-2-naphthol ammonium borate complex

(S)-(-)-1,1'-Bi-2-naphthol (1.43 g, 5 mmol), B(OH)_3 (0.16 g, 2.5 mmol) and (S)-(-)-α,α-diphenyl-2-pyrrolidinemethanol (1.26 g, 5 mmol) were taken in CH₃CN (20 mL). The contents were refluxed for 12 h. The reaction mixture was cooled to 25 °C and filtered. The precipitate was washed with CH₃CN (2 x 5 mL) and dried under nitrogen atmosphere to get the corresponding ammonium borate complex 22. It was stored under nitrogen atmosphere for further use.
3. 4. 2. 1 Typical procedure for the reaction between diethyl malonate and cyclohexenone using chiral 1,1'-bi-2-naphthol ammonium borate complex 22.

To a stirred solution of the chiral 1,1'-bi-2-naphthol ammonium borate complex 22 (0.1 g, 1 mmol) in dry THF (50 mL), KOBu (0.1 g, 1 mmol) and diethyl malonate (0.8 g, 5 mmol) were successively added under nitrogen atmosphere at 25 °C. After stirring for 30 min, cyclohexenone (0.58 g, 6 mmol) dissolved in THF (10 mL) was added slowly and the contents were further stirred at 25 °C for 12 h. The reaction mixture was treated with 1N HCl (10 mL) and extracted with Et$_2$O (3X 20 mL). The combined organic extracts were washed successively with water and brine, and dried over anhydrous magnesium sulphate and concentrated. The residue was purified by column chromatography using hexane/EtOAc (93:7) as eluent to obtain the Michael adduct as a colourless oil.

![Chemical structure](image)

Yield 1.0 g (80%)

IR (neat) (cm$^{-1}$) 1730, 1230

$^1$H-NMR (5 ppm, CDCl$_3$) L20 (q, J = 6.8 Hz, 6H), 1.4-2.5 (m, 9H), 3.2
(d, J = 7.9 Hz, 1H), 4.1 (t, J = 7.1 Hz, 4H) (Spectrum No. 16)

$^{13}$C-NMR

(δ ppm, CDCl$_3$) 13.9, 24.4, 28.6, 37.9, 40.9, 45.0, 56.8, 61.3, 167.7, 209.4 (Spectrum No. 17)

[α]$^D_{25} = (+) 0.7 \ (c 3, \text{CHCl}_3)$, \{lit\} for 78% ee, [α]$^D_{25} = (+) 2.78 \ (c 2.56, \text{CHCl}_3)$

3. 4. 3 Preparation of chiral oxazaborolidine catalyst 24 using (S)-(−)-α, α-diphenyl-2-pyrrolidinemethanol and B(OMe)$_3$

To a solution of (S)-(−)-α, α-diphenyl-2-pyrrolidinemethanol (1.26 g, 5 mmol) in dry THF (5 mL), was added trimethyl borate (0.6 g, 5.2 mmol) and the mixture was stirred under nitrogen at 25 °C for 1 h. THF was removed under reduced pressure and dried under nitrogen to get oxazaborolidine complex 24.

3. 4. 4 Michael addition reaction of cyclohexenone with various malonate derivatives

3. 4. 4. 1 Typical procedure for the Michael reaction between diethyl malonate and cyclohexenone:

To a stirred solution of the oxazaborolidine catalyst 24 (1.45 g, 5 mmol) in toluene (50 mL), KOBu$^t$ (0.1 g, 1 mmol) and diethyl malonate (0.8 g, 5 mmol) were successively added under nitrogen atmosphere at 25 °C. After stirring for
30 min, cyclohexenone (0.58 g, 6 mmol) dissolved in toluene (10 mL) was added slowly and the contents were further stirred at 25 °C for 12 h. The reaction mixture was treated with 1N HCl (10 mL) and extracted with Et₂O (3X 20 mL). The combined organic extracts were washed successively with water and brine, and dried over anhydrous magnesium sulphate and concentrated. The residue was purified by column chromatography using hexane/EtOAc (93:7) as eluent to obtain the Michael adduct as a colourless oil.

Yield 0.9g (70 %)

IR (neat) (cm⁻¹) 1730, 1230

¹H-NMR (5 ppm, CDCl₃) L20 (q, J = 6.8 Hz, 6H), 1.4-2.5 (m, 9H), 3.2 (d, J = 7.9 Hz, 1H), 4.1 (t, J = 7.1 Hz, 4H)

¹³C-NMR (5 ppm, CDCl₃) 13.9, 24.4, 28.6, 37.9, 40.9, 45.0, 56.8, 61.3, 167.7, 209.4

[α]₀²⁵

[α]₀²⁵ = (+) 2.2 (c 3, CHCl₃), [lit²⁹ for 78% ee, [α]₀²⁵ = (+) 2.78 (c 2.56, CHCl₃)]
The spectral data showed 1:1 correspondence with the reported data. The above procedure is followed for the Michael reaction of various malonate esters with cyclohexenone, cyclopentenone, chalcone and methacrylate. The results are summarized in Scheme 26. The data are given below.

3. 4. 4. 2 Michael reaction of cyclohexenone with dimethyl malonate

![Schematic diagram of the reaction]

Yield  
0.80g (70 %)

IR (neat)  
(cm⁻¹) 1736, 1259

¹H-NMR  
(8 ppm, CDCl₃) 1.4-2.6 (m, 9H), 3.30 (d, J = 7.9 Hz, 1H), 3.7 (s, 6H) (Spectrum No. 18)

¹³C-NMR  
(S ppm, CDCl₃) 24.4, 28.7, 38.0, 40.9, 45.0, 52.4, 56.4, 168.1, 209.4 (Spectrum No. 19)

[α]₀²⁵ = (+) 2.4 (c 3, CHCl₃), \{lit²⁹ for 75% ee, [α]₀²⁵ = (+) 3.01 (c 2.1, CHCl₃)\}

The spectral data showed 1:1 correspondence with the reported data.⁵
3. 4. 4. 3 Michael reaction of cyclohexenone with di-\textit{t}-butyl malonate.

![Chemical Reaction Diagram]

Yield

1.0g (65%)

IR (neat)

\(\text{cm}^{-1}\) 1734, 1209

\(^1\text{H-NMR}\)

\(\delta\) ppm, CDCl\textsubscript{3} 1.5 (s, 18H), 1.92-2.58 (m, 9H), 3.10 (d, \(J = 7.7\) Hz, 1H), (Spectrum No. 20)

\(^{13}\text{C-NMR}\)

6 ppm, CDCl\textsubscript{3} 24.5, 27.8, 28.7, 37.7, 40.9, 45.0, 58.6, 81.6, 167.0, 209.5 (Spectrum No. 21)

\([\alpha]^{25}_D\)

\([\alpha]^{25}_D = (+)\) 1.1 (c 3, CHCl\textsubscript{3}), \{lit\textsuperscript{29} for 100% ee, \([\alpha]^{25}_D = (+)\) 4.2 (c 1.02, CHCl\textsubscript{3})\}

The spectral data showed 1:1 correspondence with the reported data.
3. 4. 4. 4 Michael reaction of cyclohexenone with dibenzyl malonate.

Yield 1.28 g (68%)

M. p. 44-45 °C (Lit 43°C)

IR (neat) (cm⁻¹) 1739, 1261

¹H-NMR (δ ppm, CDCl₃) 1.4-2.8 (m, 9H), 3.4 (d, J = 7.6 Hz, 1H), 5.2 (s, 4H) 7.2-7.4 (m, 9H) (Spectrum No. 22)

¹³C-NMR (8 ppm, CDCl₃) 24.5, 28.6, 38.1, 41.0, 45.0, 56.8, 67.2, 128.3, 128.5, 128.6, 135.3, 167.5, 209.2 (Spectrum No. 23)

[α]"₅(" = (+) 0.75 (c 3, CHCl₃), {lit²⁹ for 92% ee, [α]"₅(" = (+) 1.15 (C 2.21, CHCl₃)}

The spectral data showed 1:1 correspondence with the reported data."
3. 4. 4. 5 Michael reaction of cyclohexenone with α-methyl dibenzyl malonate

Yield 1.0g (70%)

IR (neat) (cm$^{-1}$) 1732, 1231

$^1$H-NMR ft ppm, CDCl$_3$) 1.20 (m, 1H), 1.4 (s, 3H), 1.5-2.7 (m, 8H), 5.1 (s, 4H), 7.3 (m, 10H)

$^{13}$C-NMR (5 ppm, CDCl$_3$) 16.8, 24.7, 26.6, 41.0, 42.6, 43.3, 57.0, 67.1, 128.1, 128.4, 128.6, 135.4, 170.5, 170.6, 209.4

$^r_{25}$ $\alpha$ $^2_{D} = 0.07(c \, 3, \text{CHCl}_3)$, {lit$^{29}$ for 87% ee, $\alpha$ $^2_{D} = (+) 0.32 (c$ 3.93, CHCl$_3$)}

The spectral data showed 1:1 correspondence with the reported data.$^5$
3. 4. 4. 6 Michael reaction of cyclopentenone with diethylmalonate.

Yield  

0.79g (71 %)

IR (neat)  

( cm ) 1732, 1231

\(^1\)H-NMR  

(5 ppm, CDCl\textsubscript{3}) 1.45-1.76 (m, 1H), 1.96 (dd, J=1 1.7, 1H), 2.05-2.35 (m, 3H), 2.46 (dd, J=6.8 Hz, 1H), 2.65-2.95 (m, 1H), 3.34 (d, J=9.3 Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H) (Spectrum No. 24)

\(^{13}\)C-NMR  

(8 ppm, CDCl\textsubscript{3}) 27.1, 36.1, 37.8, 42.5, 52.2, 55.8, 168.3, 216.4.  
(Spectrum No. 25)

\(\nu^5\)  

\(\{\alpha\}^2\text{D} = (+) 41.4 (c 3, \text{CHCl}_3), \{\text{lit}^2\text{D}\text{ for 100 % ee}, [\alpha]_\text{D}^2 = (+) 69.0 (c 3.93, \text{CHCl}_3)\}\)

The spectral data showed 1:1 correspondence with the reported data.\(^5\)
3. 4. 4. 7 Michael reaction of chalcone with dimethyl malonate

Yield 1.1 g (64%)

IR (neat) (cm$^{-1}$) 1739, 1680

$^1$H-NMR (5 ppm, CDCl$_3$) 3.5 (s, 3H), 3.6-3.7 (m, 2H), 3.8 (s, 3H), 3.9 (d, $J = 8.3$ Hz, 1H), 4.2 (m, 1H), 7.2-7.5 (m, 8H), 7.8-8.0 (m, 2H)

$^{13}$C-NMR (8 ppm, CDCl$_3$) 40.8, 42.3, 52.3, 52.6, 57.3, 127.2, 128.1, 128.4, 128.5, 128.6, 133.0, 136.9, 140.5, 168.1, 168.7, 197.5

(Spectrum No. 26)

$[\alpha]_D^{25} = (+)$ 3.3 (c 3, CHCl$_3$), {lit$^{29}$ for 77 %ee, $[\alpha]_D^{25} = (+)$ 25.64 (c 2, CHCl$_3$)}

The spectral data showed 1:1 correspondence with the reported data.$^5$
3. 4. 4. 8 Michael reaction of methylphenylacetate with methacrylate

Yield 0.76g (65 %)

IR (neat) \( (\text{cm}^{-1}) 1739, 1680 \)

\(^1\text{HNMR} \) (5 ppm, CDCl\(_3\)) 2.1-2.6 (m, 5H), 3.65 (s, 1H), 3.66 (s, 1H), 7.2-7.3 (m, 5H)

\(^{13}\text{C-NMR} \) (5 ppm, CDCl\(_3\)) 28.3, 31.6, 50.4, 51.5, 51.9, 127.4, 127.9, 128.4, 138.2, 171.1, 173.2, 173.8. (Spectrum No. 27)

\([\alpha]_D^{25} = (+) 4.4 (c 5, \text{EtOH}), \{\text{lit}^{18} \text{ for } 100 \% \text{ee}, [\alpha]_D^{25} \approx (+) 89 (c 5, \text{EtOH})\} \)

The spectral data showed 1:1 correspondence with the reported data.

3. 4. 5 Preparation of chiral oxazaborolidine catalyst 25 using \((R)-(-)\)-phenylglycinol and B(OMe)\(_3\)

To a solution of \((R)-(-)\)-phenylglycinol (0.7 g, 5 mmol) in dry THF (5 mL), was added trimethyl borate or tributyl borate (0.6 g, 5.2 mmol) and the
mixture was stirred under nitrogen at room temperature for 1 h. THF was removed under reduced pressure and dried under nitrogen to get the oxazaborolidine complex 25. The other oxazaborolidine complexes such as 26, 27 and 28 were also prepared by following the same procedure as mentioned above.

3. 4. 5. 1 Typical procedure for the reaction between diethyl malonate and cyclohexenone using oxazaborolidine complex 25.

To a stirred solution of the oxazaborolidine catalyst 25 (0.9 g, 5 mmol) in toluene (50 mL), KOBu\(^{+}\) (0.1 g, 1 mmol) and diethyl malonate (0.8 g, 5 mmol) were successively added under nitrogen atmosphere at 25 °C. After stirring for 30 min, cyclohexenone (0.58 g, 6 mmol) dissolved in toluene (10 mL) was added slowly and the contents were further stirred at 25 °C for 12 h. The reaction mixture was treated with 1N HCl (10 mL) and extracted with Et\(_2\)O (3X 20 mL). The combined organic extracts were washed successively with water and brine, and dried over anhydrous magnesium sulphate and concentrated. The residue was purified by column chromatography using hexane/EtOAc (93:7) as eluent to obtain the Michael adduct as a colourless oil.
Yield \(0.87 \text{g}(70\%)\)

\[\alpha\] \(^{25}\_D = (+) 0.7 (c 3, \text{CHCl}_3), \{\text{lit}^{29} \text{ for } 78\% \text{ ee, } \alpha\] \(^{25}\_D = (+) 2.78 (c 2.56, \text{CHCl}_3)\}

3. 4. 6 Preparation of chiral lithium alkoxide catalyst 2 using (S)-(−)-α, α-diphenyl-2-pyrrolidinemethanol and \(n\)-BuLi

To a solution of (S)-(−)-α, α-diphenyl-2-pyrrolidinemethanol (1.26 g, 5 mmol) dry hexane (5 mL), was added \(n\)-BuLi (2.17 g, 5.2 mmol) and the mixture was stirred under nitrogen at room temperature for 1 h. The chiral lithium alkoxide 29 formed in hexane solution was directly used for the Michael addition reaction.
3. 4. 6. 1 Typical procedure for the reaction between dimethyl malonate and cyclohexenone using chiral lithium alkoxide catalyst 29.

The dimethyl malonate (0.8 g, 5 mmol) was added to a stirred solution of the chiral lithium alkoxide catalyst 29 (1.29 g, 5 mmol) under nitrogen atmosphere at 25 °C. After stirring for 30 min, cyclohexenone (0.58 g, 6 mmol) dissolved in toluene (10 mL) was added slowly and the contents were further stirred at 25 °C for 12 h. The reaction mixture was treated with 1N HCl (10 mL) and extracted with Et₂O (3X 20 mL). The combined organic extracts were washed successively with water and brine, and dried over anhydrous magnesium sulphate and concentrated. The residue was purified by column chromatography using hexane/EtOAc (93:7) as eluent to obtain the Michael adduct as a colourless oil.

Yield 0.87 g (70 %)

\[ \alpha \]_D^25 = (+) 2.8 (c 3, CHCl₃), \{lit²⁹ for 75% ee, \[ \alpha \]_D^25 = (+) 3.01 (c 2.56, CHCl₃)\}

![Chemical reaction diagram]
3.5 References


