CHAPTER IV

Per-6-Amino-β-Cyclodextrin Catalyzed Asymmetric Michael Addition of Nitromethane and Thiols to Chalcones in Water

4.1 Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities to bind substrates selectively and catalyze chemical reactions through formation of reversible host-guest complex via non–covalent interactions.1 CD have provided the basis for numerous important studies on enzyme models and molecular recognition.2 In order to improve the CD’s performance as host to specific guest molecules, natural CDs have been extensively modified to increase their stereoselectivity for each guest molecule and CDs solubility.3 CDs and their derivatives have been intensively studied not only as excellent receptors for molecular recognition but also as good selectors for chiral separation, suitable carriers for delivery and selective molecular reactors.4 Various modified CDs like partially permethylated cyclodextrins, aminocyclodextrins and carboxymethylated cyclodextrins are employed as chiral discriminating agents in enantioseparation, in capillary electrophoresis, high performance liquid chromatography and chiral NMR analysis. In asymmetric catalysis, chemical modification of cyclodextrins improves the enantioselectivity of most of the reactions.

Peramino-CDs are CD derivatives modified by persubstitution at the primary face with amino pendant groups (Fig. 4.1) which manifest compromised hydrophobic binding, but additional electrostatic binding of guest molecules relative to native CDs. Presence of chiral hydrophobic cavity with amino groups on the primary side renders this CD an unique nanoreaction vessel for various chemical processes and transformations.
4.1.1 Chiral Recognition and Catalysis by Aminocyclodextrins

Charged form of per-6-amino-β-cyclodextrin (per-NH$_3^+$-β-CD) has been used is chiral recognition of α-amino acid derivatives.$^5$ Per-NH$_3^+$-β-CD forms strong complexes with the (S)-enantiomers of N-acetylated Trp, Leu and Val in their anionic forms more preferentially than the (R)-enantiomers, though the binding constants ($K$) between the enantiomers is small. Native CDs such as α- and β-CDs exhibit a very low ability to discriminate between the enantiomers of amino acids. Stability of the complexation is rationalized by the intermolecular Coulomb interactions between the amino acid and charged CDs. Binary complex of pyrene/per-6-ABCD acts as a chiral selector at two pH values for amino acids like phenylalanine, methionine and histidine and the stability of the ternary complex of pyrene/per-6-PABD/amino acid is determined by spectrofluorimetric measurements.$^6$ Per-β-ABCD is used as a chiral selector for the enantiomer separation in different classes of anionic analytes in capillary electrophoresis.$^7$

Per-6-ABCD catalyze the Kemp elimination of 5-nitrobenzisoxazole by 210-680 folds at physiological pH$^8$ (Scheme 4.1). The rate acceleration in catalysis has been derived partly from the basic amine group of per-6-ABCD at neutral pH and in
an annulus of cationic ammonium groups which stabilize the anionic transition state. Amino CDs are used to facilitate deprotonation.\(^9\) 6\(^A\)-Amino-6\(^A\)-deoxy-\(\beta\)-cyclodextrin enhances the rate of deprotonation of 4-\(\text{tert}\)-butyl-\(\alpha\)-nitrotoluene to a greater extent than native CDs.

![Scheme 4.1 Catalysis of Kemp elimination by per-6-ABCD (I)](image)

**Scheme 4.1 Catalysis of Kemp elimination by per-6-ABCD (I)**

### 4.1.2 Michael Addition

Conjugate addition of a carbon nucleophile, generally known as Michael addition\(^{10,11}\) is an important and essential synthetic tool for the conversion of unsaturated compounds into saturated higher analogues. This catalytic asymmetric conjugate addition\(^{12}\) of stabilized carbanions to \(\alpha,\beta\)-unsaturated enones is one of the most powerful C-C bond-forming reactions to construct enantioenriched, highly functionalized carbon skeletons for the total synthesis of natural and biologically active compounds. Its strategic importance is evident by considering that a Michael addition can represent the initiating step of more complex inter- and intramolecular tandem processes.\(^{13}\)

Among the Michael acceptors, nitroalkanes are very attractive, because the nitro group\(^{14}\) is the most electron-withdrawing group known\(^{15}\) and is often described as a synthetic chameleon.\(^{16}\) The Nef reaction,\(^{17a}\) nucleophilic displacements,\(^{17b}\)
reduction to amino\(^{17c}\) group and conversion into a nitrile oxide\(^{17d}\) are some examples of the possible transformations that nitro group can undergo. Various efforts have been devoted to develop efficient catalysts for the enantioselective addition of nitroalkanes to \(\alpha,\beta\)-unsaturated carbonyl compounds. In particular enantioselective addition of nitromethane to \(\alpha,\beta\)-enones to form chiral \(\gamma\)-nitroketones, which is a versatile intermediate and serving as starting material for a variety of further elaborated structures.

4.1.2.1 Asymmetric Michael Addition

Several attempts have been made towards achieving asymmetric conjugate addition of nitromethane to chalcone in presence of various chiral catalysts to achieve good enantioselectivities. Chiral metal complexes have been employed for asymmetric induction. Nickel(II) complexes\(^{18}\) with chiral nitrogen ligand such as bipyridines, 1, 10-phenanthrolines and 1,2-diamino compounds are used as chiral catalysts in asymmetric Michael addition of nitromethane to benzalacetone, chalcone and 2-cyclohexanone. Ni(II) and Co(II) metals complexes with proline derived ligands\(^{19}\) are also reported as chiral ligands in asymmetric Michael addition and \(ee\) is upto 38% is reported.

Shibasaki \textit{et. al.}, have used \(\text{LaK}_3\text{tris-}((R)\text{-binaphthoxide}^{20}((R)\text{-LPB})\) as an efficient catalyst for addition of nitromethane to chalcones with upto 97% \(ee\) in the presence of \(1^9\text{BuOH}\) (1.2 or 2 equiv) mol % to achieve efficient catalysis (Scheme 4.2).

![Scheme 4.2 Lanthanum tris-binaphthoxide catalyzed Michael addition](image)

\(ee = 95\text{-}97\%\)
\(Yield 59\text{-}71\%\)
Yamaguchi et al., have reported proline salts\textsuperscript{21} as chiral catalysts for asymmetric Michael addition of nitroalkanes to prochiral acceptors. When (2S)-L-proline is used, acyclic (\(E\))-enones give (S)-adducts and cyclic (\(Z\))-enones give (R)-adducts predominantly.

Various alkaloids based on cinchona and ephedrine have been reported for the enantioselective Michael addition.\textsuperscript{22} Wynberg et al., have demonstrated that natural cinchona alkaloids with C-9 alcohol and a quinclidine could serve as a bifunctional chiral catalyst in Michael addition\textsuperscript{23} (Scheme 4.3). Natural cinchona alkaloid namely quinine- or quinidine-acrylonitrile copolymer is also employed as a catalyst in this reaction. Pressure plays a major role in controlling the \textit{ee} of the reaction and 56 \% \textit{ee} is achieved as maximum.

\begin{center}
\textbf{Scheme 4.3} Natural cinchona alkaloid used in asymmetric Michael addition
\end{center}

Corey et al., have been reported enantioselective Michael addition of nitromethane to an \(\alpha,\beta\)-enone, which is a key step in the synthesis of (R)-baclofen (therapeutically useful GABA\textsubscript{B} receptor)\textsuperscript{24} (Scheme 4.4)

\begin{center}
\textbf{Scheme 4.4} Synthesis of (R)-baclofen via cinchoninium salt catalysed enantioselective Michael addition
\end{center}
Vakulya et. al., have synthesized cinchona alkaloid-derived chiral bifunctional thiourea organocatalyst like epithiourea and its pseudoenantiomer having Lewis acidic thiourea moiety,\textsuperscript{25} which is successfully used as an efficient chiral catalyst for enantioselective addition of nitromethane to chalcones with good \textit{ee} upto 96\% (Scheme 4.5).

\textbf{Scheme 4.5} Asymmetric Michael addition catalyzed by thiourea derivatized cinchona alkaloid.

Sundarajan et. al., have developed a polymer chiral ligand and polymer-anchored chiral catalyst\textsuperscript{26} as promoters for asymmetric Michael addition of nitromethane to chalcone with good yield and good enantioselectivity (Scheme 4.6). In this method the chiral catalyst is recovered by simple filtration and reused. This catalyst also catalyzes the addition of thiophenols to unsaturated cycloalkenones resulting in good yield and moderate enantioselectivity.

\textbf{Scheme 4.6} Polymer-anchored chiral catalyst for asymmetric Michael addition of nitromethane to chalcone
4.1.2.2 Asymmetric Thia-Michael Addition

Construction of C-S bond is a key step in the synthesis of organo sulfur compounds in total synthesis. Carbon-sulfur bond formation by conjugate addition of thiols to α,β-unsaturated carbonyl compounds, has versatile application in chemistry and biology as it plays critical roles in (i) biosynthesis (ii) synthesis of bioactive compounds, (iii) protection of olefinic double bond of enones and (iv) generation of β-acylvinyl cations and homoenolate anion equivalents. The development of novel protocols for conjugate addition of thiols to electron deficient olefins leading to the formation of C-S bond has attracted considerable attention in synthetic organic chemistry. The Michael addition has metamorphosed over the years to allow a number of reagents and catalysts and alternative procedure to be used. For instance, a variety of inorganic salts, quaternary ammonium salts, ionic liquids (IL), a combine of IL and water, palladium, supported CeCl₃·7H₂O/NaI, clay, siliga gel, SiO₂/HClO₄, solid acid, KF/alumina, polyethylene glycol(PEG), Cu(acac)₂/IL, boric acid in water and even a micellar solution of sodium dodecyl sulfate (SDS) have been employed in thia-Michael addition. However, the development of a general and highly enantioselective 1,4-addition of thiols to α,β-unsaturated enones remains a challenging goal despite attempts involving organic catalysts, metal based catalysts and phase transfer catalysts.

Heterobimetallic asymmetric complexes like LaNa₃-tris(binaphthoxide) (LSB) and SmNa₃-tris(binaphthoxide) complexes (SmSB) have been used as efficient catalysts for asymmetric Michael addition of thiols to cycloalkenones and (R)-LSB gives the best result (Scheme 4.7).
Scheme 4.7 Asymmetric Michael additions of thiols to enones promoted by LSB

Chiral hafnium catalyst $\text{Hf(OTf)}_4$\textsuperscript{40} has been reported (Scheme 4.8) in asymmetric Michael reactions of thiols to 3-(2-alkenoyl)-2-oxazolidinones, affording the corresponding adducts in high yields with moderate to good ee. Iron/Pybox ($\text{Fe(BF}_4)_2 \cdot \text{MS}_4 \cdot \text{A}$)\textsuperscript{41} catalyst has also been used in enantioselective thiol addition to (E)-3-crotonoyloxazolidin-2-one (upto 95 % ee).

Scheme 4.8 Chiral Hafnium complex-catalyzed asymmetric Michael addition of thiols

Proline is used to catalyze the conjugate addition of thiophenol to cyclohexenone\textsuperscript{42a} which proceeds with poor enantioselectivity. Kotrusz et. al.,\textsuperscript{42b} and Meciarove et. al.,\textsuperscript{42c} have observed the same result with L-proline in ionic liquid also.

Michael addition to chalcone derivatives is very interesting and challenging as it is less facile compared to the addition of aliphatic acyclic enones and thus it is not always satisfactory with the conventional reagents used for general 1,4-addition. Recently, a number of procedures involving a variety of catalysts such as synthetic
diphosphate Na₂CaP₂O₇,⁴³ᵃ natural phosphate,⁴³ᵇ InBr₃⁴³ᶜ,ᵈ and fluorapatite⁴³ᵉ have been reported in thiol addition to chalcones. However, only a limited number of examples have been reported in asymmetric addition of thiols to chalcone. Wynberg et al.,²³ᵇ examined the Michael reaction catalyzed by chiral β-amino alcohols including cinchona alkaloids, but resulted in poor enantioselectivity. Using metal complex⁴⁴ catalyst high ee is obtained.

Recently, (+)-cinchonine⁴⁵ has been used as a good catalyst in enantioselective addition of thiophenols to chalcone (Scheme 4.9) and gives better ee upto 97 %. This is one of the best examples of asymmetric thiol addition with better enantiomeric excess.

\[
\text{O} \quad \text{O} \\
\text{SPh} \\
(+)-\text{Cinchonine (1.5 mol %)} \\
\text{Toluene} \\
\text{ee > 97 %} \\
\]

Scheme 4.9 (+)-Cinchonine catalyzed asymmetric Michael addition of thiophenol to chalcone

4.1.4 Cyclodextrin Catalyzed Michael Addition

Sakuraba et al.,⁴⁶ has first studied cyclodextrin mediated Michael addition of various arenethiols to 2-cyclohexenone and maleic acid esters in water under nitrogen atmosphere (Scheme 4.10). However this reaction show longer reaction time of over seven days and poor ee upto 2-12% only.
Recently, native β-CD catalyzed conjugate addition of arenethiols to conjugated alkenes has been reported in aqueous medium\textsuperscript{47} (Scheme 4.11). This method avoids the use of external acids/bases and gives high yield. This simple operation procedure is suitable and this reaction is catalyzed from the wider rim by secondary hydroxyl groups.

Rama Rao et al.,\textsuperscript{48} have reported environmentally benign aza-Michael addition of amines to α, β-unsaturated compounds catalyzed by β-cyclodextrin in water. The corresponding β-amino compounds are obtained in excellent yields under mild conditions. In this reaction, β-cyclodextrin can be recovered and reused.

\textit{Scheme 4.10} Cyclodextrin mediated Michael addition

\textit{Scheme 4.11} Michael addition of thiols to conjugated alkenes using β-CD in water
With green chemistry becoming a central issue in both academic and industrial research in recent days,\textsuperscript{49} the development of environmentally benign and clean synthetic procedures has become the goal of present day organic synthesis. Thus, there is need for developing Michael addition in water with a recyclable catalyst and without the use of any harmful organic solvents since water is a safe, economical and environmentally benign solvent. To achieve these ideal conditions, a good choice appears to be through supramolecular catalysis involving CDs.\textsuperscript{50} Modification in CDs also alters the reactivity and enhances its catalytic properties. Hence in the present work, aminomodified CD namely heptakis(6-amino-6-deoxy)-\(\beta\)-cyclodextrin (per-6-ABCD) \textbf{I} has been successfully employed as a chiral base catalyst and a host for conjugate addition of nitromethane and thiols to trans-chalcone in aqueous medium at room temperature and the observed results are discussed below.

\begin{center}
\textbf{Scheme 4.12} Per-6-amino-\(\beta\)-cyclodextrin catalyzed asymmetric Michael addition of nitromethane and thiols to chalcone in water
\end{center}

\section*{4.2 Results and Discussion}

Table 4.1 shows the results of our preliminary studies with per-6-ABCD \textbf{I} to mediate asymmetric 1,4-addition with different Michael acceptors and donors in water. \textbf{I} fails in the conjugate addition of diethyl malonate and malononitrile with
trans-chalcone 2. Though conjugate addition of 3 to benzylideneacetone is effectively catalyzed, very poor enantioselectivity is noticed. On the other hand 1 turns out to be a very good catalyst for the conjugate addition of 3 to 2, resulting in good conversion as well as enantiomeric excess upto 68.5%. The absolute configuration is determined as S by comparing with the reported specific rotation values.27 When the reaction is carried out with native β-cyclodextrin in water, it fails completely to catalyze the addition. When triethylamine is employed as an external base along with native β-CD, good conversion is noticed, but with very poor enantiomeric excess (-2.4%). These preliminary results clearly shows that 1 acts as an useful catalyst for the addition of 3 to 2 in aqueous medium.

**Table 4.1** Per-6-ABCD 1 catalyzed asymmetric Michael addition with different Michael acceptors and donors

<table>
<thead>
<tr>
<th>Entry</th>
<th>Michael acceptor</th>
<th>Michael donor</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% ee&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chalcone</td>
<td>Diethyl malonate</td>
<td>7.80</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Chalcone</td>
<td>Malononitrile</td>
<td>nil</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Benzylideneacetone</td>
<td>Nitromethane</td>
<td>100</td>
<td>2.80</td>
</tr>
<tr>
<td>4</td>
<td>Chalcone</td>
<td>Nitromethane</td>
<td>100</td>
<td>68.5 (&lt;i&gt;S&lt;/i&gt;)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Chalcone&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Nitromethane</td>
<td>nil</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Chalcone&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Nitromethane</td>
<td>98.0</td>
<td>-2.4</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions are carried out in water for 24 h at room temperature; <sup>b</sup> Analyzed by GC; <sup>c</sup> Analyzed by HPLC using Chiralcel AD-H column; <sup>d</sup> Absolute configuration is determined by comparing the specific rotation with that of literature data;<sup>19</sup> <sup>e</sup> With native β-cyclodextrin; <sup>f</sup> With native β-cyclodextrin and triethylamine as an external base.

Influences of other experimental parameters such as solvent, catalyst amount and temperature are also optimized using 1. Conjugate addition of 3 to 2 is studied separately in water and four different organic solvents (Table 4.2). In ACN, toluene and DMF, catalyst 1 is inactive. In methanol, better yield with low ee is observed. In water in addition to complete conversion, better enantiomeric excess is achieved under this reaction condition. Equimolar amounts of catalyst and substrate are employed in all the reactions as it forms a 1:1 complex which gives good chemical
**Table 4.2** Per-6-ABCD 1 catalyzed asymmetric Michael addition in various solvents and with different amounts of catalyst\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Per-6-ABCD: Chalcone (^b)</th>
<th>Yield (%) (^c)</th>
<th>% ee (^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ACN</td>
<td>1:1</td>
<td>nil</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>1:1</td>
<td>nil</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Methanol</td>
<td>1:1</td>
<td>100</td>
<td>34.6</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>1:1</td>
<td>nil</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Water</td>
<td>1:1</td>
<td>100</td>
<td>68.5</td>
</tr>
<tr>
<td>6</td>
<td>Water</td>
<td>1:0.25</td>
<td>100</td>
<td>66.0</td>
</tr>
<tr>
<td>7</td>
<td>Water</td>
<td>1:0.50</td>
<td>100</td>
<td>66.8</td>
</tr>
<tr>
<td>8</td>
<td>Water</td>
<td>1:2</td>
<td>100</td>
<td>67.2</td>
</tr>
<tr>
<td>9</td>
<td>Water</td>
<td>1:1</td>
<td>100</td>
<td>63.6</td>
</tr>
</tbody>
</table>

\(^a\)All reactions are carried out in room temperature for 24 h, 10 mL of solvent is used for each reaction. After completion of the reaction, solvents are evaporated in vacuum and products are extracted with ethyl acetate; \(^b\)Mole ratio; \(^c\)Analyzed by GC; \(^d\)Analyzed by HPLC using Chiralcel AD-H column; \(^e\)Carried out at 4 °C

yield and ee. When the reaction is carried out at low temperature (4 °C), no significant improvement in ee is noticed.

This procedure thus avoids environmentally hazardous organic solvents. Use of aqueous medium also has several other advantages: the reaction proceeds under simpler experimental conditions at ambient temperature with no metals and other harmful external acids or bases. The reaction is also studied with various substituted chalcones as substrates. As shown in table 4.3, addition of 3 to substituted chalcones 2a-k containing electron-withdrawing and electron-donating groups in the phenyl ring are studied. In most cases the corresponding Michael adducts are obtained in good yields and also with better enantiomeric excess suggesting that electronic factors have only a limited role to play. The highest ee is observed with 2k, which contains 3-nitro group (which may ensure a stronger binding into CD cavity). Chiral HPLC traces depicting ee in case of representative reaction are given in figs. 4.40-4.50.
Table 4.3 Per-6-ABCD 1 catalyzed asymmetric Michael addition of nitromethane 3 to chalcones 2a-k

\[
\begin{align*}
\text{Entry} & \quad \text{Chalcones} & \quad \text{Yield (\%)}^b & \quad \% \text{ ee}^c \\
1 & 2a & H & H & 4a & 100 & 68.5 \\
2 & 2b & H & 4-Cl & 4b & 100 & 55.4 \\
3 & 2c & H & 2,3-Cl & 4c & 94.0 & 57.4 \\
4 & 2d & H & 4-CH_3 & 4d & 45.1 & 70.0 \\
5 & 2e & H & 4-F & 4e & 85.3 & 72.8 \\
6 & 2f & H & 3-OCH_3 & 4f & 91.7 & 22.4 \\
7 & 2g & H & 4-CH_3 & 4g & 100 & 62.6 \\
8 & 2h & H & 3-OCH_3 & 4h & 90.0 & 54.0 \\
9 & 2i & H & 3-NO_2 & 4i & 100 & 71.4 \\
10 & 2j & H & 3-NO_2 & 4j & 56.9 & 25.0 \\
11 & 2k & H & 3-NO_2 & 4k & 100 & 87.0 \\
\end{align*}
\]

\(^a\)All reactions are carried out in water at room temperature for 24 h. All the products are characterized by \(^1\)H and \(^13\)C NMR; \(^b\) Isolated yield; \(^c\) Analyzed by HPLC using Chiralcel AD-H column.

The reusability of per-6-ABCD 1 as a catalyst is also examined. Even after three consecutive reactions, it has retained its catalytic activity resulting in hundred

Table 4.4 Reusability of per-6-ABCD 1 in asymmetric Michael addition of 3 with 2

\[
\begin{align*}
\text{Entry} & \quad \text{Substrate} & \quad \text{Run}^b & \quad \text{Yield (\%)}^c & \quad \% \text{ ee}^d \\
1 & 2a & \text{First} & 100 & 68.5 \\
2 & 2a & \text{Second} & 100 & 66.8 \\
3 & 2a & \text{Third} & 100 & 58.0 \\
\end{align*}
\]

\(^a\)Reaction is carried out in water for 24 h in room temperature; \(^b\) After completion of the reaction 1 was filtered, washed with ethyl acetate for three times, dried in vacuum and reused; \(^c\) Analyzed by GC; \(^d\) Analyzed by HPLC using Chiralcel AD-H column.
percent yield, however, the enantiomeric excess has decreased considerably only in the third run.

Though various chiral catalysts are employed for the asymmetric conjugate addition between α, β-unsaturated ketone and arenethiols, studies are not extended to addition of aliphatic thiols. To extend the scope of the present protocol further, per-6-ABCD 1 is also employed in enantioselective Michael addition of aliphatic thiols to trans-chalcones 2a, b, g under the present conditions and the observed results are given in table 4.5. Butanethiol undergoes addition to 2a with good yield and poor ee. With an increase in chain length as in octanethiol, though the yield has decreased, a marked improvement in ee is noticed. These results provide additional support that coinclusion of the Michael donor and acceptor inside the CD cavity is necessary to achieve significant ee in the presence study. On the other hand when compared with nitromethane addition, the conversion is moderate and only marginal ee is observed. With thiophenol, though the yield is good, ee is very low compared

### Table 4.5 Per-6-ABCD 1 catalyzed asymmetric Michael addition of thiols to chalcones 2a,b,g

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chalcones</th>
<th>Thiols (RSH)</th>
<th>Yield (%)</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>n-Butanethiol</td>
<td>100</td>
<td>23.0</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>n-Octanethiol</td>
<td>49.2</td>
<td>42.2</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>Thiophenol</td>
<td>75.5</td>
<td>4.00</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>n-Butanethiol</td>
<td>82.0</td>
<td>29.0</td>
</tr>
<tr>
<td>5</td>
<td>2b</td>
<td>n-Octanethiol</td>
<td>49.9</td>
<td>60.6</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td>n-Octanethiol</td>
<td>54.4</td>
<td>18.2</td>
</tr>
</tbody>
</table>

*aAll reactions are carried out in water at room temperature for 24 h and the products are characterized by $^1$H and $^{13}$C NMR; b Isolated yield; c Analyzed by HPLC using Chiralcel OD-H column*
with aliphatic thiols. In all cases, no disulphide formation is observed in water medium.

The observed reactivity and enantioselectivity in presence of 1 are rationalized by proposing a suitable mechanism. Michael addition of 3 to 2 takes place inside the cavity of 1 and the mode of inclusion is visualized as shown in scheme 4.13. The phenyl ring along with olefinic double bond is deeply penetrated inside the cavity and the benzoyl part of 2 stays out of the wider rim of 1. This type of inclusion is preferred more as evident from energy minimization studies. This mode of inclusion (Mode A, Fig. 4.2) has lower complexation energy ($\Delta E = -38.00$ Kcal M$^{-1}$) than the other mode (Mode B, Fig. 4.2) in which the benzoyl moiety penetrates inside the cavity and the phenyl group with olefinic double bond stays outside ($\Delta E = -36.60$ Kcal M$^{-1}$). This complexation is stabilized by formation of hydrogen bonding between chalcone’s 2 carbonyl group and per-6-ABCD’s 1 secondary hydroxyl groups (Fig. 4.2). During the addition of 3, a ternary complex of 2 and 3 with 1 is formed, which has a higher binding constant (3674 M$^{-1}$). This ternary complex is more stable than a binary complex (1391 M$^{-1}$) of 1 and 2 which is also supported by molecular modeling studies. Primary amino groups present in the narrow rim of 1 act as an internal base (pKa 6.5 to 8.9),$^{51}$ activating the nitromethane by abstracting a proton followed by nucleophilic attack, which is favored from the amino functionalized narrow rim side of 1. This leads to the formation of the major isomer $S$ and it is conformed from the specific rotation$^{19}$ of the adduct. If the attack takes place from the wider rim of CD, it may lead to formation of $R$ enantiomer, which is obtained as major isomer, in $\beta$-CD, triethylamine system (Table 4.1, Entry 6) and not observed with 1. Active participation and catalysis by the amino groups of 1 is also supported by the following fact that per-6-amino-$\beta$-cyclodextrin hydrochloride fails to catalyze the addition of 3 to 2. Complexation energies of two enantiomers $R$ and $S$ of Michael adduct 4a with CD are also calculated and confirms that $S$ enantiomer forms a more
stable complex with (ΔE = -46.03 Kcal M⁻¹, mode C, fig. 4.3) than the corresponding R enantiomer (ΔE = -35.47 Kcal M⁻¹, mode D, fig. 4.3).

Figure 4.2 CVFF-optimized inclusion complex of per-6-ABCD 1 with trans-chalcone 2a;
In mode A: Chalcone’s olefinic double bond is inside the CD-cavity and benzoyl part is outside the cavity.
In mode (B: olefinic double bond is outside the CD-cavity and benzoyl part is inside the cavity.
Figure 4.3 CVFF-optimized inclusion complex of per-6-ABCD 1 with S-enantiomer of Michael adduct 4a (mode C) and R-enantiomer of Michael adduct 4a (mode B).
A similar mechanism involving a ternary complex involving chalcone and thiols inside the cavity of per-6-ABCD is also proposed to account for the observed asymmetric Michael addition of thiols to chalcone.

4.3 Conclusions

In conclusion, per-6-ABCD is successfully employed for the first time as a chiral catalyst and base for asymmetric Michael addition of nitromethane and aliphatic thiols to chalcones in aqueous medium. Per-6-ABCD 1 performs a dual role, acting both as a base to catalyze the reaction and also as a chiral inductor by enhancing the enantiomeric excess. In both the additions of nitromethane and thiols, better enantioselectivities are observed and water is employed (without any cosolvent) as an eco-friendly solvent in this asymmetric Michael addition and the catalyst is reused without any loss in its activity. The reaction takes place readily at room temperature and does not require lower temperature to achieve good ee. Other advantages include much more simpler experimental conditions, ease of recovery and reuse of catalyst, absence of hazardous external acids and bases.
4.3 Experimental

4.3.1 Binding Constant Measurements

Binding constants are calculated by non-linear regression using prism software (trial version) in an IBM compatible personal computer with Microsoft Windows XP service pack 2 operating system.

**Fig. 4.4** Binding constants curve for per-6-ABCD (1) with trans-chalcone (2) in pH < 6 (calculated by non-linear curve fitting method) \([\text{chalcone}] = 6 \times 10^{-5}\) [per-6-ABCD] is varied from \(6 \times 10^{-5}\) to \(6 \times 10^{-3}\) M

**Fig. 4.5** Binding constant curve for per-6-ABCD (1), trans-chalcone (2) and nitromethane (3) for ternary complex formation in pH < 6 (calculated by non-linear curve fitting method). \([\text{chalcone}] = 6 \times 10^{-5}\) M, \([\text{nitromethane}] = 6 \times 10^{-5}\) M and [per-6-ABCD] is varied from \(6 \times 10^{-5}\) to \(6 \times 10^{-3}\) M
4.3.2 Procedure for Asymmetric Michael Addition of Nitromethane (3) to Chalcones (2)

Per-β-ABCD 1, (0.112 g, 0.1 mmol) was dissolved in water (10 mL). trans-Chalcone 2 (0.02 g, 0.1 mmol) dissolved in acetone (1 mL) was added dropwise to 1 with constant stirring and continued for an hour to complete complexation. Then nitromethane 3 (0.024 mL, 0.4 mmol) was added and allowed to stir at room temperature for 24 h. After completion of the reaction, product was extracted with ethyl acetate, dried with sodium sulphate and concentrated under reduced pressure. Resulting crude product was purified by passing over a column of siliga gel 60-120 mesh using pet-ether/ethyl acetate (8/2 ratio as an eluent) affording Michael adduct 4 as a pale yellow solid which was analyzed by NMR spectroscopy (300 MHz, CDCl₃, T = 300 K, TMS = 0 ppm) and CSP (Chiral Stationary Phase)-HPLC. Percentage ee was determined by HPLC at 254 nm using chiralcel AD-H column, with n-hexane-i-propanol (90:10) mixture at a flow rate 1.0 mL/min. After extraction of the product, per-6-ABCD is washed thrice with ethyl acetate, filtered, dried in vacuum and reused.

4.3.3 Procedure for Asymmetric Michael Addition of Thiols to Chalcones (2)

Per-β-ABCD 1, (0.112 g, 0.1 mmol) was dissolved in water (10 mL). trans-Chalcone 2 (0.02 g, 0.1 mmol) was dissolved in acetone (1 mL) and was added dropwise to 1 with constant stirring and continued for an hour to complete complexation. Then n-butane-thiol (0.01 mL, 0.1 mmol) was added and allowed to stir at room temperature for 24 h. After completion of the reaction, product was extracted with ethyl acetate, dried with sodium sulphate and concentrated under reduced pressure and resulting crude product was purified by passing over a column of siliga gel 60-120 mesh using pet-ether/ethyl acetate (9/1 ratio as an eluent) affording Michael adduct 5 as a yellow oil liquid which was analyzed by NMR.
spectroscopy (300 MHz, CDCl$_3$, T = 300 K, TMS = 0 ppm) and CSP-HPLC. Percentage $ee$ was determined by HPLC at 254 nm using chiralcel OD-H column, with n-hexane-i-propanol (90:10) mixture at a flow rate 1.0 mL/min.

**4-Nitro-1,3-diphenylbutan-1-one (4a)$^{11}$**. The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 9/1 as eluant). $[\alpha]_D^{25}$ -11.1, (c, 1.00, CH$_2$Cl$_2$), $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.91 (d, $J = 8.4$ Hz, 2H), 7.25-7.60 (m, 8H), 4.83 (ABX, $J_{AB} = 12.3$ Hz, $J_{AX} = 6.6$ Hz, $J_{BX} = 7.8$ Hz, 1H), 4.71 (ABX, $J_{AB} = 12.3$ Hz, $J_{AX} = 6.6$ Hz, $J_{BX} = 7.8$ Hz, 1H), 4.23 (br pseudo quintet, $J = 7.2$ Hz, 1H), 3.38-3.53 (m, 2H) (Fig. 4.6). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 196.8, 139.0, 136.3, 133.5, 129.0, 128.7, 128.0, 127.8, 127.4, 79.5, 41.4, 39.2 (Fig. 4.7). HPLC: 68.5% $ee$, $t_{major}$ 15.5 min, $t_{minor}$ 20.2 min. (Fig. 4.40)

**3-(4-Chlorophenyl)-4-nitro-1-phenylbutan-1-one (4b)**. The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 8/2 as eluant). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.91 (d, $J = 8.1$ Hz, 2H), 7.59 (t, $J = 7.2$ Hz, 1H), 7.46 (t, $J = 7.2$ Hz, 2H), 7.31 (d, $J = 8.7$ Hz, 2H), 7.23 (d, $J = 3.4$ Hz, 2H), 4.82 (ABX, $J_{AB} = 12.6$ Hz, $J_{AX} = 6.6$ Hz, $J_{BX} = 8.1$Hz, 1H), 4.66 (ABX, $J_{AB} = 12.6$ Hz, $J_{AX} = 6.6$ Hz, $J_{BX} = 8.1$Hz, 1H), 4.22 (br pseudo quintet, $J = 7.2$ Hz, 1H), 3.46 (ABX, $J_{AB} = 18$ Hz, $J_{AX} = 6.6$ Hz, $J_{BX} = 7.2$ Hz, 1H), 3.40 (ABX, $J_{AB} = 18$ Hz, $J_{AX} = 6.6$ Hz, $J_{BX} = 7.2$ Hz, 1H) (Fig. 4.8). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 196.4, 137.5, 136.1, 133.7, 132.2, 129.2, 128.8, 128.7, 127.9, 79.3, 41.3, 38.6 (Fig. 4.9). HPLC: 55.4% $ee$, $t_{major}$ 17.7 min, $t_{minor}$ 25.1 min. (Fig. 4.41)

**3-(2,3-Dichlorophenyl)-4-nitro-1-phenylbutan-1-one (4c)**. The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 8/2 as eluant). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.92 (d, $J$
= 8.1 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.40-7.50 (m, 4H), 7.15 (d, J = 8.1 Hz, 1H),
4.82 (ABX, J_{AB} = 12.7 Hz, J_{AX}=6.3 Hz, J_{BX} = 8.1 Hz, 1H), 4.66 (ABX, J_{AB} = 12.7 Hz, J_{AX}=6.3, J_{BX} = 8.1 Hz, 1H), 4.21 (br pseudo quintet, J = 6.9 Hz, 1H), 3.43 (d, J = 6.6 Hz, 2H) (Fig. 4.10). 

$^{13}$C -NMR (75 MHz, CDCl$_3$): δ 196.0, 139.3, 135.9, 133.8, 133.1, 132.0, 130.9, 129.5, 128.8, 127.9, 126.9, 78.9, 41.1, 38.3 (Fig. 4.11). HPLC: 57.4 % ee, $t_{\text{major}}$ 15.7 min, $t_{\text{minor}}$ 19.7 min. (Fig. 4.42).

### 3-(4-Chlorophenyl)-4-nitro-1-p-tolyllbutan-1-one (4d).

The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 8/2 as eluant). 

$^1$H-NMR (300 MHz, CDCl$_3$): δ 7.81 (d, J = 8.1 Hz, 2H), 7.21-7.37 (m, 6H), 4.82 (ABX, J_{AB} = 12.6 Hz, J_{BX} = 8.4 Hz, 1H), 4.65 (ABX, J_{AB} = 12.6 Hz, J_{BX} = 8.4 Hz, 1H) 4.21 (br pseudo quintet J = 6.9 Hz, 1H), 3.41 (ABX, J_{AB} = 17.7 Hz, J_{AX} = 6.9 Hz, J_{BX} = 8.1 Hz, 1H), 3.39 (ABX, J_{AB} = 17.7 Hz, J_{AX} = 6.9 Hz, J_{BX} = 8.1 Hz, 1H), 2.14 (s, 3H) (Fig. 4.12). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 196.0, 144.6, 137.6, 133.6, 130.5, 129.4, 129.2, 128.8, 128.1, 79.3, 41.1, 38.6, 21.6 (Fig. 4.13). HPLC: 70.0 % ee, $t_{\text{major}}$ 19.7 min, $t_{\text{minor}}$ 25.2 min. (Fig. 4.43).

### 3-(4-Fluorophenyl)-4-nitro-1-phenylbutan-1-one (4e).

The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 8/2 as eluant). 

$^1$H-NMR (300 MHz, CDCl$_3$): δ 7.91 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.26 (t, J = 8.1 Hz, 2H), 7.02 (t, J = 8.1Hz, 2H), 4.82 (ABX, J_{AB} = 12.3 Hz, J_{AX} = 6.6 Hz, J_{BX} = 8.1 Hz, 1H), 4.65 (ABX, J_{AB} = 12.3 Hz, J_{AX} = 6.6 Hz, J_{BX} = 8.1 Hz,1H) 4.22 (br pseudo quintet J = 7.5 Hz, 1H), 3.43 (dd, J = 6.9 Hz, 1.2 Hz, 2H) (Fig. 4.14). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 196.5, 163.7, 136.2, 134.7, 133.6, 129.0 (d), 128.7, 127.6, 115.9 (d), 79.5, 41.4, 38.5 (Fig. 4.15). HPLC: 72.8 % ee, $t_{\text{major}}$ 16.9 min, $t_{\text{minor}}$ 23.3 min. (Fig. 4.44)
1-(4-Bromophenyl)-4-nitro-3-phenylbutan-1-one (4f). The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 8/2 as eluant). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.77 (d, $J$ = 8.7 Hz, 2H), 7.59 (d, $J$ = 8.4 Hz, 2H), 7.26-7.36 (m, 5H), 4.81 (ABX, $J_{AB}$ = 12.3 Hz, $J_{AX}$ = 6.6 Hz, $J_{BX}$ = 7.5 Hz, 1H), 4.68 (ABX, $J_{AB}$ = 12.3 Hz, $J_{AX}$ = 6.6 Hz, $J_{BX}$ = 7.5 Hz, 1H), 4.20 (br pseudo quintet, $J$ = 7.2 Hz, 1H), 3.42 (dd, $J$ = 6.6, 2.7 Hz, 2H) (Fig. 4.16). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 195.8, 138.8, 134.9, 132.0, 129.5, 129.1, 128.8, 127.9, 79.4, 41.4, 39.1 (Fig. 4.17). HPLC: 22.4 % ee, $t_{major}$ 23.1 min, $t_{minor}$ 29.0 min. (Fig. 4.45)

3-(4-Methoxyphenyl)-4-nitro-1-phenylbutan-1-one (4g). The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 8/2 as eluant). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.92 (d, $J$ = 7.9 Hz, 2H), 7.58 (t, $J$ = 7.8 Hz, 1H), 7.46 (t, $J$ = 7.8 Hz, 2H), 7.20 (d, $J$ = 8.7 Hz, 2H), 6.86 (d, $J$ = 8.7 Hz, 2H), 4.80 (ABX, $J_{AB}$ = 12.3 Hz, $J_{AX}$ = 6.6 Hz, $J_{BX}$ = 7.8 Hz, 1H), 4.64 (ABX, $J_{AB}$ = 12.3 Hz, $J_{AX}$ = 6.6 Hz, $J_{BX}$ = 7.8 Hz, 1H), 4.18 (br pseudo quintet, $J$ = 7.2 Hz, 1H), 3.77 (s, 3H), 3.42 (dd, $J$ = 6.6, 2.7 Hz, 2H) (Fig. 4.18). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 197.3, 159.4, 136.7, 133.9, 131.3, 129.1, 128.9, 128.4, 114.8, 80.2, 55.6, 42.0, 39.0 (Fig. 4.19). HPLC: 62.6 % ee, $t_{major}$ 23.1 min, $t_{minor}$ 29.0 min. (Fig. 4.46)

3-(3-Methoxyphenyl)-4-nitro-1-phenylbutan-1-one (4h). The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 8/2 as eluant). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.29 (d, $J$ = 7.8 Hz, 2H), 7.58 (t, $J$ = 8.1 Hz, 1H), 7.46 (t, $J$ = 7.5 Hz, 2H), 7.26 (s, 1H). 6.18 (m, 3H), 4.82 (ABX, $J_{AB}$ = 12.3 Hz, $J_{AX}$ = 6.6 Hz, $J_{BX}$ = 7.9 Hz, 1H), 4.67 (ABX, $J_{AB}$ = 12.3 Hz, $J_{AX}$ = 6.6 Hz, $J_{BX}$ = 7.9 Hz, 1H), 4.20 (br
pseudo quintet, \( J = 7.2 \text{ Hz}, \ 1\text{H} \), 3.45 (m, 2H), 3.78 (s, 3H) (Fig. 4.20). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \( \delta 196.7, 159.8, 140.6, 136.2, 133.5, 130.0, 128.7, 127.9, 119.4, 113.6, 112.8, 79.4, 55.1, 41.4, 39.2 \) (Fig. 4.41). HPLC: 54.0 % \( ee \), \( t_{\text{major}} \) 18.9 min, \( t_{\text{minor}} \) 22.6 min. (Fig. 4.47)

1-(4-Hydroxyphenyl)-4-nitro-3-phenylbutan-1-one (4i). The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 7/3 as eluant). \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \( \delta 7.85 \) (d, \( J = 8.7 \text{ Hz}, 2\text{H} \), 7.26-7.33 (m, 5H), 6.86 (d, \( J = 9 \text{ Hz}, 2\text{H} \), 6.23 (s, 1H), 4.83 (ABX, \( J_{\text{AB}} = 12.3 \) Hz, \( J_{\text{AX}} = 6.6 \) Hz, \( J_{\text{BX}} = 8.1 \) Hz, 1H) 4.68 (ABX, \( J_{\text{AB}} = 12.3 \) Hz, \( J_{\text{AX}} = 6.6 \) Hz, \( J_{\text{BX}} = 8.1 \) Hz, 1H), 4.21 (br pseudo quintet, \( J = 7.2 \text{ Hz}, 1\text{H} \), 3.40 (m, 2H) (Fig. 4.22). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \( \delta 195.6, 160.6, 139.1, 130.6, 129.0, 127.8, 127.4, 115.4, 79.6, 41.1, 39.4 \) (Fig. 4.23). HPLC: 71.4 % \( ee \), \( t_{\text{major}} \) 15.6 min, \( t_{\text{minor}} \) 20.2 min. (Fig. 4.48)

1-(2-Hydroxyphenyl)-4-nitro-3-phenylbutan-1-one (4j). The crude product was purified by column chromatography on silica gel (pet-ether ethyl acetate = 7/3 as eluant). \(^1\)H-NMR (300 MHz,CDCl\(_3\)): \( \delta 12.01 \) (s, 1H), 8.22 (t, \( J = 2.1 \text{ Hz}, 1\text{H} \), 8.18 (d, \( J = 8.5 \text{ Hz}, 2\text{H} \), 7.95 (d, \( J = 8.1 \text{ Hz}, 2\text{H} \), 7.72 (d, \( J = 7.8 \text{ Hz}, 2\text{H} \), 7.52-7.66 (m, 1H), 7.50 (t, \( J = 7.8 \text{ Hz}, 1\text{H} \), 4.92 (ABX, \( J_{\text{AB}} = 12.9 \) Hz, \( J_{\text{AX}} = 6.3 \) Hz, \( J_{\text{BX}} = 8.4 \) Hz, 1H), 4.72 (ABX, \( J_{\text{AB}} = 12.9 \) Hz, \( J_{\text{AX}} = 6.3 \) Hz, \( J_{\text{BX}} = 8.4 \) Hz, 1H), 4.41 (br pseudo quintet \( J = 8.1 \text{ Hz}, 1\text{H} \), 3.55 (d, \( J = 6.9\text{Hz}, 2\text{H} \) (Fig. 4.24). \(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \( \delta 202.6, 162.4, 138.6, 136.8, 129.1, 128.6, 128.2, 127.3, 127.0, 118.8, 79.4, 55.8, 41.0, 39.0 \) (Fig. 4.25). HPLC: 25.0 % \( ee \), \( t_{\text{major}} \) 13.0 min, \( t_{\text{minor}} \) 15.3 min. (Fig. 4.49)
4-Nitro-3-(3-nitrophenyl)-1-phenylbutan-1-one (4k). The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 8/2 as eluant). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 8.22 (t, $J$ = 2.1 Hz, 1H), 8.18 (d, $J$ = 8.5 Hz, 1H), 7.95 (d, $J$ = 8.1 Hz, 2H), 7.72 (d, $J$ = 7.8 Hz, 1H), 7.52-7.66 (m, 2H), 7.50 (t, $J$ = 7.8 Hz, 2H), 4.92 ( ABX, $J_{AB}$= 12.9 Hz, $J_{AX}$ = 6.3 Hz, $J_{BX}$ = 8.4 Hz, 1H), 4.72 (ABX, $J_{AB}$ = 12.9 Hz, $J_{AX}$ = 6.3 Hz, $J_{BX}$ = 8.4 Hz, 1H), 4.41 (br pseudo quintet, $J$ = 8.1 Hz, 1H), 3.55 (d, $J$ = 6.9 Hz, 2H) (Fig. 4.26). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 196.3, 148.9, 141.7, 136.3, 134.8, 134.3, 130.5, 129.2, 128.4, 123.4,122.6, 79.3, 41.5, 39.2 (Fig. 4.27). HPLC: 87.0 % ee, $t_{\text{major}}$ 33.2 min, $t_{\text{minor}}$ 40.6 min. (Fig. 4.50)

3-(Butylthio)-1,3-diphenylpropan-1-one (5a). The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 9/1 as eluant). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.91 (d, $J$ = 7.5 Hz, 2H), 7.54 (t, $J$ = 7.5 Hz, 1H), 7.43 (t, $J$ = 7.8 Hz, 4H), 7.30 (t, $J$ = 7.2 Hz, 2H), 7.20 (t, $J$ = 7.5 Hz, 1H), 4.55 (s, $J$ = 6.9 Hz, 1H), 3.53 (d, $J$=6.9 Hz, 2H), 2.33 (m, 2H), 1.46 (m, 2H), 1.31 (m, 2H), 0.83 (t, $J$ = 7.2 Hz, 3H) (Fig. 4.28). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 197.0, 142.2, 136.7, 133.2, 128.6, 128.0, 127.8, 127.1, 45.4, 44.2, 31.2, 31.1, 29.7, 21.9, 13.6 (Fig. 4.29). HPLC: 23.0 % ee, $t_{\text{major}}$ 5.0 min, $t_{\text{minor}}$ 5.2 min. (Fig. 4.51)

3-(Octylthio)-1,3-diphenylpropan-1-one (5b). The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 9/1 as eluant). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7. 90 (d, $J$ = 7.9 Hz, 2H), 7.52 (t, $J$ = 7.2 Hz, 1H), 7.42 (dd, $J$ = 6.9 Hz, 1.8 Hz, 4H), 7.29 (t, $J$ = 7.2 Hz, 2H), 7.20 (t, $J$ = 7.2 Hz, 1H), 4.55 (t, $J$ = 6.9 Hz, 1H), 3.54 (d, $J$ = 6.6 Hz, 2H), 1.48 (m, 2H), 1.32 (m, 2H), 1.25 (m, 10H), 0.865 (t, $J$ = 6.6, 3H) (Fig. 4.28) (Fig. 4.30). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 196.9, 142.2, 136.7, 133.1, 128.5,
128.4, 128.0, 127.8, 127.1, 45.3, 44.2, 31.7, 31.4, 29.2, 29.1, 29.0, 28.8, 22.6, 14.1 (Fig. 4.31). HPLC: 42.2 % ee, \( t_{\text{major}} \) 4.6 min, \( t_{\text{minor}} \) 4.8 min. (Fig. 4.52)

**1,3-Diphenyl-3-(phenylthio)propan-1-one (5c).** The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 9/1 as eluant). \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.91 (d, \( J = 7.2 \) Hz, 2H), 7.58 (t, \( J = 7.2 \) Hz, 1H), 7.46 (t, \( J = 7.8 \) Hz, 2H), 7.36 (m, 5H), 7.25 (m, 5H), 4.99 (t, \( J = 7.2 \) Hz, 1H), 3.65 (m, \( J = 17.4 \) Hz, 8.1 Hz, 5.7 Hz, 2H) (Fig. 4.32). \(^1\)C-NMR (75 MHz, CDCl\(_3\)): \( \delta \) 197.4, 141.5, 137.1, 134.6, 133.6, 133.1, 129.4, 129.2, 128.8, 128.4, 128.2, 127.8, 127.7, 48.5, 47.0 (Fig. 4.33). HPLC: 4.00 % ee, \( t_{\text{major}} \) 6.4 min, \( t_{\text{minor}} \) 6.8 min. (Fig. 4.53)

**3-(Butylthio)-3-(4-chlorophenyl)-1-phenylpropan-1-one (5d).** The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 9/1 as eluant). \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.91 (d, \( J = 7.8 \) Hz, 2H), 7.54 (t, 2H, \( J = 6.9 \) Hz, 2H), 7.43 (t, \( J = 7.8 \) Hz, 1H), 7.33 (d, \( J = 8.4 \) Hz, 2H), 6.83 (d, \( J = 8.4 \) Hz, 2H), 4.52 (t, \( J = 7.2 \) Hz, 1H), 3.50 (dd, \( J = 7.8 \) Hz, 2.7 Hz, 2H), 2.31 (m, 2H), 1.48 (m, 2H), 1.30 (m, 2H), 0.83 (t, \( J = 7.2 \) Hz, 3H) (Fig. 4.34). \(^1\)C-NMR (75 MHz, CDCl\(_3\)): \( \delta \) 197.1, 158.5, 136.8, 134.1, 133.1, 128.8, 128.5, 128.1, 113.8, 45.5, 43.6, 31.2, 31.0, 21.9, 13.6 (Fig. 4.35). HPLC: 29.0 % ee, \( t_{\text{major}} \) 4.9 min, \( t_{\text{minor}} \) 5.0 min. (Fig. 4.54)

**3-(4-Chlorophenyl)-3-(octylthio)-1-phenylpropan-1-one (5e).** The crude product was purified by column chromatography on silica gel (pet-ether/ethyl acetate = 9/1 as eluant). \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.93 (d, \( J = 7.2 \) Hz, 2H), 7.57 (t, \( J = 7.2 \) Hz, 1H), 7.46 (t, \( J = 7.8 \) Hz, 2H), 7.40 (d, \( J = 8.4 \) Hz, 2H), 7.29 (d, \( J = 8.4 \) Hz, 2H), 4.56 (t, \( J = 7.2 \) Hz, 1H), 3.54 (d, \( J = 7.2 \) Hz, 2H), 2.35 (m, 2H), 1.53 (m, 2H), 1.29 (m, 10H), 0.91 (t, \( J = 7.2 \) Hz, 3H) (Fig. 4.36). \(^1\)C-NMR
3-(4-Methoxyphenyl)-3-(octylthio)-1-phenylpropan-1-one (5f). The crude product was purified by column chromatography on silica gel (pet-ether ethyl acetate = 9/1 as eluant). \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.20 (d, \(J = 7.2\) Hz, 2H), 7.51 (t, \(J = 7.2\) Hz, 1H), 7.40 (t, \(J = 7.2\) Hz, 2H), 7.30 (d, \(J = 8.7\) Hz, 2H), 6.80 (d, \(J = 8.7\) Hz, 2H), 4.50 (t, \(J = 7.2\) Hz, 1H), 3.74 (s, 3H), 3.48 (dd, \(J = 7.5\) Hz and 3.0 Hz, 2H), 2.28 (m, 2H), 1.46 (m, 2H), 1.19 (m, 10H), 0.84 (t, \(J = 6.3\) Hz, 3H) (Fig. 4.38). \(^1\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta\) 197.1, 158.5, 136.7, 134.1, 133.1, 128.8, 128.5, 128.0, 113.7, 55.1, 45.5, 43.6, 31.7, 31.3, 29.16, 29.13, 29.11, 28.8, 22.6, 14.1 (Fig. 4.39). HPLC: 18.2 % ee, \(t_{\text{major}}\) 8.1 min, \(t_{\text{minor}}\) 8.4 min. (Fig. 4.56)
References


Fig. 4.6 $^1$H-NMR spectrum of 4-nitro-1,3-diphenylbutan-1-one (4a)

Fig. 4.7 $^{13}$C-NMR spectrum of 4-nitro-1,3-diphenylbutan-1-one (4a)
Fig. 4.8 $^1$H-NMR spectrum of 3-(4-chlorophenyl)-4-nitro-1-phenylbutan-1-one (4b)

Fig. 4.9 $^{13}$C-NMR spectrum 3-(4-chlorophenyl)-4-nitro-1-phenylbutan-1-one (4b)
Fig. 4.10 $^1$H-NMR spectrum of 3-(2,3-dichlorophenyl)-4-nitro-1-phenylbutan-1-one (4c)

Fig. 4.11 $^{13}$C-NMR spectrum of 3-(2,3-dichlorophenyl)-4-nitro-1-phenylbutan-1-one (4c)
Fig. 4.12 $^1$H-NMR spectrum of 3-(4-chlorophenyl)-4-nitro-1-p-tolylbutan-1-one (4d)

Fig. 4.13 $^{13}$C-NMR spectrum of 3-(4-chlorophenyl)-4-nitro-1-p-tolylbutan-1-one (4d)
Fig. 4.14 $^1$H-NMR spectrum of 3-(4-fluorophenyl)-4-nitro-1-phenylbutan-1-one (4e)

Fig. 4.15 $^{13}$C-NMR spectrum of 3-(4-fluorophenyl)-4-nitro-1-phenylbutan-1-one (4e)
Fig. 4.16 $^1$H-NMR spectrum of 1-(4-bromophenyl)-4-nitro-3-phenylbutan-1-one (4f)

Fig. 4.17 $^{13}$C-NMR spectrum of 1-(4-bromophenyl)-4-nitro-3-phenylbutan-1-one (4f)
Fig. 4.18 $^1$H-NMR spectrum of 3-(4-methoxyphenyl)-4-nitro-1-phenylbutan-1-one (4g)

Fig. 4.19 $^{13}$C-NMR spectrum of 3-(4-methoxyphenyl)-4-nitro-1-phenylbutan-1-one (4g)
**Fig. 4.20** $^1$H-NMR spectrum of 3-(3-methoxyphenyl)-4-nitro-1-phenylbutan-1-one (4h)

**Fig. 4.21** $^{13}$C-NMR spectrum of 3-(3-methoxyphenyl)-4-nitro-1-phenylbutan-1-one (4h)
Fig. 4.22 $^1$H-NMR spectrum of 1-(4-hydroxyphenyl)-4-nitro-3-phenylbutan-1-one (4i)

Fig. 4.23 $^{13}$C-NMR spectrum of 1-(4-hydroxyphenyl)-4-nitro-3-phenylbutan-1-one (4i)
Fig. 4.24 $^1$H-NMR spectrum of 1-(2-hydroxyphenyl)-4-nitro-3-phenylbutan-1-one (4j)

Fig. 4.25 $^{13}$C-NMR spectrum of 1-(2-hydroxyphenyl)-4-nitro-3-phenylbutan-1-one (4j)
Fig. 4.26 1H-NMR spectrum of 4-nitro-3-(3-nitrophenyl)-1-phenylbutan-1-one (4k)

Fig. 4.27 13C-NMR spectrum of 4-nitro-3-(3-nitrophenyl)-1-phenylbutan-1-one (4k)
Fig. 4.28 \(^1\)H NMR spectrum of 3-(butylthio)-1,3-diphenylpropan-1-one (5a)

Fig. 4.29 \(^{13}\)C NMR spectrum of 3-(butylthio)-1,3-diphenylpropan-1-one (5a)
Fig. 4.30 $^1$H NMR spectrum of 3-(octylthio)-1,3-diphenylpropan-1-one (5b)

Fig. 4.31 $^{13}$C NMR spectrum of 3-(octylthio)-1,3-diphenylpropan-1-one (5b)
Fig. 4.32 $^1$H NMR spectrum of 1,3-diphenyl-3-(phenylthio)propan-1-one (5c)

Fig. 4.33 $^{13}$C NMR spectrum of 1,3-diphenyl-3-(phenylthio)propan-1-one (5c)
Fig. 4.34 $^1$H NMR spectrum of 3-(butylthio)-3-(4-chlorophenyl)-1-phenylpropan-1-one (5d)

Fig. 4.35 $^{13}$C NMR spectrum of 3-(butylthio)-3-(4-chlorophenyl)-1-phenylpropan-1-one (5d)
**Fig. 4.36** $^1$H NMR spectrum of 3-(4-chlorophenyl)-3-(octylthio)-1-phenylpropan-1-one (5e)

**Fig. 4.37** $^{13}$C NMR spectrum of 3-(4-chlorophenyl)-3-(octylthio)-1-phenylpropan-1-one (5e)
Fig. 4.38 $^1$H NMR spectrum of 3-(4-methoxyphenyl)-3-(octylthio)-1-phenylpropan-1-one (5f)

Fig. 4.39 $^{13}$C NMR spectrum of 3-(4-methoxyphenyl)-3-(octylthio)-1-phenylpropan-1-one (5f)
Fig. 4.40 HPLC trace of 4-nitro-1,3-diphenylbutan-1-one (4a). (Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

Fig. 4.41 HPLC trace of 3-(4-chlorophenyl)-4-nitro-1-phenylbutan-1-one (4b). (Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

Fig. 4.42 HPLC trace of 3-(2,3-dichlorophenyl)-4-nitro-1-phenylbutan-1-one (4c). (Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)
Fig. 4.43 HPLC trace of 3-(4-chlorophenyl)-4-nitro-1-p-tolylbutan-1-one (4d). (Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

Fig. 4.44 HPLC trace of 3-(4-fluorophenyl)-4-nitro-1-phenylbutan-1-one (4e). (Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

Fig. 4.45 HPLC trace of 1-(4-bromophenyl)-4-nitro-3-phenylbutan-1-one (4f). (Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)
Fig. 4.46 HPLC trace of 3-(4-methoxyphenyl)-4-nitro-1-phenylbutan-1-one (4g).
(Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

% ee 62.6

Fig. 4.47 HPLC trace of 3-(3-methoxyphenyl)-4-nitro-1-phenylbutan-1-one (4h)
(Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

% ee 54

Fig. 4.48 HPLC trace of 1-(4-hydroxyphenyl)-4-nitro-3-phenylbutan-1-one (4i).
(Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

% ee 71.4
Fig. 4.49 HPLC trace of 1-(2-hydroxyphenyl)-4-nitro-3-phenylbutan-1-one (4j). (Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

Fig. 4.50 HPLC trace of 4-nitro-3-(3-nitrophenyl)-1-phenylbutan-1-one (4k). (Chiralcel AD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

Fig. 4.51 HPLC trace of 3-(butylthio)-1,3-diphenylpropan-1-one (5a). (Chiralcel OD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)
Fig. 4.52 HPLC trace of 3-(octylthio)-1,3-diphenylpropan-1-one (5b). (Chiralcel OD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

Fig. 4.53 HPLC trace of 1,3-diphenyl-3-(phenylthio)propan-1-one (5c). (Chiralcel OD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

Fig. 4.54 HPLC trace of 3-(butylthio)-3-(4-chlorophenyl)-1-phenylpropan-1-one (5d). (Chiralcel OD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)
Fig. 4.55 HPLC trace 3-(4-chlorophenyl)-3-(octylthio)-1-phenylpropan-1-one \((5e)\). (Chiralcel OD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

% ee 18.2

Fig. 4.56 HPLC trace of 3-(4-methoxyphenyl)-3-(octylthio)-1-phenylpropan-1-one \((5f)\). (Chiralcel OD-H column, 10% isopropyl alcohol in n-hexane, 1mL/min)

% ee 60.6