Chapter-3

Organocatalyzed Ring Opening of Epoxides with Amines

3.1 Introduction

Over the years catalysts promoted organic reactions has emerged as a powerful method for the synthesis of new chemical entities. Catalytic reactions are in great demand since they increase efficiency both in the form of preserving energy and resources and address the environmental concerns of modern society. In the recent past metal based catalysts have been the mainstay of most new synthetic methodologies, but their increased use has been dogged by their toxicity and accumulation in the environment. Recently, the use of small organic molecules as catalytic promoter of organic reactions has emerged as a new area in chemical catalysis of organic reaction, that are considered to be non-toxic or less-toxic. Most of these organocatalysts are expected to be biodegradable since they are synthesized from naturally occurring molecules and are environmentally benign.

Chemists have been inspired by Nature for hundreds of years, not only trying to understand the chemistry that occurs in living systems, but also trying to extend Nature based on the learned facts. In recent years development and application of biomimetic strategies have been used successfully in organic synthesis. The development of organocatalysts has been initiated from the understanding of enzyme catalysis of different biochemical reactions. One recent example is the success of amine based catalyst which has been modeled on the catalysis of aldol reaction by the aldolase type I enzyme.

Another emerging organocatalyst system is based on the double hydrogen bonding motif which has been found to be present in the epoxide hydrolase enzyme where phenolic H’s of two tyrosine residues are involved in the activation of epoxides through hydrogen bonding (as discussed in chapter 2). These principles can be translated into an organocatalytic approach whereby a double hydrogen bonding catalyst activates the oxygen containing functional group in an analogous fashion. Urea and thiourea derivatives are among these class of catalysts that have been recognized to activate oxygen containing functional group, which has been demonstrated in seminal

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work by Curran\textsuperscript{2,1e} and subsequently studies by Jacobson,\textsuperscript{3c} Schreiner\textsuperscript{3d,1e} and Connon.\textsuperscript{3}

After achieving good results in biocatalytic asymmetric epoxide ring opening reaction catalyzed by epoxide hydrolase of \textit{Bacillus alcalophilus}, we extend our idea of epoxide ring opening with bio-inspired organocatalysts \textit{i.e.} double hydrogen bonding urea/thiourea catalysts which activate the oxiranes ring by double hydrogen bonding (\textbf{Scheme 3.1}). Before discussing the results of this investigation it will be advantageous to discuss the recent development in epoxide ring opening reaction by hydrogen bonding catalysts. A brief review of literature on hydrogen bonding catalyzed ring opening of epoxides is presented in the next section.

\textbf{Scheme 3.1}

\begin{footnotesize}
\begin{itemize}
\end{itemize}
\end{footnotesize}
3. Review of Literature

Epoxides are widely utilized as versatile synthetic intermediate and are considered as “spring-loaded” rings for nucleophilic ring opening. Literature reports a large number of methods for the ring opening of epoxides, which mainly includes metal catalysts such as metal triflates, metal amides, metal alkoxides and metal halides. However, metal catalysis has one or more limitations such as deactivation of Lewis acid catalyst as a consequence of formation of stable complex between metal ion and nucleophile, use of hazardous solvents, long reaction time, high cost of catalyst, poor regioselectivity, difficulty in work up, inert atmosphere conditions, side reactions, etc. So the development of cheaper, simpler, and more efficient methods, especially environmentally benign, is highly desirable. One of the ways for achieving this target is to explore alternative expeditious reaction conditions that employ metal free catalysis. Literature records few processes employing either uncatalyzed or metal free catalysis (Organocatalyzed) for nucleophilic ring opening of epoxides. Among the organocatalyzed epoxide ring opening reactions the focus of the present review is on the hydrogen bonding catalysis.

The double hydrogen bonding motifs have become a powerful tool in organocatalysis for the activation of carbonyl groups and related compounds through weak hydrogen bond interactions. Bidentate hydrogen bond donors urea and thiourea derived catalysts are certainly amongst the most competent structures and are useful for many transformation. The success story of explicit double hydrogen-bonding (thio)urea organocatalysts started with seminal studies performed by Hine and co-workers who identified meta- and para-substituted phenols and biphenylenediols (1) as catalysts for


addition of diethylamine to phenyl glycidyl ether (Scheme 3.2). They proposed that the enhanced activity of the biphenylenediol (1) in solution relative to phenol results from simultaneous donation of two H-bonds to the electrophile (Figure 3.1).\(^8\)

![Scheme 3.2](image_url)

**Scheme 3.2**

Inspired by Hine's report, Braddock et al. investigated the use of 4,12-dihydroxy[2.2]paracyclophanediol (PHANOL; 2), and its para-substituted derivatives 3, 4 and 5 to catalyze ring opening reactions of epoxide with amines (Scheme 3.3). The mode of catalysis by the PHANOLs involves double hydrogen bonding to the two lone pairs of the epoxide. The more electron-deficient PHANOLs were found to be less

![Scheme 3.3](image_url)

**Scheme 3.3**

active catalysts for ring opening of epoxide with piperidine. This was attributed to the increasing capability of the amine to deprotonate the increasingly acidic PHANOLs,

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reducing the amount of active catalyst. This approach was extended to the enantioselective epoxide ring opening catalyzed by using \((R)-\text{PHANOL}\), but unfortunately the product obtained was racemic.\(^9\)

Schreiner \textit{et al}. have reported the \(N,N'\)-bis[3,5- bis(trifluoromethyl) phenyl] thiourea (6) catalyzed ring opening of epoxides with different nucleophiles such as amines, thiols and phenols in water (\textbf{Scheme 3.4}). This method suffers from poor regioselectivity (1:1 to 1:4) as well as long reaction time (24 h).\(^10\)

![Scheme 3.4](image)

Alcoholysis of styrene oxide catalyzed by a cooperative organocatalytic system of mandelic acid (7) and \(N,N'\)-bis-[3,5-bis-(trifluoromethyl)phenyl]-thiourea (6) using nucleophile as solvent, provides \(\beta\)-alkoxy alcohol in good to excellent yields (41-96\%) and high regioselectivity (99\%) (\textbf{Scheme 3.5}).\(^11\)

![Scheme 3.5](image)

Connon \textit{et al}. have used \(N\)-tosyl urea for the ring opening of styrene oxide with 1,2-dimethylindole and amines using dichloromethane as solvent at room temperature (\textbf{Scheme 3.6}) to obtain 3-alkylindole derivatives and \(\beta\)-amino alcohols in excellent


\(^10\) Kleiner, C. M.; Schreiner, P. R. \textit{Chem. Commun.} \textbf{2006}, \textit{4315-4317}.

yield (75-98%). The regioselectivity in most of the reactions are good (92:8 to 96:4), but the reaction time is generally high (91-147 h).\(^\text{12}\)

![Scheme 3.6](image)

**Scheme 3.6**

The fluoroalkyl alcohols such as 2,2,2-trifluoroethanol\(^\text{13}\) and hexafluoro-2-propanol\(^\text{14}\) have been shown to be convenient reaction media for epoxide ring opening reaction where the fluoroalkyl group is believed to activate the oxirane ring toward nucleophilic attack through hydrogen bonding. The reaction of epoxides with aromatic amines in hexafluoro-2-propanol yields the β-amino alcohols in high yields (70-92%). However, the same reaction with alkyl amines was not successful.

The use of hot water as a modest acid catalyst, reactant, and solvent has been reported for the hydrolysis of epoxides and aziridines at 60 or 100 °C yielding the corresponding ring opened product in quantitative yields (62-99%) (Scheme 3.7).\(^\text{15}\) This methodology was also extended to other nucleophiles such as amines, sodium azide, and thiophenol. It was proposed that hot water acted as a modest acid catalyst, reactant, and solvent in the hydrolysis reactions. Rate acceleration in hot water may be due to the self-ionization of water which enhances as temperature rises. The -log Kw (Kw is the self-ionization constant of water) value of water at 100 °C is 12, where both H\(^+\) and OH\(^-\) are 10 times more abundant than that in ambient water (-log Kw = 14 at 25 °C), therefore water itself can act as a modest acid catalyst.


Organocatalyzed Ring Opening of Epoxides with Amines

Chapter 3

\[
\begin{array}{c}
\begin{array}{c}
\text{R}^1\text{X} \\
\text{R}^2
\end{array}
\end{array}
\xrightarrow{\text{Nu}}
\begin{array}{c}
\begin{array}{c}
\text{R}^1\text{XH} \\
\text{R}^2
\end{array}
\end{array}
\]

Nu = Water, amines, sodium azide, thiophenol

60°C or 100°C

Scheme 3.7

In another report, Pizzo et al. have showed that by controlling the pH of the aqueous medium, the aminolysis of 1,2-epoxides by both alkyl and aryl amines can be performed efficiently at 60 °C.16 Hot water has also been used as a medium for the synthesis of β-hydroxy sulfones by regioselective ring opening of epoxides with sodium salt of sulfinate (Scheme 3.8).17

\[
\begin{array}{c}
\begin{array}{c}
\text{R}^1
\end{array}
\end{array}
\xrightarrow{\text{Water}}
\begin{array}{c}
\begin{array}{c}
\text{OH} \\
\text{SO}_2\text{R}
\end{array}
\end{array}
\]

R\text{ = alkyl, aryl; R = H, CH}_3

Scheme 3.8

β-Cyclodextrin in water have also been shown to catalyze the ring opening of epoxide with various nucleophiles such as NaCN,18 thioacids,19 phenoxides,20 thiophenoxides,21 halohydrins22 and amines23 to give β-hydroxy nitriles, β-hydroxy thioesters, β-hydroxy ethers, β-hydroxy sulfides, β-halohydrins and β-amino alcohols, respectively in good to excellent yields (75-96%). The role of β-cyclodextrin is to activate the oxiranes by hydrogen bonding and also to promote highly regioselective ring opening via inclusion complex formation of epoxide with cyclodextrin (Figure 3.2). In this type of complex, β-attack predominates to give a single regioisomer, since the α-position of the epoxide is more hindered.

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The above brief review of literature shows that there are few reports on organocatalyzed ring opening of epoxides. There is great scope to discover new and highly efficient organocatalyst. The desired approach requires the development of catalytic methods that are ‘benign by design’. So, the present research work has been targeted to develop thiourea based organocatalyzed nucleophilic ring opening reactions of epoxides. The results of our studies have been discussed in next section.
3.3 Result and Discussion

Epoxides are versatile intermediate in organic synthesis as their ring can be easily opened by a variety of nucleophiles such as carbanions,\textsuperscript{24} alcohols,\textsuperscript{25,11} amines\textsuperscript{26} and thiols\textsuperscript{27} and provide a suitable route for the formation of C-C, C-O, C-N and C-S σ – bond, respectively. The ring opening of epoxides by amines results in β-amino alcohols, which are important intermediates in the synthesis of a large number of biologically active natural and synthetic products. This transformation is also the key step for the synthesis of β\textsubscript{2}-adrenoreceptors agonists,\textsuperscript{28} anti HIV-agents,\textsuperscript{29} anti malarial agent,\textsuperscript{30} taxol side chain,\textsuperscript{31} liposidomycin B class of antibiotics,\textsuperscript{32} glycosidase inhibitor,\textsuperscript{33} naturally occurring brassinosteroids,\textsuperscript{34} unnatural amino acids\textsuperscript{35} and chiral auxiliaries\textsuperscript{36} for asymmetric synthesis.

β-Amino alcohols have been prepared by ring opening of epoxides by amines in the presence of metal catalysts.\textsuperscript{26} But the use of metal catalysts suffer from limitations such as aliphatic amines fail to react with epoxide in the presence of metal catalysts because of deactivation of metal catalyst due to formation of stable complex between

\begin{thebibliography}{99}
\item[(a)] Mohgadam, M.; Tangestaninejad, S.; Mirkhani, V.; Shaibani, R. \textit{Tetrahedron} \textbf{2004}, 60, 6105-6111;
\item[(a)] Lindsay, K. B.; Pyne, S. G. \textit{Tetrahedron} \textbf{2004}, 60, 4173-4176.
\item[(a)] Ager, D. J.; Prakash, I.; Schaad, D. R. \textit{Chem. Rev.} \textbf{1996}, 96, 835-876.
\end{thebibliography}
metal ion and amine, difficulty in work up and inert atmosphere conditions. To overcome these limitations, the use of small organic molecules as catalysts is the best alternative to metal catalysts for the synthesis of β-amino alcohols in the environmentally benign conditions. In literature, there are only few reports for organocatalyzed ring opening of epoxides by amines using achiral catalysts which includes tertiary amines such as tributylphosphine, tributylphosphine, Et₃N and DABCO (1,4-diazabicyclic[2.2.2]octane) and double hydrogen bonding meta- and para-substituted phenols, biphenylenediols, and thioureas as catalysts but there is only one report by on the organocatalyzed asymmetric ring opening of epoxide by amines in which they have used β-cyclodextrin as catalyst.

Due to our interest in developing environmentally benign green processes for the epoxide ring opening reactions we planned to synthesize thioureas based organocatalyst for the regioselective epoxide ring opening reaction by amines (Section 3.3.1) and to extend this idea for the synthesis of chiral thiourea catalysts for asymmetric epoxide ring opening reactions by amines (Section 3.3.2). The results of these investigations have been discussed in the following sub-sections:

**Section 3.3.1:** N,N’-bis[3,5-bis(trifluoromethyl)phenyl]thiourea catalyzed aminolysis of epoxides

**Section 3.3.2:** Chiral thiourea catalyzed asymmetric ring opening of epoxide by amines.

**Section 3.3.1:** N,N’-bis[3,5-bis(trifluoromethyl)phenyl]thiourea catalyzed aminolysis of epoxides.

Initially, the aminolysis of styrene oxide 9a (1 mmol) with aniline 10a (1 mmol) was chosen as a model reaction and the effect of diphenyl thiourea catalyst under solvent free conditions was investigated at 60 °C (Table 3.1). The diphenyl thiourea (5) (30 mol%) was added to a stirred reaction mixture of styrene oxide 9a (1 mmole) and aniline 10a (1 mmol) under solvent free conditions at 60 °C. The progress of the reaction was monitored by running a TLC at regular intervals. After 3 h the reaction mixture was extracted with chloroform, dried over anhydrous sodium sulphate and

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concentrated to obtain the crude product. The crude product was analysed by NMR spectroscopy for calculating the conversion of the reaction and the ratio of the two regio-isomers, 11aa and 12aa formed as a result of the attack of aniline on the both Cα and Cβ carbon of the styrene oxide (9a), respectively. Then, the crude product was purified by column chromatography using mixture of hexane and ethyl acetate as eluent to obtain major regioisomer 11aa in 42% yield. The structure of the compound was determined by recording the $^1$H NMR spectroscopy. The $^1$H NMR of the product showed one broad singlet at δ 3.06 due to –OH and NH, two double doublets at δ 3.56 and 3.75 due to two diastereotropic protons of CH$_2$, one double doublet at δ 4.36 due CH, one doublet at δ 6.50 and three multiplets at δ 6.61-6.66, 7.02-7.08 and 7.17-7.31 due to aromatic protons. The $^{13}$C NMR spectra of the product showed signal at δ 59.8, 67.2, 113.8, 117.8, 126.7, 127.5, 128.7, 129.1, 140.1, and 147.2. The IR spectrum of the product showed broad absorption band at 3401 cm$^{-1}$ due to hydroxyl group and NH group. Thus, based on this spectral data the product has been assigned the structure 1-phenyl-2-(phenylamino)ethanol (11aa).

Further, we screened different diarylurea and diarylthiourea derivatives to observe their catalytic abilities under solvent free condition, in the hope of identifying other urea and thiourea derivatives with best catalytic effects under these conditions. The experimental results in Table 3.1 show that thiourea derivatives are better catalysts than urea derivatives, giving almost complete conversion to products. This difference in their catalytic ability stems from the inherent ability of sulfur to stabilize the negative charge, which increases the hydrogen bond donor ability of thiourea derivatives relative to urea derivatives. The difference is also reflected in their acidities, for example, diphenylthiourea (pKa = 13.5) is more acidic than diphenylurea (pKa = 19.5).$^{39}$ In addition, self association of thiourea molecules is less favorable due to the lower electronegativity of sulfur. The low conversion in the case of thiourea 15 is probably due to its inability to homogenize with the reaction mixture. Our results reveal that as the electron withdrawing nature of aromatic ring substituents of urea and thiourea derivatives increases, so does the rate of the reaction. $N,N'$-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (6) emerged as the best catalyst for this transformation (Table 3.1, Entry 8). It catalyzes the reaction with highest

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regioselectivity (90:10; 11aa:12aa) in 5 min (Figure 3.3) when used in 30 mol %, we therefore planned further studies with this catalyst.

Figure 3.3: $^1$H NMR spectra of crude reaction mixture of the reaction between styrene oxide and aniline catalyzed by $N,N'$-bis[3,5-bis(trifluoromethyl)phenyl]thiourea (6).

Table 3.1: Screening of various urea and thiourea catalysts for ring opening of styrene epoxide with aniline.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>11aa:12aa&lt;sup&gt;f&lt;/sup&gt;</th>
<th>Conversion (%)&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td><img src="image" alt="Catalyst 13" /></td>
<td>3.0</td>
<td>73:27</td>
<td>68</td>
</tr>
</tbody>
</table>
Optimization of the amount of catalyst (Table 3.2) shows that on decreasing the amount of catalyst from 30 to 5 mol %, there is slight change in regioselectivity, but at 1 mol % regioselectivity decreases (11aa:12aa; 71:29) significantly. The decrease in regioselectivity is probably due to the contribution from the uncatalyzed reaction. Thus for all subsequent reactions 5 mol % catalyst was used.
Table 3.2: Effect of catalyst loading on the aminolysis of styrene oxide catalyzed by 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Time (h)</th>
<th>Regioselectivity (11aa:12aa)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>5 min</td>
<td>90:10</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>0.75</td>
<td>85:15</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>1.00</td>
<td>85:15</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>2.75</td>
<td>85:15</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>6.00</td>
<td>71:29</td>
<td>70</td>
</tr>
</tbody>
</table>

Optimizing the reaction temperature (Table 3.3) shows that as the temperature increases the rate of our model reaction also increases without affecting the regioselectivity; at 60 °C the reaction completes in 2.75 h. But we were troubled by the general belief that hydrogen bonding interactions are weak at higher temperatures. So, in order to know the role of catalyst 6 we performed the reaction using equimolar amounts of styrene oxide and aniline in the absence of catalyst at 60 °C. We found that in the absence of catalyst it takes 18 h for the reaction to complete to 98%. This does suggest that the catalyst 6 activates the epoxide under solvent free conditions at a higher temperature. In addition to the differences in reaction time, the catalyzed and uncatalyzed reactions also show differences in regioselectivities (Table 3.3, entry 1 and 2, Table 3.4, entry 1 and 2, entry 6 and 7). The catalyzed reaction shows higher

Table 3.3: Effect of temperature on the aminolysis of styrene oxide catalyzed by 6.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>11aa:12a&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>2.50</td>
<td>75:25</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>2.75</td>
<td>85:15</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>3.50</td>
<td>85:15</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>12.00</td>
<td>85:15</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>18.00</td>
<td>85:15</td>
<td>100</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by 1H NMR spectroscopy.
regioselectivity in favour of 11aa, which is formed as a result of the attack of amine nitrogen on Cα of epoxide.\[^{40}\] This indicates the role of thiourea in enhancing the regioselectivity of the reaction. To obtain further evidence, we envisaged the use of additives which form strong hydrogen bonds with hydrogen bonding donor motifs, and thus can inhibit the reaction. The model reaction was therefore performed in the presence of 5 mol% DMSO, which was equimolar to the amount of catalyst 6. In 2.75 h only 69% of reaction occurred, while after 6 h the completion was 90%. In another similar experiment, the addition of 100 mol % of DMSO resulted in the formation of trace amounts of adduct after 2.75 h, while after 24 hours the conversion was only 30%. These experiments clearly show that the catalyst 6 activates the epoxide ring and facilitates the adduct formation with aniline at 60 °C.

The epoxide ring activation by the thiourea catalyst toward the nucleophilic attack is due to electronic features of the thiourea catalyst. The electron withdrawing group containing phenyl substituents on the nitrogen atom of thiourea and the inherent ability of sulfur to stabilize the negative charge (eq. 1) increases the acidity of N-H bond.\[^{39}\] Thus, the mode of activation of the epoxide ring may be rationalized on the basis of the highly polarized N-H bond which may undergo dissociation to provide a proton at higher temperatures as shown in Scheme 3.9.

\[ \text{Scheme 3.9} \]

In order to find the best solvent for the ring opening of epoxides we performed our test reaction in different solvents and found a significant solvent effect. The reaction under neat condition was faster than the reaction in aprotic polar and non polar solvents.

\[^{40}\] Upon activation by acids styrene epoxides are known to react at Cα of styrene epoxide. Chini, M.; Crotti, P.; Macchia, F.; J. Org. Chem. 1991, 56, 5939-5942.
However protic solvents gave reaction at a much faster rate than any other solvent but slower than the neat condition (Figure 3.4).

![Figure 3.4](image)

**Figure 3.4**

Further optimization of the reaction conditions by increasing the amount of amine had negligible effect on the rate of the reaction. At the same time it resulted in decreased regioselectivity (Table 3.4). This clearly indicates that the catalyst controls the rate as well as the regioselectivity of the reaction. Thus, stirring a mixture of epoxide (1mmol), amine (1mmol) and catalytic amount (5 mol%) of 6 at 60 °C under solvent free condition provides optimal conditions for this transformation.

**Table 3.4:** Effect of increasing the amount of amine on aminolysis of styrene oxide catalyzed by 6.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine (mmol)</th>
<th>Time (h)</th>
<th>Regioselectivity (11aa:12aa)*</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>2.75</td>
<td>85:15</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>2.50</td>
<td>78:22</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>4.0</td>
<td>2.50</td>
<td>75:25</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>8.0</td>
<td>2.50</td>
<td>70:30</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>12.0</td>
<td>2.50</td>
<td>68:32</td>
<td>100</td>
</tr>
</tbody>
</table>

* Determined by 1H NMR spectroscopy.

Under the optimized conditions, the aminolysis of styrene oxide with various amines shows that the aromatic amines preferably attack at the benzylic position (Cα) of epoxide whereas, the aliphatic amines attack at the less hindered methylene carbon
(Cβ) of the epoxide (Table 3.5). Anilines with electron donating as well as electron withdrawing groups such as Me, OMe, Cl, F, were well tolerated and gave the corresponding β-amino alcohols in quantitative yields. Even sterically hindered amines such as o-methylaniline, o-methoxyaniline, 2,4-dimethylaniline and α-napthylamine also react smoothly. However, the rate of the reaction depends strongly on the nucleophilicity of the amine so that as the nucleophilicity of the amine decreases, the rate also decreases.

Table 3.5. Aminolysis of styrene oxide by alkyl- and aryl- amines catalyzed by 6 under solvent free conditions at 60°C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Time (h)</th>
<th>11:12&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>TON/TOF&lt;sup&gt;41&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>2.75</td>
<td>85:15</td>
<td>96</td>
<td>19.2/6.98</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10a</td>
<td>18.00</td>
<td>70:30</td>
<td>85</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>10b</td>
<td>1.00</td>
<td>80:20</td>
<td>97</td>
<td>19.4/19.4</td>
</tr>
<tr>
<td>4</td>
<td>10c</td>
<td>1.75</td>
<td>80:20</td>
<td>96</td>
<td>19.2/10.9</td>
</tr>
<tr>
<td>5</td>
<td>10d</td>
<td>3.00</td>
<td>87:13</td>
<td>87</td>
<td>17.4/5.8</td>
</tr>
</tbody>
</table>

<sup>41</sup>Ton, turnover number (number of substrate molecules converted to product per catalyst molecule) i.e conversion / catalyst mol %. TOF, turnover frequency = TON per unit hour.
This protocol was extended to the aminolysis of other styrene oxide derivatives and alkyl-1,2-epoxides (Table 3.6). The aminolysis of styrene oxide derivatives shows that substituents exert a significant effect on the direction as well as the rate of ring opening. The electron donating substituents on the styrene oxide ring increase the rate of reaction (Table 3.6, entry 1 and 3), while the electron withdrawing substituents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>$p$-Value</th>
<th>Isolated Yield</th>
<th>Isolated Yield</th>
<th>Rate Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td><img src="10e" alt="Amide" /></td>
<td>7.00</td>
<td>83:17</td>
<td>93</td>
<td>18.6/2.65</td>
</tr>
<tr>
<td>7</td>
<td><img src="10f" alt="Amide" /></td>
<td>4.00</td>
<td>85:15</td>
<td>90</td>
<td>18.0/4.5</td>
</tr>
<tr>
<td>8</td>
<td><img src="10g" alt="Amide" /></td>
<td>7.00</td>
<td>84:16</td>
<td>78</td>
<td>15.6/2.23</td>
</tr>
<tr>
<td>9</td>
<td><img src="10h" alt="Amide" /></td>
<td>7.00</td>
<td>84:16</td>
<td>75</td>
<td>15.0/2.14</td>
</tr>
<tr>
<td>10</td>
<td><img src="10i" alt="Amide" /></td>
<td>5.00</td>
<td>82:18</td>
<td>95</td>
<td>19.0/3.8</td>
</tr>
<tr>
<td>11</td>
<td><img src="10j" alt="Amide" /></td>
<td>1.00</td>
<td>30:70</td>
<td>92</td>
<td>18.4/18.4</td>
</tr>
<tr>
<td>12</td>
<td><img src="10k" alt="Amide" /></td>
<td>1.00</td>
<td>30:70</td>
<td>94</td>
<td>18.8/18.0</td>
</tr>
<tr>
<td>13</td>
<td><img src="10l" alt="Amide" /></td>
<td>1.75</td>
<td>17:83</td>
<td>94</td>
<td>18.8/10.7</td>
</tr>
<tr>
<td>14</td>
<td><img src="10m" alt="Amide" /></td>
<td>2.00</td>
<td>19:81</td>
<td>94</td>
<td>19.0/9.5</td>
</tr>
</tbody>
</table>

- Determined by $^1$H NMR spectroscopy.
- Isolated yield after chromatography.
- Reaction performed in the absence of catalyst.
decrease the rate (Table 3.6, entry 4-6, and 8). 4-Methoxy-, 4-methyl-, 4-fluoro- and 4-chloro-styrene oxides gave products with regioselectivity in line with styrene oxide (Table 3.6, entries 1, 3-5). Surprisingly, 3-nitro- and 4-nitro-styrene oxide gave products with reversal of regioselectivity (Table 3.6, entries 6 and 8). This reversal of regioselectivity can be attributed to electronic factors. In case of alkyl-1,2-epoxides,

Table 3.6: Ring opening of epoxides by aniline catalyzed by 6 under solvent free conditions at 60 °C.

![Chemical structure of epoxides and aniline](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Epoxide</th>
<th>Time (h)</th>
<th>11:12</th>
<th>Yield (%)</th>
<th>TON/TOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Epoxide" /></td>
<td>0.2</td>
<td>&gt;99:1</td>
<td>95</td>
<td>19/95</td>
</tr>
<tr>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image" alt="Epoxide" /></td>
<td>1.5</td>
<td>97:3</td>
<td>93</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Epoxide" /></td>
<td>0.5</td>
<td>87:13</td>
<td>94</td>
<td>18.8/37.6</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Epoxide" /></td>
<td>4.0</td>
<td>86:14</td>
<td>94</td>
<td>18.8/4.7</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Epoxide" /></td>
<td>4.0</td>
<td>86:14</td>
<td>93</td>
<td>18.6/4.65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6</th>
<th><img src="https://example.com/structure1.png" alt="Chemical Structure" /></th>
<th>6.5</th>
<th>30:70</th>
<th>83</th>
<th>16.6/2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>7'</td>
<td><img src="https://example.com/structure2.png" alt="Chemical Structure" /></td>
<td>24.0</td>
<td>18:82</td>
<td>84</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td><img src="https://example.com/structure3.png" alt="Chemical Structure" /></td>
<td>6.5</td>
<td>30:70</td>
<td>84</td>
<td>16.8/2.58</td>
</tr>
<tr>
<td>9</td>
<td><img src="https://example.com/structure4.png" alt="Chemical Structure" /></td>
<td>3.5</td>
<td>0:100</td>
<td>80</td>
<td>16/4.57</td>
</tr>
<tr>
<td>10</td>
<td><img src="https://example.com/structure5.png" alt="Chemical Structure" /></td>
<td>3.5</td>
<td>0:100</td>
<td>81</td>
<td>16/4.62</td>
</tr>
<tr>
<td>11</td>
<td><img src="https://example.com/structure6.png" alt="Chemical Structure" /></td>
<td>3.5</td>
<td>0:100</td>
<td>80</td>
<td>16/4.57</td>
</tr>
<tr>
<td>12</td>
<td><img src="https://example.com/structure7.png" alt="Chemical Structure" /></td>
<td>3.5</td>
<td>0:100</td>
<td>80</td>
<td>16/4.57</td>
</tr>
<tr>
<td>13</td>
<td><img src="https://example.com/structure8.png" alt="Chemical Structure" /></td>
<td>3.5</td>
<td>0:100</td>
<td>80</td>
<td>16/4.57</td>
</tr>
<tr>
<td>14</td>
<td><img src="https://example.com/structure9.png" alt="Chemical Structure" /></td>
<td>6.0</td>
<td>0:100</td>
<td>72</td>
<td>14.4/2.4</td>
</tr>
</tbody>
</table>

* Determined by $^1$H NMR spectroscopy.  
* Isolated yield after chromatography.  
* Reaction performed in the absence of catalyst.
excellent yields of desired β-amino alcohols were obtained (Table 3.6, entries 9 to 15). In aliphatic epoxides both steric and electronic factors facilitate the attack of amine at the less hindered β-carbon of the epoxide ring. Further, in case of glycidyl ethers (9h-9m) the hydrogen bonding between the ethereal oxygen and amine provides favorable positioning of amine for attack at β-carbon via six-membered cyclic intermediate (Figure 3.5).\textsuperscript{43}

\[
\begin{align*}
\text{A} & \quad \text{B}
\end{align*}
\]

\textbf{Figure 3.5}

The substituent dependent reversal of regioselectivity of nucleophilic addition to styrene oxide derivative originates from the activation of the epoxide ring by a thiourea catalyst. The hydrogen bond donor activation of the epoxide ring results in the activation of both Ca-O and Cβ-O bonds. The incipient positive charge on α-carbon is stabilized due to conjugation with the phenyl ring, which leads to the activation and elongation of Ca-O, with respect to the Cβ-O bond. Thus the nucleophile preferentially attacks at the α-carbon (Scheme 10a).\textsuperscript{44} However, under the powerful electron-withdrawing effect of the nitro group, the conjugative stabilization of the positive charge on Ca is inhibited, which deactivates the Ca towards nucleophilic attack (Scheme 10b), consequently the nucleophile preferably reacts at Cβ, although at a slow rate.

Further, $^{13}$C NMR spectroscopy provides a useful measure of electron density on the carbon atom. The up field chemical shift of carbon resonance corresponds to higher electron density and hence greater shielding of the carbon nuclei. The comparison of the $^{13}$C NMR resonance of Ca and Cβ of the substituted styrene oxides (Table 3.7, Figure 3.6) shows that Ca-carbon resonates downfield than Cβ-carbon except in the case of nitrostyrene oxide (Figure 3.6). Thus the lower electron density at Cβ in nitrostyrene oxide makes it the preferred site for nucleophilic attack. The

difference in chemical shift of $\text{C}_\alpha$ and $\text{C}_\beta$, $\Delta\delta(\text{C}_\alpha - \text{C}_\beta)$ can be correlated with regioselectivity of the nucleophilic epoxide ring opening reaction. In case of nitro derivatives the $\Delta\delta$ is the reverse of that obtained with substituted styrene oxides that have positive $\Delta\delta$ values (Table 3.7).

![Scheme 3.10](image)

**Table 3.7**: $^{13}$C NMR resonance of $\text{C}_\alpha$ and $\text{C}_\beta$ carbons of styrene oxide and its derivatives.

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>$\delta$ ($\text{C}_\alpha$)</th>
<th>$\delta$ ($\text{C}_\beta$)</th>
<th>$\Delta\delta$ ($\text{C}<em>\alpha$ - $\text{C}</em>\beta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>52.11</td>
<td>50.97</td>
<td>1.14</td>
</tr>
<tr>
<td>9b</td>
<td>51.96</td>
<td>50.70</td>
<td>1.26</td>
</tr>
<tr>
<td>9c</td>
<td>52.28</td>
<td>51.02</td>
<td>1.26</td>
</tr>
<tr>
<td>9d</td>
<td>51.79</td>
<td>51.11</td>
<td>0.68</td>
</tr>
<tr>
<td>9e</td>
<td>51.53</td>
<td>50.96</td>
<td>0.43</td>
</tr>
<tr>
<td>9f</td>
<td>51.39</td>
<td>51.63</td>
<td>-0.24</td>
</tr>
</tbody>
</table>
Figure 3.6: $^{13}$C spectra of epoxides (9a-9f)
In order to obtain atomic level details of the model reaction and to estimate the thermodynamic vs. kinetic control on the reaction, quantum chemical calculations have been performed. The epoxides 9a, 9b and 9f have been chosen as representative epoxides; reaction with aniline (10a) in the presence of the unsubstituted thiourea (19) was studied using B3LYP/6-31+G(d) method.

Since, under the studied experimental conditions it is evident that the activation of epoxide by thiourea takes place prior to the nucleophilic attack by aniline, it is necessary to study the complexation of thiourea with various epoxides to understand the potential energy surface of the nucleophilic epoxide ring opening. The stabilization energy due to complexation of thiourea (19) with 9a, 9b and 9f, respectively are 6.31, 6.76 and 4.40 kcal/mol. This can be traced to the electron density (charge) on the bridging oxygen atom of the epoxides: -0.554 (9a) -0.557 (9b) and -0.546 (9f). The greater the charge on the O-atom of the epoxide, the greater is the complexation energy. The complexation energy in p-nitrostyrene oxide is much less than styrene oxide and p-methoxystyrene oxide, co-relatable to the relatively low rate of reaction. Also, the complexation energy in p-methoxystyrene oxide is largest among the three and again co-relatable to the highest rate of the reaction observed in the experimental conditions.

Table 3.8: NBO Charge analysis of the epoxide, epoxide-thiourea complexes and the transition states at B3LYP/6-31+G(d).

<table>
<thead>
<tr>
<th>Molecule</th>
<th>α-C</th>
<th>β-C</th>
<th>O</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epoxide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9a</td>
<td>0.038</td>
<td>-0.130</td>
<td>-0.554</td>
<td>9a</td>
</tr>
<tr>
<td>9b</td>
<td>0.040</td>
<td>-0.133</td>
<td>-0.557</td>
<td>9b</td>
</tr>
<tr>
<td>9f</td>
<td>0.030</td>
<td>-0.124</td>
<td>-0.546</td>
<td>9f</td>
</tr>
<tr>
<td><strong>Epoxide thiourea complexes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C9a</td>
<td>0.044</td>
<td>-0.124</td>
<td>-0.590</td>
<td>-0.290</td>
</tr>
<tr>
<td>C9b</td>
<td>0.045</td>
<td>-0.126</td>
<td>-0.595</td>
<td>-0.293</td>
</tr>
<tr>
<td>C9f</td>
<td>0.034</td>
<td>-0.120</td>
<td>-0.577</td>
<td>-0.266</td>
</tr>
</tbody>
</table>

9a, 9b and 9f correspond to styrene, p-methoxystyrene and p-nitrostyrene oxide, respectively. And C9a, C9b, C9f corresponds to Epoxide-thiourea complexes.
Complexation with H$^+$ has been shown to increase the C-O bond length in epoxides like 2- methyl-1,2-epoxypropane,$^{45}$ however only a marginal lengthening of C-O bond lengths (~0.01 Å) has been observed for the epoxide-thiourea complexes. Notable changes have been observed in the atomic charges at α (positive) and β (negative) carbons of the epoxide upon complexation with thiourea. The electron density at both the carbons marginally decreased due to complexation with thiourea, however the difference between the atomic charges at α and β carbons are deterministically modulated. The positive charge at both the carbons marginally increases due to complexation. NBO charge analysis shows that the charge difference between α and β carbons in styrene oxide-thiourea complex is 0.168 which decreases to 0.154 in p-nitrostyrene oxide-thiourea complex but increases marginally to 0.171 in p-methoxystyrene oxide-thiourea complex (Table 3.8). This analysis indicates that the charge balance at α and β carbons in styrene oxide-thiourea complex is differentially modulated by nitro and methoxy groups at the para-position of phenyl ring in styrene oxide-thiourea complex. Though these values are very small, they seem to contribute to the delicate balance between α and β preference for nucleophilic attack and the trends are in line with experimental observations.

Further, following trends have been observed during the analysis of the potential energy surface of the epoxide ring opening reaction (Table 3.9, Figure 3.7).

**Table 3.9**: Transition state barriers (kcal/mol) for the catalyzed and un-catalyzed epoxide ring opening reaction with anilne.

<table>
<thead>
<tr>
<th>R =</th>
<th>Ph (9a)</th>
<th>MeOPh (9b)</th>
<th>NO$_2$Ph (9f)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha$</td>
<td>$\beta$</td>
<td>$\alpha$-$\beta$</td>
</tr>
<tr>
<td>Un-catalyzed</td>
<td>39.24</td>
<td>33.61</td>
<td>5.63</td>
</tr>
<tr>
<td>Catalyzed</td>
<td>26.68</td>
<td>23.73</td>
<td>2.95</td>
</tr>
<tr>
<td>Difference</td>
<td>12.56</td>
<td>9.88</td>
<td>12.74</td>
</tr>
</tbody>
</table>

---

Thiourea stabilizes the transition state leading to the products by about ~12 kcal/mol. The intermediates are stabilized to a similar extent. For the aliphatic class of epoxides the β-attack is favored over the α-attack (on kinetic scale) by ~2.5 kcal/mol in the un-catalyzed reaction. This difference is only marginally affected in the catalyzed reaction.

The nucleophilic attack can take place on α as well as β carbons of the epoxide. In styrene epoxide the barrier for α-attack (39.24 kcal/mol) is only marginally larger than that of β-attack (33.61 kcal/mol) under un-catalyzed conditions. This indicates that there is a delicate balance between α and β nucleophilic attacks, supporting the observed experimental trends. This balance gets further delicate under the catalytic conditions as the difference between barriers in α and β paths gets reduced from 5.63 to 2.95 kcal/mol. Electron releasing groups like methoxy show a decrease in the difference of the reaction barrier (4.47 kcal/mol for un-catalyzed and 1.74 kcal/mol for catalyzed reaction), while electron withdrawing substituents like nitro lead to an increase in this difference (7.59 kcal/mol for un-catalyzed and 4.40 kcal/mol for catalyzed reaction).

In catalyzed reaction the barrier for the α-attack is reduced to a greater extent than that of β-attack (Table 3.9), showing that in the presence of thiourea catalyst the preference for α-attack is increased. These results are in accordance with our experimental observations.
Figure 3.8: Structures of the transition states along the path of aniline attack on 9a, 9b and 9f epoxide-thiourea complex. The geometrical parameters are obtained at B3LYP/6-31+G(d) level, distances are in Å units and angles in degrees.
The nucleophilic attack follows an SN2 mechanism thus as the nucleophile approaches the epoxide carbons C-O bond elongation takes place. The C-O bond elongation during α-attack is relatively larger than that of C-O bond elongation during β-attack. The O-C-C angles in the transition state structure are also significantly different during α-attack (≈97°) in comparison to β-attack (≈87°). The transition state is achieved relatively late in the case of α-attack (C---N distance ~1.92Å) in comparison to the β-attack (C---N distance ~1.95Å). All these geometric details indicate that the transition structures during α-attack are relatively more close to that of intermediates during the α-attack in comparison to β-attack (Figure 3.8).

Also the comparison of the Cα-O bond lengths in p-nitrostyrene oxide (2.12 Å), styrene oxide (2.16 Å) and p-methoxystyrene oxide (2.19 Å) during the α-attack shows the greatest elongation of Cα-O in p-methoxystyrene oxide. This shows that there is higher preference for α-attack in p-methoxystyrene oxide (Figure 3.8).

Thus from the above discussion it can be summarized that, the nucleophilic attack can take place at both α and β carbons in aromatic epoxides. On purely electrostatic count the attack at α position should be preferred. However, steric factors seem to counter the preference due to electrostatic factors. The barrier for the nucleophilic (aniline) attack at α position in styrene oxide is 26.68 kcal/mol and for the attack at β position is 23.73 kcal/mol, thus preference for β-attack is 2.95 kcal/mol in terms of energy. However, this preference gets reduced to 1.74 kcal/mol in p-methoxystyrene oxide but increases to 4.40 kcal/mol in the p-nitrostyrene oxide. Also the comparison of the bond lengths shows the marginal elongation of Cα-O in p-methoxystyrene oxide. This clearly indicates that the balance in the α/β product ratios gets opposite due to nitro and methoxy substitution.

In conclusion, we have developed a reactant economizing and environmentally benign process for the regioselective aminolysis of epoxides using equimolar quantities of reactants under solvent free conditions catalyzed by N,N’-bis[3,5-bis(trifluoromethyl)phenyl]thiourea catalyst. The study reveals the electronic control of regioselective ring opening of substituted styrene oxides as substantiated by $^{13}$C NMR data and DFT based quantum chemical calculations at B3LYP/6-31+G(d) level.
3.3.1.1 Experimental

3.3.1.1.1 General

NMR spectra were obtained at 300 MHz (JEOL AL-300) using either CDCl$_3$ as solvents with Me$_4$Si in CDCl$_3$ as internal standard. The chemical shifts are reported in δ values relative to TMS and coupling constants (J) are expressed in Hz. Spectral patterns are designated as s = singlet; d = doublet; dd = doublet of doublets; q = quartet; t = triplet; br = broad; m = multiplet. Carbon NMR spectra were recorded on the same instrument (75.45MHz) with total proton decoupling. High-resolution mass spectra (HRMS) were recorded with a Micromass Q-TOF mass spectrometer. IR spectra were obtained with FT-IR Bruker (270-30) spectrophotometer and Varian 660-IR FT-IR spectrometer and reported in wave numbers (cm$^{-1}$). Mass spectra were recorded on Bruker Esquire 300 LC Mass spectrometer and JEOL AccuTOF DART mass spectrometer. Analytical thin-layer chromatography (TLC) was performed on either (i) aluminum sheets pre-coated with silica gel 60F$_{254}$ (Merck, India) or (ii) glass plates (7.5 x 2.5 cm) coated with silica gel GF-254 (Spectrochem India) containing 13% calcium sulphate as binder and various combinations of ethyl acetate and hexane were used as eluents. Visualization of the spots was accomplished by exposing to UV light or iodine vapors. Column chromatography was performed on silica gel (60-120 mesh) and (100-200 mesh) using mixture of ethyl acetate and hexane as eluent.

*Ab initio* DFT calculations have been performed using B3LYP method and 6-31+G(d) basis set. Complete optimization of all the systems under consideration has carried out using Gaussian03 suite of programmes. Analytical frequencies have been estimated by carrying out frequency calculations at the B3LYP/6-31+G(d) level to characterize the optimized structures as minima or transition state (one negative frequency) on the potential energy surface. The estimated zero point vibrational energy (ZPVE) values have been scaled by 0.9806 and employed in correcting the absolute

---


energy values. Partial atomic charges have been estimated by performing Natural Bond Orbital (NBO) analysis.\textsuperscript{48}

3.3.1.1.2. Material used: Organic substrates, epoxides (9a and 9n) and amines was purchased from Sigma Aldrich and used as received, whereas epoxides 9b-9m were prepared by methods reported in the literature.

3.3.1.1.3. General procedure for the synthesis of epoxides (9a-9e)\textsuperscript{49}

Trimethylsulfonium iodide\textsuperscript{50} \((\text{CH}_3)_3\text{S}^+\text{I}^-\) (0.12 mol) was dissolved in 200 mL of DMSO. To this solution was added 0.12 mol of NaH at room temperature. After the solution was stirred for 20 min, 0.1 mol of the corresponding aldehyde in 40 mL of DMSO was added dropwise within 20 min. After being stirred for 10-15 h at room temperature, the reaction mixture was poured into 1 L water, and the epoxide was extracted with 2 X 150 mL of ether. The collected ether fractions were washed two times with 300 mL water, dried over Na\textsubscript{2}SO\textsubscript{4}, and concentrated. The crude epoxide was purified by column chromatography using mixture of hexane and ethyl acetate (except for epoxide 9b which decompose after the column chromatography, so it was used as such).

3.3.1.1.4. Procedure for the synthesis of \(p\)-nitro styrene oxide (9f).\textsuperscript{51}

**Step 1. Synthesis of 4-Nitrophenacetyl bromide:** To a stirred solution of 4-nitroacetophenone (10 g, 60 mmole) in glacial acetic acid (40 ml) in a RBF (250 ml) bromine (9.6 g, 3 ml, 60 mmole) was slowly added over a period of 15 min from a dropping funnel. The temperature of the reaction mixture was maintained below 20 \(^\circ\)C for 30 min. After addition of bromine, the contents were allowed to stir overnight at room temperature. The reaction mixture was diluted by adding ice cold water. The precipitates formed were separated out and filtered on Buchner funnel and then recrystallized with absolute ethanol.

**Step 2.** To a stirred solution of 5 g (20 mmol) of \(\omega\)-bromo-4-nitroacetophenone in 50ml of methanol in an ice bath was added 0.83g (22 mmol) of sodium borohydride. After the addition ice bath was removed, stirring was continued for 3 hours. Then, 2.76 g (20


\textsuperscript{49} Cleij, M.; Archelas, A.; Furstoss, R. J. Org. Chem. 1999, 64, 5029-5035

\textsuperscript{50} Trimethylsulfonium iodide was formed by stirring 1mmole of dimethyl sulfide (CH\textsubscript{3})\textsubscript{2}S and 1mmol of methyl iodide (MeI) under neat condition at 0-5 \(^\circ\)C for 2h.

mmol) of potassium carbonate was added in the same flask. After 20 hours of stirring, 30ml of water was added and mixture was extracted with diethyl ether (3 times), washed twice with brine and dried over sodium sulfate. Evaporation under reduced pressure yield crude product. The crude product was purified by column chromatography (hexane: ethylacetate: 95:5).

**2-Phenyloxirane (9a)**

Colourless oil; Rf (hexane/AcOEt 95:5) 0.7; $^1$H NMR (300 MHz, CDCl$_3$): $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.79-2.86 (m, 1H, CH$_2$), 3.13-3.21 (m, 1H, CH$_2$) 3.85-3.91 (m, 1H, CH), 7.24-7.38 (m, 5H, ArH); $^{13}$C NMR (75.45 MHz, CDCl$_3$): $\delta$ 51.0, 52.1, 125.3, 127.9, 128.0, 128.1, 128.3, 137.5.

**2-(4-Methoxyphenyl)oxirane (9b)**

Colourless oil; Rf (hexane/AcOEt 95:5) 0.8; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.74 (dd, $J = 2.4$ and 5.6 Hz, 1H, CH$_2$), 3.08 (dd, $J = 3.9$ and 5.6 Hz, 1H, CH$_2$) 3.74-3.82 (m, 4H, CH, OCH$_3$), 6.80-6.87 (m, 2H, ArH), 7.13-7.17 (m, 2H, ArH); $^{13}$C NMR (75.45 MHz, CDCl$_3$): $\delta$ 50.7, 52.0, 55.0, 113.9, 126.7, 129.5, 159.6.

**2-(4-Methylphenyl)oxirane (9c)**

Colourless oil; Rf (hexane/AcOEt 95:5) 0.75; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.34 (s, 3H, CH$_3$), 2.78 (dd, $J = 2.7$ and 5.4 Hz, 1H, CH$_2$), 3.12 (dd, $J = 3.9$ and 5.4 Hz, 1H, CH$_2$), 3.82 (dd, $J = 2.4$ and 3.9 Hz, 1H, CH), 7.07-7.23 (m, 4H, ArH); $^{13}$C NMR (75.45MHz, CDCl$_3$): $\delta$ 21.1, 51.0, 52.3, 125.4, 129.1, 129.4, 129.6, 134.4, 137.9.

**2-(4-Flourophenyl)oxirane (9d)**

Colourless oil; Rf (hexane/AcOEt 95:5) 0.75; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.75 (dd, $J = 2.4$ and 5.7 Hz, 1H, CH$_2$), 3.10-3.13 (m, 1H, CH$_2$), 3.83 (dd, $J = 2.7$ and 3.9 Hz, 1H, CH), 6.93-7.07 (m, 2H, ArH), 7.20-7.28 (m, 2H, ArH); $^{13}$C NMR (75.45 MHz, CDCl$_3$): $\delta$ 51.1, 51.8, 115.3, 115.6, 127.1, 127.2, 133.2, 133.3, 161.0, 164.3.

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2-(4-Chlorophenyl)oxirane \(^{52}\) (9e)

Colourless oil; Rf (hexane/AcOEt 95:5) 0.6; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.67 (dd, \(J = 2.4\) and 5.7 Hz, 1H, CH\(_2\)), 3.20 (dd, \(J = 3.9\) and 5.4 Hz, 1H, CH\(_2\)), 3.93 (dd, \(J = 2.4\) and 3.9 Hz, 1H, CH), 7.12-7.19 (m, 2H, ArH), 7.22-7.31 (m, 2H, ArH); \(^{13}\)C NMR (75.45 MHz, CDCl\(_3\)): \(\delta\) 50.9, 51.5, 126.7, 128.7, 129.1, 133.9, 136.3.

2-(4-Nitrophenyl)oxirane \(^{52}\) (9f)

Yellow solid; mp: 84°C; Rf (hexane/AcOEt 95:5) 0.7; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.74 (dd, \(J = 2.4\) and 5.7 Hz, 1H, CH\(_2\)), 3.20 (dd, \(J = 4.2\) and 5.7 Hz, 1H, CH\(_2\)), 3.93 (dd, \(J = 2.4\) and 3.9 Hz, 1H, CH), 7.42-7.46 (m, 2H, ArH), 8.19-8.23 (m, 2H, ArH); \(^{13}\)C NMR (75.45 MHz, CDCl\(_3\)): \(\delta\) 51.4, 51.6, 123.7, 126.2, 145.2, 147.7.

2-(3-Nitrophenyl)oxirane (9g)

Yellow oil; Rf (hexane/AcOEt 95:5) 0.7; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.79 (dd, \(J = 2.4\) and 5.4 Hz, 1H, CH\(_2\)), 3.21 (dd, \(J = 4.2\) and 5.4 Hz, 1H, CH\(_2\)), 3.95 (dd, \(J = 2.4\) and 3.9 Hz, 1H, CH), 7.50-7.62 (m, 2H, ArH), 8.14-8.17 (m, 2H, ArH); \(^{13}\)C NMR (75.45 MHz, CDCl\(_3\)): \(\delta\) 51.32, 51.34, 120.5, 123.0, 129.5, 131.4, 140.1, 148.4.

3.3.1.1.5. General procedure for the synthesis of thiourea catalysts

To a stirred solution of amine (1mmol) in dichloromethane (1ml) in RBF (10 ml) was added isothiocyanate (1.1 equivalent). The reaction mixture was stirred overnight. The progress of the reaction was monitored by TLC. After completion of the reaction the dichloromethane was distilled off and the crude product was purified by column chromatography using varying mixtures of hexane and ethyl acetate.

1-(4’-Nitrophenyl)-3-phenylthiourea (15)

Yellow solid; Rf (hexane/AcOEt 85:15) 0.70; IR (KBr) \(\nu_{\text{max}}\) (cm\(^{-1}\)): 3334, 2920, 2576, 2428, 2115, 1588, 1548, 1492, 1423, 1321, 1244, 1172, 1110, 933, 845, 731, 691; \(^1\)H NMR (300 MHz, CDCl\(_3\)+Acetone-d\(_6\)): \(\delta\) 7.22
(t, J = 7.5, 1H, ArH), 7.35-7.48 (m, 4H, ArH), 7.81-7.86 (m, 2H, ArH), 8.14-8.19 (m, 2H, ArH), 9.00 (bs, 1H, NH); $^{13}$C NMR (75.45 MHz, Acetone-d$_6$): 123.2, 125.0, 125.3, 126.8, 129.8, 138.8, 144.4, 146.3, 164.6, 180.4.

1-(3’,5’-Bis(trifluoromethyl)phenyl)-3-phenylthiourea (16)

Colourless solid; m.p. - 132-134°C; Rf (hexane/AcOEt 85:15) 0.60; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3175, 3040, 2978, 2788, 1604, 1555, 1498, 1467, 1384, 1324, 1274, 1199, 1131, 984, 907, 890, 858, 716, 681; $^1$H NMR (300 MHz, Acetone-d$_6$): $\delta$ 7.24 (t, J = 7.5, 1H, ArH), 7.41 (t, J = 7.5, 2H, ArH), 7.54 (d, J = 6.0, 2H, ArH), 7.76 (s, 1H, ArH) 8.33 (s, 2H, ArH), 9.52 (bs, 1H, NH); $^{13}$C NMR (75.45 MHz, Acetone-d$_6$): 113.3, 118.1, 124.7, 125.3, 126.7, 129.8, 131.5, 131.9, 142.7, 150.0, 171.0; HRMS: calculated for C$_{15}$H$_{10}$F$_6$N$_2$S 387.0367 [M+Na]$^+$; found 387.0360.

1,3-Bis(4′-nitrophenyl)thiourea (18)

Yellow solid; m.p. 184-186°C; Rf (hexane/AcOEt 85:15) 0.60; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3330, 2922, 2579, 2432, 2121, 1592, 1546, 1495, 1427, 1320, 1244, 1178, 1113, 931, 847, 736, 694; $^1$H NMR (300 MHz, CDCl$_3$+DMSO-d$_6$): $\delta$ 7.87 (s, 4H, ArH), 8.2 (s, 4H, ArH), 10.6 (s, 2H, NH); $^{13}$C NMR (75.45 MHz, CDCl$_3$+DMSO-d$_6$): 121.4, 127.4, 143.2, 144.4, 179.8.

1-(3’, 5’-Bis(trifluoromethyl)phenyl)-3-(4-nitrophenyl) thiourea (19)

Yellow solid; m.p. 170-172°C; Rf (hexane/AcOEt 85:15) 0.58; IR (KBr) $\nu_{\text{max}}$ (cm$^{-1}$): 3577, 3352, 3274, 3226, 3177, 3100, 2850, 2582, 1787, 1573, 1503, 1474, 1379, 1331, 1270, 1177, 1109, 981, 886, 851, 750, 699; $^1$H NMR (300 MHz, Acetone-d$_6$): $\delta$ 7.24 (t, J = 7.5, 1H, ArH), 7.94-7.98 (m, 2H, ArH), 8.23-8.32 (m, 4H, ArH), 9.93 (bs, 1H, NH); $^{13}$C NMR (75.45 MHz, Acetone-d$_6$): 118.8, 122.4, 123.5, 124.9, 125.0, 125.3, 126.0, 131.9, 132.3, 142.1, 144.8, 146.0, 181.3; HRMS calculated for C$_{15}$H$_{10}$F$_6$N$_3$O$_2$S 432.0217 [M+Na]$^+$; found 432.0215.
1,3-Bis(3',5'-bis(trifluoromethyl)phenyl)thiourea (6)

White solid; m.p. 172–174°C; Rf (hexane/AcOEt 85:15) 0.6; IR (KBr): 3175, 3050, 2791, 1555, 1467, 1376, 1285, 1180, 1132, 1005, 929, 891, 849, 714, 683; \(^1\)H NMR (300 MHz, CDCl\(_3\)+DMSO-d\(_6\)): 7.63 (s, 2H, ArH), 8.15 (s, 2H, ArH), 10.0 (s, 2H, NH); \(^{13}\)C NMR (75.45 MHz, CDCl\(_3\)+DMSO-d\(_6\)): 117.5, 120.9, 123.1, 124.5, 130.8, 131.3, 140.2, 180.0.

3.3.1.1.6. General procedure for the nucleophilic ring opening reaction

To a 10 ml RBF amine (1mmol), epoxide (1mmol) and thiourea catalyst were consecutively added and the resulting mixture was stirred at 60°C for the time indicated. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was loaded on the chromatography column and eluted with mixture of ethyl acetate and hexane to obtain the pure regioisomers.

1-Phenyl-2-(phenylamino)ethanol\(^53\) (11aa)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.50; IR (CHCl\(_3\)) \(\nu_{\text{max}}\) (cm\(^{-1}\)): 3341, 3267, 3047, 2972, 2847, 1605, 1543, 1438, 1361, 1232, 1128, 1045, 878, 746; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 3.06 (bs, 2H, NH,OH), 3.56 (dd, 1H, \(J = 3.9\) and 7.4 Hz, CH\(_2\)), 3.75 (dd, 1H, \(J = 3.9\) and 11.4 Hz, CH\(_2\)), 4.36 (dd, 1H, \(J = 7.5\) and 12.4 Hz, CH), 6.50 (d, 2H, \(J = 6.0\) Hz, ArH), 6.61-6.66 (m, 1H, ArH), 7.02-7.08 (m, 2H, ArH), 7.17-7.31 (m, 5H, ArH). \(^{13}\)C NMR (75.45 MHz, CDCl\(_3\)): \(\delta\) 59.8, 67.2, 113.8, 117.8, 126.7, 127.5, 128.7, 129.1, 140.1, 147.2; EIMS: m/z: 213 (M\(^+\)).

2-(4'-methoxyphenylamino)-2-phenylethanol\(^54\) (11ab)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.45; IR (CHCl\(_3\)) \(\nu_{\text{max}}\) (cm\(^{-1}\)): 3385, 3271, 3049, 2937, 2851, 1614, 1546, 1438, 1361, 1293,


1202, 1138, 1045, 1065, 878, 741; $^1$H NMR (300 MHz, CDCl₃): δ 3.37 (bs, 2H, NH, OH), 3.66 (dd, 1H, J = 7.2 and 12.0 Hz, CH₂), 3.76 (s, 3H, OCH₃), 3.84 (dd, 1H, J = 4.2 and 11.4 Hz, CH₂), 4.37 (dd, 1H, J = 4.2 and 7.2, CH), 6.49-6.52 (m, 2H, ArH), 6.60-6.61 (m, 2H, ArH), 7.01-7.12 (m, 3H, ArH), 7.19-7.23 (m, 2H, ArH). $^{13}$C NMR (75.45 MHz, CDCl₃): 55.6, 60.8, 67.2, 114.7, 115.3, 126.7, 127.5, 128.7, 140.4, 141.4, 152.3; HRMS [M + H]$^+$ calculated for C₁₅H₁₈NO₂ 244.1338; found 244.1340.

2-(2’-Methoxyphenylamino)-2-phenylethanol$^{55}$ (11ac)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.56; IR (CHCl₃) $\nu_{max}$ (cm$^{-1}$): 3381, 3274, 3042, 2931, 2856, 1611, 1538, 1431, 1362, 1291, 1200, 1130, 1041, 1063, 879, 739; $^1$H NMR (300 MHz, CDCl₃): δ 3.80 (m, 1H, CH₂), 3.95 (m, 4H, NH and OH), 4.55 (m, 1H, CH), 6.40 (m, 1H, ArH), 6.75 (m, 3H, ArH), 7.38 (m, 5H, ArH); $^{13}$C NMR (75.45 MHz, CDCl₃): 55.3, 59.7, 67.3, 109.3, 111.4, 117.0, 121.0, 126.6, 127.4, 128.6, 136.9, 140.2, 147.0. HRMS [M + H]$^+$ calculated for C₁₅H₁₈NO₂ 244.1338; found 244.1342.

2-(4’-Chlorophenylamino)-2-phenylethanol$^{53}$ (11ad)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.56; IR (CHCl₃) $\nu_{max}$ (cm$^{-1}$): 3401, 3061, 3023, 2912, 2871, 1592, 1481, 1314, 813; $^1$H NMR (300 MHz, CDCl₃): δ 2.66 (bs, 1H, OH), 3.66 (dd, 1H, J = 7.2 and 11.1 Hz, CH₂), 3.85 (dd, 1H, J = 3.9 and 11.0 Hz, CH₂), 4.37 (dd, 1H, J = 3.9 and 7.2 Hz, CH), 6.42 (d, 2H, J = 8.1 Hz, ArH), 6.99 (d, 2H, J = 8.1 Hz, ArH), 7.05-7.35 (m, 6H, ArH, NH). $^{13}$C NMR (75.45 MHz, CDCl₃): 59.8, 67.1, 114.4, 114.8, 122.3, 122.4, 125.8, 126.6, 126.8, 126.9, 127.7, 128.6, 128.7, 128.8, 128.9, 129.1, 129.4, 139.5, 145.7. HRMS: calculated for C₁₄H₁₄ClNO 248.0842 [M+H]$^+$; found 248.0843.

2-(3’-Chlorophenylamino)-2-phenylethanol (11ae)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.50; IR (CHCl₃) $\nu_{max}$ (cm$^{-1}$): 3404, 3062, 3028, 2926, 2875, 1597, 1485; $^1$H NMR (300 MHz, CDCl₃): δ 1.60-1.95 (bs, 1H, OH), 3.74

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(dd, $J = 6.6$ and 11.1 Hz, 1H, CH$_2$), 3.93 (dd, $J = 4.2$ and 11.1 Hz, 1H, CH$_2$), 4.45 (dd, $J = 4.2$ and 6.6 Hz, 1H, CH), 6.39-6.43 (m, 1H, ArH), 6.53 (t, $J = 2.1$ Hz, 1H, ArH), 6.61-6.64 (m, 1H, ArH), 6.98 (t, $J = 8.1$ Hz, 1H, ArH), 7.25-7.36 (m, 6H, ArH, NH); $^{13}$C NMR (75.45 MHz, CDCl$_3$): $\delta$ 59.6, 67.2, 111.9, 113.5, 117.6, 126.6, 127.8, 128.7, 128.8, 130.1, 134.8, 139.4, 148.3; HRMS: calculated for C$_{14}$H$_{14}$ClNO 248.0842 [M+H]$^+$; found 248.0844.

2-(4'-Fluorophenylamino)-2-phenylethanol (11af)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.45; IR (CHCl$_3$) $\nu_{max}$ (cm$^{-1}$): 3386, 3061, 3030, 2926, 2876, 1614, 1510; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.40-2.90 (bs, 2H), 3.64 (dd, $J = 6.9$ and 11.4 Hz, 1H, CH$_2$), 3.84 (dd, $J = 4.2$ and 11.4 Hz, 1H, CH$_2$), 4.32 (dd, $J = 4.2$ and 6.9 Hz, 1H, CH), 6.35-6.42 (m, 2H, ArH), 6.65-6.77 (m, 2H, ArH), 7.16-7.32 (m, 5H, ArH); $^{13}$C NMR (75.45 MHz, CDCl$_3$): $\delta$ (52.8), 60.1, 67.1, (72.2), 114.9, 115.0, 115.4, 115.6, 115.9, 125.8, 126.7, 126.9, 127.7, 128.0, 128.5, 128.6, 128.8, 139.7, 143.2, 154.5, 157.6; HRMS: calculated for C$_{14}$H$_{14}$FNO 254.0957 [M+Na]$^+$; found 254.0943.

2-(2'-Methylphenylamino)-2-phenylethanol (11ag)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil. IR (CHCl$_3$) $\nu_{max}$ (cm$^{-1}$): 3394, 3014, 2919, 1606, 1510, 1451; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.11 (bs, 1H, OH), 2.25 (s, 3H, CH$_3$), 3.72 (dd, 1H, $J = 7.2$ and 10.95 Hz, CH$_2$), 3.90 (dd, 1H, $J = 4.2$ and 10.5Hz, CH$_2$), 4.48 (dd, 1H, $J = 4.2$ and 7.0 Hz, CH), 6.35 (d, 1H, $J = 8.1$ Hz, ArH), 6.61 (t, 1H, $J = 7.2$ Hz, ArH), 6.93 (t, 1H, $J = 8.1$ Hz, ArH), 7.05 (d, 1H, $J = 7.2$ Hz, ArH), 7.18-7.37 (m, 5H, ArH). $^{13}$C NMR (75.45 MHz, CDCl$_3$): 17.5 59.6, 67.3, 111.4, 117.4, 122.5, 125.8, 126.6, 126.9, 127.1, 127.4, 128.0, 128.5, 128.7, 130.0, 130.2, 140.1, 145.0. EIMS (m/z): 227 (M$^+$).
2-(2',4'-Dimethylphenylamino)-2-phenylethanol (11ah)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.46; IR (CHCl₃) ν_max (cm⁻¹): 3402, 3062, 3026, 3005, 2921, 2858, 1619, 1513; ¹H NMR (300 MHz, CDCl₃): δ 3.74 (dd, J = 7.2 and 11.1 Hz, 2H, CH₂), 3.94 (dd, J = 4.2 and 11.1 Hz, 1H, CH), 4.70 (dd, J = 4.2 and 7.2 Hz, 1H, CH), 6.22 (d, J = 8.1 Hz, 1H, CH₂), 6.57 (d, J = 8.1 Hz, 1H, ArH), 6.68-6.71 (m, 1H, ArH), 7.20-7.34 (m, 5H, ArH); ¹³C NMR (75.45 MHz, CDCl₃): δ 17.4, 17.6, 20.4, 52.2, 60.2, 67.4, 72.2, (111.1), 111.9, 122.7, (123.0), 125.8, 126.7, 127.2, 127.3, 127.4, 127.5, 127.9, 128.8, 130.1, 131.2, 140.4, 142.6, 143.1, 127.7, 128.0, 128.5, 128.6, 128.8, 139.7, 143.2, 154.5, 157.6; HRMS: calculated for C₁₆H₁₉NO₂ 264.1364 [M+Na]⁺; found 264.1351.

2-(Naphtylamino)-2-phenylethanol (11ai)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; ¹H NMR (300 MHz, CDCl₃); δ 3.42 (bs, 1H, OH), 3.84 (dd, 1H, J = 7.2 and 11.1 Hz, CH₂), 4.00 (dd, 1H, J = 3.9 and 11.1Hz, CH₂), 4.60 (dd, 1H, J = 3.9 and 7.2 Hz, CH), 6.34 (d, 1H, J = 7.2 Hz), 7.10-7.46 (m, 12H, ArH, NH) 7.44-7.77 (m, 1H, ArH), 8.00-8.08 (m, 1H, ArH); ¹³C NMR (75.45 MHz, CDCl₃): 60.5, 67.2, 107.5, 118.4, 120.1, 123.8, 125.0, 125.8, 126.2, 126.8, 127.7, 128.6, 128.8, 134.2, 139.2, 141.3; EIMS: m/z : (M⁺) 263.

1-Phenyl-2-(pyrrolidin-1-yl)ethanol (12aj)

The title compound was isolated by column chromatography (CHCl₃:MeOH 97:3) as white solid; m.p. 72–73°C; Rf (CHCl₃:MeOH 97:3) 0.40; ¹H NMR (300 MHz, CDCl₃) δ 1.81 (m, 4H, 2CH₂), 2.48 (dd, J = 3.3 and 12.3 Hz, 1H, CH₂), 2.50–2.60 (m, 2H, CH₂), 2.77 (m, 2H, CH₂), 2.79 (dd, J = 10.5 and 12.3 Hz, 1H, CH₂), 4.07 (br s, 1H, OH), 4.71 (dd, J = 3.3 and 10.5 Hz, 1H, CH), 7.25–7.45 (m, 5H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ 23.6, 53.8, 64.1, 70.6, 125.8, 127.4, 128.3, 142.4; EIMS: m/z: 191 (M+).
1-phenyl-2-(piperidin-1-yl)ethanol (12ak)

The title compound was isolated by column chromatography (CHCl₃:MeOH 95:5) as pale yellow oil; Rf (CHCl₃:MeOH 95:5) 0.45; ¹H NMR (200 MHz, CDCl₃): δ 1.50 (m, 2H, CH₂), 1.59 (m, 4H, 2 x CH₂), 2.40 (m, 4H, 2 x CH₂), 2.70 (m, 2H, CH₂), 4.69 (dd, J = 3.7, 10.6 Hz, 1H, CH) 7.22–7.30 (m, 5H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 21.1, 24.4, 26.1, 54.3, 66.8, 68.6, 125.4, 125.9, 127.2, 142.4. EIMS: m/z: 205 (M+).

2-(Butylamino)-1-phenylethanol⁵⁵ (12al)

The title compound was isolated by column chromatography (CHCl₃:MeOH 95:5) as yellow oil; Rf (CHCl₃:MeOH 95:5) 0.40; IR (CHCl₃) ν max (cm⁻¹): 3375, 3242, 3054, 2940, 2860, 1631, 1580, 1516, 1470, 1410, 1389, 1310, 1290, 1162, 1086, 1015, 868, 748 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 0.95 (t, 3H, J = 6.5 Hz, CH₃), 1.30–1.40 (m, 2H, CH₂), 1.45–1.55 (m, 2H, CH₂), 2.35 (br s, 2H, OH, NH), 2.55–2.65 (m, 2H, CH₂), 3.80–3.90 (m, 2H, CH₂), 4.25 (d, 1H, J = 6.0 Hz, CH), 7.30–7.45 (m, 5H, ArH); ¹³C NMR (75 MHz, CDCl₃): 14.0, 20.4, 20.5, 54.9, 55.2, 63.0, 63.7, 70.6, 71.9, 125.8, 125.9, 127.5, 127.6, 128.3, 128.5, 142.2, 142.4; EIMS: m/z: 193 (M+).

2-(Hexylamino)-1-phenylethanol (12am)

The title compound was isolated by column chromatography (CHCl₃:MeOH 98:2) as yellow oil; Rf (CHCl₃:MeOH 98:2) 0.48; ¹H NMR (300 MHz, CDCl₃): δ 0.85-0.89 (m, 3H, CH₃), 1.25-1.46 (m, 3 x CH₂, NH, OH), 2.42-2.85 (m, 4H, 2 x CH₂), 4.71-4.77 (m, 1H, CH), 7.18-7.36 (m, 5H, ArH); ¹³C NMR (75.45 MHz, CDCl₃): δ 14.0, 22.6, 27.0, 29.7, 31.7, 63.1, 63.8, 70.7, 72.0, 125.9, 126.0, 127.6, 128.4, 142.2, 142.4. EIMS: m/z: 221 (M+).

2-(4’-Methoxyphenyl)-2-(phenylamino)ethanol (11ba)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.48; IR (CHCl₃) ν max (cm⁻¹): 3395, 3051, 2933, 2836, 1603,
1510; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 3.20-3.50\) (bs, 2H), 3.62 dd, 1H, \((J= 7.5, \text{ and } 11.0\) Hz, CH\(_2\)), 3.72 (s, 3H, OCH\(_3\)), 3.80 (dd, \(J = 4.2\) and 11.1 Hz, 1H, CH\(_2\)), 4.38 (dd, \(J = 4.2\) and 7.5 Hz, 1H, CH), 6.52-6.55 (m, 2H, ArH), 6.63-6.65 (m, 1H, ArH), 6.68-6.84 (m, 2H, ArH), 7.04-7.10 (m, 2H, ArH) 7.19-7.24 (m, 2H, ArH); \(^1^3\)C NMR (75.45 MHz, CDCl\(_3\)): \(\delta 55.1, 59.2, 67.2, 113.8, 114.1, 117.7, 127.7, 129.0, 132.0, 147.2, 158.8\); HRMS: calculated for C\(_{15}\)H\(_{17}\)NO\(_2\) 266.1157 [M+Na]\(^+\); found 266.1161.

2-(4'-Methylphenyl)-2-(phenylamino)ethanol (11ca)

![Image](image_url)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.5; IR (CHCl\(_3\)) \(v\)\(_{\text{max}}\) (cm\(^{-1}\)): 3395, 3021, 2923, 2870, 1602, 1504; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 2.28\) (s, 3H), 3.24-3.33 (bs, 2H, NH, OH), 3.63 (dd, \(J = 7.2\) and 11.1 Hz, 1H, CH\(_2\)), 3.82 (dd, \(J = 4.2\) and 11.1 Hz, 1H, CH\(_2\)), 4.40 (dd, \(J = 4.2, \text{ and } 7.2\) Hz, 1H, CH), 6.53 (d, \(J = 7.8\) Hz, 2H, ArH), 6.65 (t, \(J = 7.5\) Hz, 1H, ArH), 7.04-7.11 (m, 4H, ArH), 7.14-7.25 (m, 2H, ArH); \(^1^3\)C NMR (75.45 MHz, CDCl\(_3\)): \(\delta 21.0, 59.6, 67.2, 113.8, 117.7, 126.5, 129.0, 129.2, 129.4, 137.0, 137.1, 147.3\); HRMS: calculated for C\(_{15}\)H\(_{17}\)NO\(_2\) 250.1208 [M+Na]\(^+\); found 250.1208.

2-(4'-Fluorophenyl)-2-(phenylamino)ethanol (11da)

![Image](image_url)

The title compound was isolated by column chromatography (hexane/AcOEt 90:10) as yellow oil; Rf (hexane/AcOEt 85:15) 0.5; IR (CHCl\(_3\)) \(v\)\(_{\text{max}}\) (cm\(^{-1}\)): 3391, 2925, 2854, 1602, 1506; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 2.83-2.90\) (bs, 2H), 3.67 (dd, \(J = 7.2\)and 11.0 Hz, 1H, CH\(_2\)), 3.88 (dd, \(J = 4.2\) and 11.0 Hz, 1H, CH\(_2\)), 4.44 (dd, \(J = 4.2\) and 7.2 Hz, 1H, CH), 6.51- 6.54 (m, 2H), 6.65-6.71 (m, 1H), 6.97-7.19 (m, 4H), 7.29-7.35 (m, 2H); \(^1^3\)C NMR (75.45 MHz, CDCl\(_3\)): \(\delta 59.2, 67.2, 113.5, 113.8, 115.5, 115.7, 118.0, 128.2, 128.3, 129.1, 129.4, 135.7, 135.8, 147.0, 160.5, 163.8\); HRMS: calculated for C\(_{14}\)H\(_{14}\)FNO 254.0957 [M+Na]\(^+\); found 250.0950.

2-(4'-Chlorophenyl)-2-(phenylamino)ethanol (11ea)

![Image](image_url)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.48; IR (CHCl\(_3\)) \(v\)\(_{\text{max}}\) (cm\(^{-1}\)): 3385, 2955, 2924, 2853, 1602,
1503, 1491; \( ^1 \)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 3.67 (dd, \( J = 7.2 \) and 11.0 Hz, 1H, CH\(_2\)), 3.88 (dd, \( J = 4.2 \) and 11.0 Hz, 1H, CH\(_2\)), 4.43 (dd, \( J = 4.2 \) and 7.2 Hz, 1H, CH), 6.50-6.53 (m, 2H, ArH), 6.66-6.71 (m, 1H, ArH), 7.06-7.12 (m, 2H, ArH), 7.28 (m, 5H, ArH); \(^{13}\)C NMR (75.45 MHz, CDCl\(_3\)): \( \delta \) 59.3, 67.1, 113.5, 113.8, 118.1, 118.4, 127.2, 128.1, 128.7, 128.9, 129.1, 129.4, 133.2, 133.6, 133.7, 147.5; HRMS: calculated for C\(_{14}\)H\(_{14}\)ClNO 286.0401 [M+K]\(^+\); found 286.0878.

**1-(4’-Nitrophenyl)-2-(phenylamino)ethanol (12fa)**

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.48; IR (CHCl\(_3\)) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3406, 2923, 2853, 1602, 1517; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 3.06 (bs, 2H, NH and OH), 3.22 (dd, \( J = 8.7 \) and 13.5 Hz, 1H, CH\(_2\)), 3.43 (dd, \( J = 3.6 \) and 13.5 Hz, 1H, CH), 4.99 (dd, \( J = 3.6 \) and 8.7 Hz, 1H, CH), 6.64 (m, 3H, ArH), 6.72-6.76 (m, 2H, ArH), 7.55 (d, \( J = 8.7 \) Hz, 2H, ArH), 8.14-8.22 (m, 2H, ArH); \(^{13}\)C NMR (75.45 MHz, CDCl\(_3\)): \( \delta \) 51.9, 71.4, 113.6, 118.8, 123.7, 126.6, 129.5, 147.3, 147.5, 149.0; HRMS: calculated for C\(_{14}\)H\(_{14}\)N\(_2\)O\(_3\) 259.1083 [M+H]\(^+\); found 259.1093.

**1-(3’-Nitrophenyl)-2-(phenylamino)ethanol (12ga)**

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.48; IR (CHCl\(_3\)) \( \nu_{\text{max}} \) (cm\(^{-1}\)): 3387, 2922, 2852, 1603, 1528; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 2.58 (bs, 1H), 3.26 (dd, \( J = 8.7 \) and 13.5 Hz, 1H, CH\(_2\)), 3.47 (dd, \( J = 3.6 \) and 13.5 Hz, 1H, CH\(_2\)), 5.02 (dd, \( J = 3.6 \) and 8.7 Hz, 1H, CH), 6.64-6.75 (m, 3H, ArH), 7.14-7.30 (m, 2H, ArH), 7.54 (t, \( J = 7.8 \) Hz, 1H, ArH), 7.74 (d, \( J = 7.8 \) 1H, Hz, ArH), 8.14-8.18 (m, 1H, ArH), 8.28 (s, 1H, ArH); \(^{13}\)C NMR (75.45 MHz, CDCl\(_3\)): \( \delta \) 52.0, 71.4, 113.6, 118.8, 120.9, 122.8, 129.4, 129.5, 131.8, 144.4, 147.4, 148.6; HRMS: calculated for C\(_{14}\)H\(_{14}\)N\(_2\)O\(_3\) 281.0902 [M+Na]\(^+\); found 281.0896.

**1-(phenoxo)-3-(phenylamino)propan-2-ol\(^{53}\) (12ha)**

The title compound was isolated by column chromatography (hexane/AcOEt 90:10) as yellow oil;
Rf (hexane/AcOEt 85:15) 0.50; IR (CHCl₃) ν_max (cm⁻¹): 3392, 3042, 2920, 2850, 1594, 1482; ¹H NMR (300 MHz, CDCl₃): δ 3.27 (dd, 1H, J = 7.2 and 12.9 Hz, CH₂), 3.42 (dd, 1H, J = 4.2 and 12.9 Hz, CH₂), 3.88-4.08 (m, 2H, CH₂), 4.20-4.27 (m, 1H, CH), 6.65-6.76 (m, 3H, ArH), 6.89-6.99 (m, 3H, ArH), 7.15-7.20 (m, 2H, ArH), 7.26-7.31 (m, 2H, ArH). ¹³C NMR (75.45 MHz, CDCl₃): δ 46.5, 68.6, 69.9, 113.2, 114.4, 117.9, 121.2, 129.2, 129.5, 147.9, 158.3. EIMS: m/z : 243 (M⁺).

1-(2’-Methylphenoxy)-3-(phenylamino)propan-2-ol (12ia)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as light grey solid; m.p 64-65°C; Rf (hexane/AcOEt 85:15) 0.50; IR (CHCl₃) ν_max (cm⁻¹): 3406, 3053, 2923, 2852, 1602, 1493; ¹H NMR (300 MHz, CDCl₃): δ 2.25 (s, 3H, CH₃), 3.27 (dd, J = 7.1 and 13.0 Hz, 1H, CH₂), 3.45 (dd, J = 4.2 and 13.0 Hz, 1H, CH₂), 4.03 (d, J = 4.9 Hz, 2H, CH₂), 4.19-4.32 (m, 1H, CH), 6.64-6.92 (m, 5H, ArH), 7.11-7.22 (m, 4H, ArH); ¹³C NMR (75.45 MHz, CDCl₃): δ 16.7, 47.3, 69.3, 70.6, 111.6, 113.8, 118.5, 121.5, 127.4, 129.8, 131.3, 148.2, 157.3; HRMS: calculated for C₁₆H₁₉NO₂ 280.1313 [M+Na]⁺; found 280.1310.

1-(3’-Methylphenoxy)-3-(phenylamino)propan-2-ol (12ja)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as yellow oil; Rf (hexane/AcOEt 85:15) 0.45; IR (CHCl₃) ν_max (cm⁻¹): 3383, 3054, 3025, 2923, 1602, 1497; ¹H NMR (300 MHz, CDCl₃): δ 2.23 (s, 3H, CH₃), 3.23 (dd, J = 7.0 and 13.0 Hz, 1H, CH₂), 3.38 (dd, J = 4.2 and 13.0 Hz, 1H, CH₂), 3.00-3.44, (bs, 2H, NH and OH), 3.97-3.98 (m, 2H, CH₂), 4.12-4.22 (m, 1H, CH), 6.62-6.82 (m, 5H, ArH), 7.05-7.21 (m, 4H, ArH); ¹³C NMR (75.45 MHz, CDCl₃): δ 16.2, 46.7, 68.7, 69.9, 111.0, 113.2, 117.9, 120.9, 126.5, 126.8, 129.2, 130.7, 148.0, 156.3; HRMS: calculated for C₁₆H₁₉NO₂ 280.1313 [M+Na]⁺; found 280.1310.

1-(4’-Methylphenoxy)-3-(phenylamino)propan-2-ol (12ka)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as light grey solid; M.p. 78-79°C; Rf (hexane/AcOEt
85:15) 0.48; IR (CHCl₃) ν_max (cm⁻¹): 3399, 3028, 2922, 2855, 1604, 1510; ¹H NMR (300 MHz, CDCl₃): δ 2.28 (s, 3H, CH₃), 3.23 (dd, J = 7.0 and 13.0 Hz, 1H, CH₂), 3.38 (dd, J = 4.2 and 13.0 Hz, 1H, CH₂), 3.96 (m, 2H, CH₂), 4.14-4.24 (m, 1H, CH), 6.62-6.82 (m, 5H, ArH), 7.05-7.21 (m, 4H, ArH); ¹³C NMR (75.45 MHz, CDCl₃): δ 20.6, 46.7, 68.9, 70.3, 113.4, 114.5, 118.1, 129.4, 130.2, 130.7, 148.2, 156.4; HRMS: calculated for C₁₆H₁₉NO₂ 258.1494 [M+H]⁺; found 258.1493.

1-(4’-Chlorophenoxy)-3 (phenylamino)propan-2-ol (12la)

The title compound was isolated by column chromatography (hexane/AcOEt 85:15) as light brown solid; m.p. 80-81°C; Rf (hexane/AcOEt 85:15) 0.47; IR (CHCl₃) ν_max (cm⁻¹): 3404, 3053, 3022, 2926, 1602, 1492; ¹H NMR (300 MHz, CDCl₃): δ 3.05 (bs, 1H), 3.29 (dd, J = 7.2 and 13.5 Hz, 1H, CH₂), 3.46 (dd, J = 4.2 and 12.9 Hz, 1H, CH₂), 3.97-4.09 (m, 2H CH₂), 4.21-4.28 (m, 1H, CH), 6.62-6.86 (m, 5H, ArH), 7.13-7.25 (m, 4H, ArH); ¹³C NMR (75.45 MHz, CDCl₃): δ 46.5, 68.6, 70.3, 113.3, 115.8, 118.1, 126.1, 129.3, 129.4, 147.9, 157.0; HRMS: calculated for C₁₅H₁₅ClNO₂ 300.0767 [M+Na]⁺; found 300.0780.

1-(Allyloxy)-3-(phenylamino)propan-2-ol⁵⁶ (12ma)

The title compound was isolated by column chromatography (hexane/AcOEt 90:10) as yellow oil; Rf (hexane/AcOEt 85:15) 0.47; IR (CHCl₃) ν_max (cm⁻¹): 3395, 3053, 3013, 2917, 2856, 1604; ¹H NMR (300 MHz, CDCl₃): δ 2.70-3.00 (bs, 1H), 3.14 (dd, J = 7.2 and 12.9 Hz, 1H, CH₂), 3.30 (dd, J = 4.2 and 12.9 Hz, 1H, CH₂), 3.45-3.57 (m, 2H, CH₂), 4.00-4.04 (m, 3H, CH₂, CH), 5.19-5.31 (m, 2H, CH₂ olefinic), 5.86-5.95 (m, 1H, CH), 6.61-6.74 (m, 3H, ArH), 7.14-7.24 (m, 2H, ArH); ¹³C NMR (75.45 MHz, CDCl₃): δ 46.6, 68.9, 72.2, 72.3, 113.09, 117.4, 117.6, 129.1, 134.2, 148.1; HRMS: calculated for C₁₂H₁₇NO₂ 230.1157 [M+Na]⁺; found 230.1013.

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⁵⁶
Section 3.3.2. Chiral Thiourea Catalyzed Asymmetric Ring Opening of \textit{meso} Epoxides with Amines.

The development of methodologies for the production of chiral building blocks is of crucial importance because such enantiomerically pure molecules are required as key intermediates in the synthesis of various pharmaceuticals, agrochemicals, etc. Chiral epoxides are among the most versatile building blocks for organic synthesis and their asymmetric ring opening by variety of nucleophiles is an appealing strategy for the synthesis of enantiomerically enriched product. Despite extensive studies on regio- and stereochemical selectivity in epoxide ring opening reactions, an enantioselective variant appeared only after Yamashita’s seminal report in 1985 on the first asymmetric ring opening (ARO) of a \textit{meso}-epoxide by aryl and alkyl thiols in the presence of zinc tartrate complex. This reaction yield \textit{trans}-2-arylthio-/alkylthio- cyclohexanols in good yield (up to 96%) and moderate ee (52-85%). In 1987 Yamashita reported that the asymmetric ring opening of \textit{meso} epoxides by aniline or trimethylsilyl azide is effectively catalyzed by zinc (2R,3R)-tartrate or cupric (2R,3R)-tartrate to provide \textit{trans}-\beta-amino alcohol or \textit{trans}-O-trimethylsilyl-2-azido alcohols with moderate enantioselectivity of 17-52%. Sinou and co-workers extended this method to the use of a titanium tartrate complex to provide similarly low enantioselectivity. The first highly-selective method for epoxide desymmetrization published by Nugent in 1992, involves a zirconium(IV)trialkanolamine complex which catalyzes a highly enantioselective addition of \textit{i}-PrMe$_2$SiN$_3$ to a variety of \textit{meso}-epoxides.

After the pioneering studies on the desymmetrization of \textit{meso}-epoxides by Yamashita and Nugent, Jacobsen \textit{et al.} developed chiral-(salen) complexes for the asymmetric activation of \textit{meso}- and racemic- epoxides towards nucleophilic attack. The chiral-(salen) complex catalyzed the epoxide ring opening by a variety of nucleophiles providing ring opened product in excellent enantioselectivity (>99%). Till today, there are large numbers of literature reports for the ARO of epoxides by chiral metal catalysts but a very limited reports exists on the use of organocatalysts. The metal free

ARO of epoxides include, the ring opening of aryl glycidyl ether with alkyl amines in the presence of stoichiometric amounts of β-cyclodextrin, the enantioselective ring opening of epoxides with silicon tetrachloride to obtain optically active chlorohydrin catalyzed by chiral phosphoramides and bipyridine N,N-dioxide derivatives and enantioselective rearrangement of 3-phospholene epoxides to 3-hydroxy-2-phospholene using cinchona alkaloids as chiral catalyst. So, there is great scope in the designing of organocatalysts for asymmetric epoxide ring opening reaction.

Inspired by the results from regioselective ring opening of epoxides catalyzed by \(N,N'\)-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea 6 to afford β-amino alcohols, it was planned to synthesize chiral thiourea derivatives for enantioselective ring opening of meso-epoxides with amines. Cinchona alkaloids were chosen to provide the chiral scaffold for asymmetric synthesis. Based on this idea cinchona alkaloid based thiourea derivatives were prepared by slightly modified procedure reported in the literature.\(^{67}\)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{O} & \\
\text{HN} & \quad \text{N-Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\[20\] + \[21a\] \[10\text{ mol% catalyst (22)}\] \[25\mu\text{L acetonitrile, r.t.}\] \[\rightarrow\]

\[
\begin{align*}
\text{HO} & \\
\text{N} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\[23a\]

Initially, the aminolysis of \(\text{cis-}\)stilbene oxide (20) with \(N\)-phenylpiperazine (21a) catalyzed by quinidine-thiourea (QD-TU, 22a) was chosen as model reaction. The QD-TU (22a) (10 mol%) was added to a stirred reaction mixture of \(\text{cis-}\)stilbene oxide (0.125 mmol) and \(N\)-phenylpiperazine (0.125 mmol) in 25μL acetonitrile. The progress of the reaction was monitored by running a TLC at regular intervals. After 7 days the reaction mixture was extracted with chloroform, dried over anhydrous sodium sulphate and concentrated to obtain the crude product. The crude product was purified by column chromatography using mixture of hexane and ethyl acetate as eluent to obtain

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pure white crystalline product in 60\% yield. The structure of the compound was
determined by recording the \textsuperscript{1}H NMR spectroscopy. The \textsuperscript{1}H NMR of the product
showed three 2H, 2H and 4H multiplet at \(\delta\) 2.54-2.56, 2.84-2.87 and 3.20-3.31 out of
which two multiplets are due to two protons of CH\(_2\) of piperazine ring and third
multiplet corresponds to the four protons (2 x CH\(_2\)) of piperazine ring, two doublet at \(\delta\)
3.67 and \(\delta\) 5.10 with \(J\) value of 10.2 Hz due to two CH groups and two 3H and 10H
multiplets at 6.82-6.89 and 7.08-7.28 due to aromatic protons. The \textsuperscript{13}C NMR spectrum
(CDCl\(_3\)) shows negative signal at \(\delta\) 48.9 and 49.7, and positive signal at \(\delta\) 70.5, 76.4,
116.3, 120.1, 127.3, 127.4, 128.0, 129.1, 129.9, 132.7 and 132.8 while the signal due to
quaternary carbons at \(\delta\) 141.2 and 151.2 that appeared in normal \textsuperscript{13}C NMR spectrum
were absent in DEPT experiment. Mass spectrum shows a parent ion peak at m/z 358.
These spectral data corresponds to the ring opened product of \textit{cis} -stilbene oxide (20)
with \textit{N}-phenylpiperazine (21a) \textit{i.e} 1,2-diphenyl-2-(4-phenylpiperazin-1-yl)ethanol
(23a). The enantiomeric excess of 23a was determined to be 50\% by HPLC (Figure
3.10 b) using a chiral column (Chiralpak IB, Daicel) with hexane/ iso-propanol (90:10
v/v) as mobile phase, at a flow rate of 1 mL/min and at \(\lambda\) = 254 nm. The two
enantiomers of 23a were eluted at a retention time of \(t_R\) (\textit{major}) 10.556 min (T1), \(t_R\)
(\textit{minor}) 13.034 min (T2).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.9.png}
\caption{\textsuperscript{1}H NMR Spectra of 23a}
\end{figure}
Encouraged by these results, different cinchona alkaloid thioureas derivatives such as cinchonine-thiourea (C-TU, 22b), quinine-thiourea (Q-TU, 22c) and cinchonodine-thiourea (CD-TU, 22d) were screened in order to find the best catalyst for this transformation (Table 3.10). The epoxide ring opening reaction catalyzed by C-TU (22b) yielded the same enantiomer of 23a as QD-TU (22a) in 50% yield and 13% ee, whereas, Q-TU (22c) and CD-TU (22d) gave the opposite enantiomer of 23a in yield of 70% and 55%, respectively and with enantiomeric excess of 8% and 70%, respectively.

Of all the cinchona alkaloid thiourea derivatives, CD-TU (22d) gave the highest selectivity (70% ee) for the epoxide ring opening reaction, but this was quite low. So, it was planned to synthesize a new class of catalysts by incorporating an amino acid moiety between cinchona alkaloid scaffold and thiourea, which was thought to block the approach of nucleophile on one face of the epoxide, thus preferably allowing the attack from other side only and hence, may lead to improvement in the enantioselectivity of the product (23a). With this idea, three new chiral thiourea catalysts were synthesized and used as a catalyst for the reaction between cis-stilbene oxide (20) and N-phenylpiperazine (21a). The catalyst 22e gave the β-amino alcohol (23a) with good yield of 75% and highest enantioselectivity of 94%, in 7 days, while,
catalyst 22f and 22g afforded 23a with comparatively lower enantioselectivity (Table 3.10, entry 7 and 8). But to our surprise all the three catalyst (22e-22g) yield the same enantiomer of the product, configuration of which was same as that obtain with 22c and 22d, which indicated that the chiral centre nearest to the thiourea moiety controls the stereochemistry of the ring opened product. This observation was further supported by the use of catalyst 22h (where D-phenylalanine was used in place of L-phenylalanine) in the ring opening reaction, which afforded that the opposite enantiomer of 23a with an ee of 36% and yield of 50%. Out of these eight catalysts, catalyst 22e gave the highest enantioselectivity (94%) and highest yield (75%) of 23a and thus was chosen for further optimization.

![Catalysts](image)

**Figure 3.11**

The variation in the amount of solvent was studied. It has been observed that on increasing the amount of acetonitrile from 25 µL to 100 µL the yield decreases from
Table 3.10: Screening of catalyst for ring opening of stilbene oxide (20) with N-phenyl piperazine (21a).

<table>
<thead>
<tr>
<th>S. No</th>
<th>Catalyst</th>
<th>Time (D)</th>
<th>T1</th>
<th>T2</th>
<th>Yield* (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22a</td>
<td>7</td>
<td>major</td>
<td>60</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22b</td>
<td>7</td>
<td>major</td>
<td>50</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>22c</td>
<td>7</td>
<td>major</td>
<td>70</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>22d</td>
<td>7</td>
<td>major</td>
<td>55</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>22e</td>
<td>7</td>
<td>major</td>
<td>75</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>22f</td>
<td>7</td>
<td>major</td>
<td>70</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>22g</td>
<td>7</td>
<td>major</td>
<td>50</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>22h</td>
<td>7</td>
<td>major</td>
<td>50</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

* Isolated yield after chromatography. b Determined by HPLC.

75% to 25% but the enantioselectivity remains same (94%) (Table 3.11). This shows that increasing the amount of solvent results in the dilution of the reaction mixture which slow down the reaction and lower the yield. Thus, increase in the amount of solvent decreases the yield of the product whereas the enantioselectivity remain same.

Table 3.11: Variation in amount of ACN with catalyst 22e.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Amount (µl)</th>
<th>Yield (%)*</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>75</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>65</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>55</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>25</td>
<td>94</td>
</tr>
</tbody>
</table>

* Isolated yield after chromatography. b Determined by HPLC. c Time of reaction = 7 days

Further, optimization of the reaction condition by increasing the amount of N-phenylpiperazine (21a) shows that on increasing the amount of N-phenylpiperazine from 1.1 to 3.0 equivalent, the enantioselectivity remains almost same (94-96%), whereas the yield decreases from 75% to 60% (Table 3.12).
Table 3.12. Variation of amount of N-phenylpiperazine with catalyst 22e.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Amount (equiv)</th>
<th>Time (Days)</th>
<th>Yield (%) (^a)</th>
<th>ee (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>7</td>
<td>75</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>7</td>
<td>75</td>
<td>96.5</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>7</td>
<td>74</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>7</td>
<td>74</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>7</td>
<td>60</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield after chromatography. \(^b\) Determined by HPLC. * Solvent used for the reaction = Acetonitrile

A survey of ten solvents (Table 3.13) revealed that reaction could be performed in all the solvents but yield varied. Even in the neat condition the ee of the required product was 93.5% with 80% isolated yield. However, excellent ee value (>99%) was obtained from CHCl\(_3\) and THF with high yields of 96% and 70%, respectively for the required product 23a. In light of these results CHCl\(_3\) was chosen as best solvent for this transformation and used for subsequent studies.

Table 3.13. Screening of solvents for asymmetric ring opening of stilbene oxide (20) with N-phenylpiperazine (21a).

<table>
<thead>
<tr>
<th>S. No</th>
<th>Solvents</th>
<th>Yield (%) (^a)</th>
<th>ee (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Neat</td>
<td>80</td>
<td>93.5</td>
</tr>
<tr>
<td>2</td>
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<td>97</td>
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<tr>
<td>3</td>
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<td>70</td>
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<tr>
<td>4</td>
<td>DCM</td>
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<td>86</td>
</tr>
<tr>
<td>5</td>
<td>CHCl(_3)</td>
<td>96</td>
<td>&gt;99</td>
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<tr>
<td>6</td>
<td>THF</td>
<td>70</td>
<td>&gt;99</td>
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<tr>
<td>7</td>
<td>Benzene</td>
<td>75</td>
<td>97</td>
</tr>
<tr>
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<td>DMF</td>
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<tr>
<td>9</td>
<td>H(_2)O</td>
<td>92</td>
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<tr>
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<td>MeOH</td>
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<tr>
<td>11</td>
<td>1,4-dioxane</td>
<td>47</td>
<td>95.5</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield after chromatography. \(^b\) Determined by HPLC. * Time of reaction = 5 days
Further the effect of catalyst loading on the rate of reaction and enantioselectivity of the product was studied. On reducing the catalyst loading from 10 mol% to 5 mol% lower yield (65%) and lower ee (90%) of the product was obtained. Increasing the catalyst loading to 15 mol% led to similar yield but lower ee (92%) (Table 3.14). So, all further reactions were performed using 10 mol% of catalyst.

Table 3.14. Variation in loading of catalyst 22e.

<table>
<thead>
<tr>
<th>Catalyst Loading (mol %)</th>
<th>Time (days)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6</td>
<td>65</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>96</td>
<td>92</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after chromatography. <sup>b</sup> Determined by HPLC

Thus, stirring a mixture of epoxide (0.125 mmol), amine (0.125 mmol) and catalytic amount (10 mol%) of 22e at room temperature using 25 µL of CHCl₃ as solvent provides optimal conditions for this transformation.

Under the optimized conditions, the aminolysis of cis-stilbene oxide (20) with various aliphatic amines was carried out. The reaction of cis-stilbene oxide (20) with N-methylpiperazine (21b) gave the ring opened product in 60% yield and 15% ee in 7 days (Table 3.15, entry 2), whereas the reaction with piperidine (21b) (Table 3.15, entry 3) and morpholine (21c) (Table 3.15, entry 4), yielded the corresponding β-amino alcohol in 50% and 60% isolated yield and ee of 12% and 18%, respectively. The long chain aliphatic primary amines (21e-21g) (Table 3.15, entry 5-7), were also used as nucleophile. It was observed that the hexyl amine (21e) react at very slow rate to give the ring opened product in traces after 7 days whereas n-heptyl (21f) and n-decyl amine (21g) do not react even after 7 days.

Further to explore the substrate scope, other meso epoxides were subjected to epoxide ring opening reaction under the optimized conditions. Cyclohexene oxide (24) undergoes asymmetric epoxide ring opening reaction to yield the required product in 74% yield and 6% ee in 5 days whereas, cyclopentene oxide and cyclododecene oxide do not react under the reaction condition.
Table 3.15. Epoxide ring opening of stilbene oxide with various amines

<table>
<thead>
<tr>
<th>S. No</th>
<th>Amine</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="21a" /></td>
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</tr>
<tr>
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<td>60</td>
<td>18</td>
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<td>5</td>
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</tr>
<tr>
<td>6</td>
<td><img src="image" alt="21f" /></td>
<td>No rxn after 7 days</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="22g" /></td>
<td>No rxn after 7 days</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after chromatography. <sup>b</sup> Determined by HPLC

In conclusion, first organocatalytic methodology has been developed for asymmetric epoxide ring opening reaction with aliphatic amines using chiral thioureas as catalysts. The asymmetric epoxide ring opening yield chiral β-amino alcohols in good yield and enantioselectivity.
3.3.2.1 Experimental

3.3.2.1.1 General methods

NMR spectra were obtained at 300 MHz (JEOL AL-300) using either CDCl₃ as solvents with Me₄Si in CDCl₃ as internal standard. The chemical shifts are reported in δ values relative to TMS and coupling constants (J) are expressed in Hz. Spectral patterns are designated as s = singlet; d = doublet; dd = doublet of doublets; q = quartet; t = triplet; br = broad; m = multiplet. Carbon NMR spectra were recorded on the same instrument (75.45 MHz) with total proton decoupling. High-resolution mass spectra (HRMS) were recorded with a Micromass Q-TOF mass spectrometer. IR spectra were obtained with FT-IR Bruker (270-30) spectrophotometer and Varian 660-IR FT-IR spectrometer and reported in wave numbers (cm⁻¹). Mass spectra were recorded on Bruker Esquire 300 LC Mass spectrometer and JEOL AccuTOF DART mass spectrometer. Analytical thin-layer chromatography (TLC) was performed on either (i) aluminum sheets pre-coated with silica gel 60F₂₅₄ (Merck, India) or (ii) glass plates (7.5 x 2.5 cm) coated with silica gel GF-254 (Spectrochem India) containing 13% calcium sulphate as binder and various combinations of ethyl acetate and hexane were used as eluents. Visualization of the spots was accomplished by exposing to UV light or iodine vapors. Column chromatography was performed on silica gel (60-120 mesh) and (100-200 mesh) using mixture of ethyl acetate and hexane as eluent. The enantiomeric excess of the product were determined by HPLC (Dionex, USA) using chiral columns (Daicel Chiralpak IB, AD-H and AS-H).

Organic substrates cis-stilbene oxie, cyclohexeneoxide, cyclopentene oxide and cyclododecene oxide, N-Phenylpiperazine, n-hexyl amine, n-heptyl amine, and n-dodecyl amine were purchased from Sigma Aldrich and N-Methylpiperazine, morpholine and piperidine were purchased from Spectochem. India and used as received.

3.3.2.1.2 General procedure for the synthesis of catalyst 22a-22d
Step 1: Quinidine (A) (3.23 g, 10.0 mmol) and triphenylphosphine (3.15 g, 12.0 mmol) were dissolved in 50 mL of dry THF and the solution was cooled to 0°C. Diisopropyl azodicarboxylate (2.43 g, 12.0 mmol) was added all at once. Then solution of diphenyl phosphoryl azide (3.30 g, 12.0 mmol) in 20 mL of dry THF was added dropwise at 0°C. The mixture was allowed to warm to room temperature. After being stirred for 12 h, the solution was heated to 50°C for 2 h. Then triphenylphosphine (3.41 g, 13.0 mmol) was added and heating was maintained until the gas evolution has ceased (2 h). The solution was cooled to room temperature, and 1 mL of water was added and the solution was stirred for 3 h. Solvents were removed in vacuo and the residue was dissolved in CH$_2$Cl$_2$ and 10% hydrochloric acid (1:1, 100 mL). The aqueous phase was washed with CH$_2$Cl$_2$ (4 × 50 mL). Then the aqueous phase was made alkaline with excess cc. aqueous ammonia and was washed with CH$_2$Cl$_2$ (4 × 50 mL). The organic phases was dried over Na$_2$SO$_4$ and concentrated. The residue was purified by column chromatography on silica gel (CHCl$_3$/MeOH; 90:10 as eluant) affording the title compound (B) as a yellowish viscous oil in 50% isolated yield.

Step 2: To a solution of B (1 mmol) in dry DCM (1mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.1 mmol) in 1 mL of dry DCM at ambient temperature. The mixture was stirred overnight, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (CHCl$_3$/MeOH 95:5 as eluant) affording thiourea 22a as light yellow solid in 80% isolated yield.

3.3.2.1.3. General procedure for the synthesis of catalyst 22e-22i:
To an ice cold stirred solution of N-Boc protected phenylalanine C (4.3 mmol) and B (0.453 mL, 5.1 mmol) in dichloromethane (15 mL), a solution of dicyclohexylcarbodiimide (0.98 g, 4.75 mmol) in dichloromethane was added dropwise. The resulting mixture was stirred and the temperature of the reaction mixture was allowed to rise to room temperature. The progress of the reaction was monitored by TLC (ethyl acetate–hexane). After completion of the reaction, the reaction mixture was filtered and concentrated under reduced pressure to obtain the crude product, which was purified on column chromatography to obtain a thick liquid in 70% yield. The thick liquid was redissolved in CH₂Cl₂ and cooled to 0°C, then TFA (10 equivalent) in CH₂Cl₂ (TFA/CH₂Cl₂) was added dropwise. The resulting mixture was stirred for 8 to 12 h until the reaction was complete (TLC) and then concentrated under reduced pressure. The resulting residue was redissolved in CH₂Cl₂ and neutralized with saturated solution of sodium carbonate and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography using CHCl₃–MeOH as an eluent to obtain a light yellow/orange liquid E in 80–85% yield.

To a solution of E (1 mmol) in dry DCM (1 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenylisothiocyanate (1.1 mmol) in 0.5 mL of dry DCM at ambient temperature. The mixture was stirred overnight, and the solvent was removed by evaporation on water bath. The residue was purified by column chromatography on silica gel (CHCl₃/MeOH 95:5 as eluant) affording thiourea as light yellow solid.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((R)-(6-methoxyquinolin-4-yl)(5-vinylquinuclidin-2-yl)methyl)thiourea (22a)

The title compound was isolated by column chromatography (CHCl₃:MeOH; 95:5) as yellow solid; [α]D25 +28.0 (c 0.50, CHCl₃); ¹H NMR (500 MHz, CD₃OD) δ ppm 1.60 (br m, 1H, CH₂); 1.87 (m, 1H, CH) 1.96 (br m, 1H, CH₂), 2.04 (m, 1H, CH₂), 2.08 (m, 1H, CH₂), 2.37 (br m, 1H, CH), 2.55 (ddd, J = 15.6, 13.8, 4.9 Hz, 1H, CH₂), 2.70 (ddd, J = 13.6, 4.7, 2.3 Hz, 1H, CH₂), 3.05 (dd, J = 13.6, 9.9 Hz, 1H, CH₂), 3.11 (ddd, J = 15.6, 10.5, 7.8, 2.3 Hz, 1H, CH₂), 3.68 (br m, 1H, CH), 4.03 (s, 3H, OCH₃), 5.08 (dt, J
= 17.2, 1.5 Hz, 1H, CH=CH$_2$), 5.10 (dt, J = 10.5, 1.5 Hz, 1H, CH=CH$_2$), 6.03 (ddd, J = 17.2, 10.5, 6.2 Hz, 1H, CH=CH$_2$), 6.84 (d, J = 11.0 Hz, 1H, CH), 7.41 (dd, J = 9.3, 2.6 Hz, 1H, ArH), 7.57 (d, J = 4.7 Hz, 1H, ArH), 7.60 (br s, 1H, ArH), 7.94 (d, J = 9.3 Hz, 1H, ArH), 8.00 (br s, 2H, ArH), 8.16 (br d, J = 2.6 Hz, 1H, ArH), 8.70 (d, J = 4.7 Hz, 1H, ArH); $^{13}$C NMR (125.0 MHz, CDCl$_3$): δ 24.3, 27.2, 28.0, 39.7, 41.7, 54.1, 55.5, 56.0, 59.0, 103.1, 113.8, 117.1, 119.5, 122.7, 122.8, 123.5, 129.0, 130.1, 131.7, 141.4, 141.7, 144.3, 146.2, 147.2, 158.7, 182.5; HRMS (ESI): Calcd for C$_{29}$H$_{28}$F$_6$N$_4$OS [M+H]$^+$ 595.2120; Found: 595.2124.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((R)-(quinolin-4-yl)(5-vinylquinuclidin-2-yl)methyl) thiourea$^{66}$ (22b)

The title compound was isolated by column chromatography (CHCl$_3$:MeOH; 95:5) as yellow solid; m.p. 120-122°C; $[\alpha]_{25}^D$ +116.0 (c 0.45, CHCl$_3$); Rf (CHCl$_3$: MeOH; 90:10) 0.70; $^1$H NMR (500 MHz, CD$_3$OD) δ 0.82 (m, 2 H), 1.17 (m, 1H), 1.47 (m, 4 H), 2.29 (dd, J = 6.8, 14.5 Hz, 1 H), 2.95 (m, 3 H), 3.17 (m, 3 H), 5.12 (dd, J = 9.7, 13.8 Hz, 1H), 5.88 (ddd, J = 6.2, 10.5, 17.0 Hz, 1 H), 6.23 (d, J = 10.3 Hz, 1H), 7.53 (m, 2 H), 7.63 (m, 1H), 8.75 (t, J = 4.1 Hz, 1H), 7.72 (dd, J = 6.0, 13.2 Hz, 1 H), 7.98 (t, J = 7.0 Hz, 2H), 8.57 (t, J = 7.3 Hz, 1H); $^{13}$C NMR (125 MHz, CD$_3$OD) δ 26.4, 27.5, 29.0, 40.7, 57.1, 62.0, 115.7, 118.0, 123.6, 123.7, 124.2, 126.0, 126.2, 128.2, 129.3, 130.2, 131.2, 133.0, 142.2, 143.4, 149.3, 151.2, 183.1; IR (KBr): ν 3244, 1634, 752, 681 cm$^{-1}$; HRMS (ESI) m/z calcd for (C$_{28}$H$_{27}$N$_4$F$_6$S): 565.1852, found: 565.1850.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((S)-(6-methoxyquinolin-4-yl)(8-vinylquinuclidin-2-yl)methyl) thiourea$^{66}$ (22c)

The title compound was isolated by column chromatography (CHCl$_3$:MeOH; 95:5) as yellow solid; m.p. 106-107°C; $[\alpha]_{25}^D$ $-$117.0 (c 0.50, CHCl$_3$); Rf (CHCl$_3$:MeOH; 95:5) 0.50; $^1$H NMR (400 MHz, CDCl$_3$): δ 0.99 (m, 1H, CH), 1.44-1.50 (m, 1H, CH), 1.63-1.77 (br, m, 3H, CH$_2$, CH), 2.40 (br m, 1H, CH), 2.82-2.95
(m, 2H), 3.18-3.24 (m, 1H, CH₂), 3.54 (br m, 2H), 3.93-3.94 (m, 1H, CH), 3.98 (s, 3H, OCH₃), 4.99-5.03 (m, 2H, CH=CH₂), 5.51-5.72 (m, 1H, CH=CH₂), 6.17 (br s, 1H), 7.25-7.28 (m, 1H, ArH), 7.32-7.38 (m, 1H, ArH), 7.61-7.64 (m, 1H, ArH), 7.84-7.98 (m, 4H, ArH), 8.57-8.60 (m, 1H, ArH); ¹³C NMR (100.62 MHz, CDCl₃): δ 25.2 (-ve), 26.7 (-ve), 26.9 (+ve), 38.3 (+ve), 41.7 (-ve), 54.6 (-ve), 55.7 (+ve), 55.9 (+ve), 61.2, 77.3 (+ve), 100.0, 102.2 (+ve), 115.8 (-ve), 118.5 (+ve), 121.6, 122.3 (+ve), 123.3 (+ve), 124.3 (+ve), 131.5 (+ve), 132.0, 132.3, 139.3 (+ve), 144.6, 147.4 (+ve), 158.3, 180.8; IR (KBr): ν 3244, 1634, 752, 681 cm⁻¹; HRMS (EI) Exact mass calculated for C₂₉H₂₈F₆N₄OS [M⁺] 594.1882; Found: 594.1876.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((S)-(quinolin-4-yl)(8-vinylquinuclidin-2-yl)methyl) thiourea⁶⁶ (22d)

The title compound was isolated by column chromatography (CHCl₃:MeOH; 95:5) as yellow solid; m.p. 108-110°C; [α]D²⁵ -53.7 (c 0.37, CHCl₃); ¹H NMR (300 MHz, CHCl₃): δ 1.24 (br m, 1H), 1.37 (m, 1H), 1.75 (m, 4H), 2.38 (m, 1H), 2.80 (m, 2H), 3.19 (t, J = 12, 1H), 3.40 (m, 2H), 4.95-5.01 (m, 2H, CH₂), 5.60 (br m, 1H, CH), 7.38 (d, J = 4.2, 1H, ArH), 7.63-7.62 (m, 3H, ArH), 7.70-7.74 (m, 2H, ArH), 7.88 (m, 2H, ArH), 8.12 (d, J = 8.1, 1H, ArH), 8.40 (br s, 1H, NH), 8.79 (br s, 1H, ArH); ¹³C NMR (75.45 MHz, CHCl₃) δ 25.1, 25.8, 27.4, 38.7, 47.2, 48.9, 116.3, 118.8, 123.5, 124.0, 125.2, 127.6, 130.0, 132.8, 139.0, 150.4, 180.1; EIMS: m/z : 565 (M⁺).

1-((S)-1-((R)-(Quinolin-4-yl)(5-vinylquinuclidin-2-yl)methylcarbamoyl)-2-phenylethyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (22e)

The title compound was isolated by column chromatography (CHCl₃: MeOH; 93:7) as light yellow solid; m.p. 150-152°C; [α]D²⁵ +12.5 (c 0.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 0.88-0.99 (br m, 1H), 1.11 (br m, 1H), 1.24-1.29 (m, 1H), 1.42-1.52 (m, 2H), 1.73-1.80 (m, 1H), 2.04-2.20 (m, 2H), 2.67-3.42 (br m, 6H), 3.58-3.69 (m, 1H), 3.70-3.79 (m, 1H), 4.10-4.14 (m, 1H), 5.01 (m,
1H), 5.11 (m, 1H), 5.21-5.28 (m, 1H), 5.45 (m, 1H), 6.93-6.98 (m, 2H), 7.00-7.18 (m, 3H), 7.45 (t, $J = 8.4$, 1H), 7.50 (m, 1H), 7.62-7.69 (m, 2H), 7.81-7.91 (br m, 1H), 7.99-8.15 (m, 2H), 8.78 (dd, $J = 4.0$ and 7.04 Hz, 2H), 9.10 (br s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 24.8, 25.5, 26.6, 36.8, 36.9, 38.3, 40.3, 46.3, 47.9, 48.6, 55.8, 59.7, 59.9, 118.2, 119.0, 121.7, 122.5, 123.8, 124.4, 127.1, 127.3, 128.6, 128.7, 129.0, 129.6, 130.5, 131.0, 131.3, 131.6, 132.0, 135.5, 135.6, 140.0, 148.3, 150.0, 181.1; EIMS: m/z : 711 (M+).

1-((S)-1-(((S)-(6-Methoxyquinolin-4-yl)(8-vinylquinuclidin-2-yl)methylcarbamoyl)-2-phenylethyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (22f)

The title compound was isolated by column chromatography (CHCl$_3$:MeOH; 92:8) as light yellow solid; m.p. 135-136°C; $^1$H NMR (300 MHz, CDCl$_3$) δ 1.26 (br m, 1H), 2.09 (br m, 3H), 2.85 (m, 1H), 2.94-3.02 (m, 1H), 3.12-3.20 (m, 1H), 3.53 (m, 1H), 3.61-3.69 (m, 1H), 3.88 (m, 2H), 3.97 (s, 3H), 4.76-4.90 (m, 3H), 5.89-6.95 (m, 1H), 6.02-6.21 (m, 1H), 6.69-6.70 (d, $J = 4.2$ Hz, 1H), 7.05-7.15 (m, 4H), 7.52-7.63 (m, 2H), 7.69-7.71 (m, 1H), 7.83 (br m, 1H), 8.01 (m, 1H), 8.18-8.26 (m, 1H), 8.29 (br m, 1H); 8.87-8.89 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 27.2, 28.0, 30.2, 40.6, 46.0, 57.7, 59.5, 62.7, 63.1, 64.3, 81.7, 106.7, 120.5, 124.2, 127.2, 127.4, 128.8, 128.9, 129.1, 130.1, 130.6, 131.7, 132.5, 134.9, 135.4, 139.7, 141.1, 141.5, 144.6, 146.6, 150.5, 164.1, 180.7; EIMS: m/z : 741 (M+).

1-((S)-1-(((S)-(Quinolin-4-yl)(8-vinylquinuclidin-2-yl)methylcarbamoyl)-2-phenylethyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea$^{68}$ (22g)

The title compound was isolated by column chromatography (CHCl$_3$:MeOH; 93:7) as light yellow solid; m.p. 130-132°C; [α]$^D_{25}$ -62.5 (c 0.4, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$): δ 0.72 (br, 1H), 1.26-1.28 (m, 2H), 1.58-1.60 (m, 3H), 2.26

(br, 1H), 2.64-2.71 (m, 3H), 3.07-3.45 (m, 4H), 4.89-4.98 (m, 2H), 5.17 (br, 1H), 5.54-5.71 (m, 1H), 7.13-7.35 (br, 9H), 7.42 (m, 1H), 7.62 (br, 1H), 8.11-8.13 (d, J = 8.2 Hz, 1H), 8.29-8.33 (m, 1H), 8.45 (br, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 25.5, 27.0, 27.6, 29.7, 38.5, 39.2, 40.9, 55.6, 59.1, 67.9, 114.1, 114.9, 118.3, 118.9, 121.6, 122.3, 124.3, 124.9, 126.7, 127.0, 127.4, 128.1, 128.2, 128.5, 128.9, 129.2, 130.1, 130.2, 130.5, 130.9, 131.2, 136.0, 139.0, 140.7, 147.8, 149.9, 173.5, 181.7; HRMS calcd for C$_3$H$_{3}$F$_6$N$_5$OS [M+H]$^+$ 712.2569, found 712.2696.

1-((R)-1-((R)-(Quinolin-4-yl)(5-vinylquinuclidin-2-yl)methylcarbamoyl)-2-phenylethyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (22h)

![Chemical structure of 1-((R)-1-((R)-(Quinolin-4-yl)(5-vinylquinuclidin-2-yl)methylcarbamoyl)-2-phenylethyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea](image)

The title compound was isolated by column chromatography (CHCl$_3$:MeOH; 93:7) as light yellow solid; $^1$H NMR (300 MHz, CDCl$_3$): δ 0.87 (d, J = 6.9, 1H), 1.26 (br, m, 3H), 1.42 (br m, 4H), 2.34 (m, 1H), 3.01-3.60 (m, 6H), 4.94 (m, 1H), 5.28-5.31 (m, 2H), 5.76-5.78 (m, 1H), 7.01-7.09 (m, 5H), 7.22-7.40 (m, 2H), 7.55-7.72 (m, 3H), 7.84 (m, 3H), 8.06-8.25 (m, 3H), 8.74 (m, 1H); $^{13}$C NMR (300 MHz, CDCl$_3$): 24.7, 25.4, 26.5, 36.7, 36.9, 38.1, 40.3, 46.1, 47.8, 48.5, 55.9, 59.6, 59.7, 118.1, 119.0, 121.6, 122.4, 123.8, 124.1, 127.1, 127.3, 128.5, 128.7, 129.1, 129.4, 130.2, 131.0, 131.2, 131.5, 132.1, 135.5, 135.6, 140.0, 148.2, 150.2, 181.0.

3.3.2.1.4. General Produce for the epoxide ring opening reaction

To a 10 ml RBF epoxide (0.125mmol), amine (1.1 equivalent), thiourea catalyst (10 mol%) and CHCl$_3$ (25µL) were consecutively added and the resulting mixture was stirred at room temperature for the time indicated. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was loaded on the chromatography column and eluted with mixture of ethyl acetate and hexane to obtain the pure product.
**1,2-Diphenyl-2-(4’-phenylpiperazin-1-yl)ethanol (23a)**

The title compound was isolated by column chromatography (hexane:ethyl acetate: 90:10) as white solid; m.p. 169-170°C; Rf (hexane:ethyl acetate: 90:10) 0.60; [α]D25 -23.5 (c 0.14, CHCl3); 1H NMR (300 MHz, CDCl3): δ 2.54-2.56 (m, 2H, CH2), 2.84-2.87 (m, 2H, CH2), 3.20-3.31 (m, 4H, 2×CH2), 3.67 (d, J = 10.2, 1H, CH), 5.10 (d, J = 10.2, 2H, CH, OH), 6.82-6.89 (m, 3H, ArH), 7.08-7.28 (m, 12H, ArH); 13C NMR (75.45 MHz, CDCl3): δ 48.9 (-ve), 49.7 (-ve), 70.5 (+ve), 76.4 (+ve), 116.3 (+ve), 120.1 (+ve), 127.3 (+ve), 127.4 (+ve), 128.0 (+ve), 129.1 (+ve), 129.9 (+ve), 132.7 (+ve), 132.8 (+ve), 141.2, 151.2; enantiomeric excess 99%; determined by HPLC (Daicel Chiralpak IB, hexane/i-PrOH 90:10); flow rate 1 mL/min; λ = 254 nm; tR (minor) 11.80 min, tR (major) 14.66 min; EIMS: m/z: 358 (M+).

**2-(4’-Methylpiperazin-1-yl)-1,2-diphenylethanol (23b)**

The title compound was isolated by column chromatography (CHCl3:MeOH 97:3) as yellow oil; Rf (CHCl3:MeOH 97:3) 0.50; 1H NMR (300 MHz, CDCl3): δ 2.25 (s, 3H, CH3), 2.27-2.71 (m, 8H, 4×CH2), 3.59 (d, J = 10.4, 1H, CH, OH), 5.05 (d, J = 10.5, 1H, CH), 7.04-7.24 (m, 10H, ArH); 13C NMR (75.45 MHz, CDCl3): δ 29.7, 45.7, 55.3, 70.4, 76.184, 127.3, 127.4, 127.8, 127.88, 127.93, 129.88, 132.7, 141.2; enantiomeric excess 15%; determined by HPLC (Daicel Chiralpak AS-H, hexane/i-PrOH 90:10); flow rate 1 mL/min; λ = 254 nm; tR (minor) 7.36 min, tR (major) 8.76 min; EIMS: m/z: 296 (M+).

**1,2-Diphenyl-2-(piperidin-1-yl)ethanol (23c)**

The title compound was isolated by column chromatography (hexane:ethyl acetate: 90:10) as colourless oil; Rf (hexane:ethyl acetate: 90:10) 0.60; [α]D25 -5.2 (c 0.82, CHCl3); 1H NMR (300 MHz, CDCl3): δ 1.25-1.35 (m, 2H, CH2), 1.49 (br s, 5H, 2×CH2, OH) 2.46 (m, 2H, CH2) 2.63 (m, 2H, CH2), 3.53 (d, J = 10.4, 1H, CH), 5.03 (d, J = 10.4, 1H, CH), 6.99-7.23 (m, 10H, ArH); 13C
NMR (75.45 MHz, CDCl$_3$): $\delta$ 24.2 (-ve), 26.5 (-ve), 70.3 (+ve), 77.1 (+ve), 127.2 (+ve), 127.6 (+ve), 127.7 (+ve), 127.9 (+ve), 128.0 (+ve), 129.9 (+ve), 132.6, 141.0; enantiomeric excess 12%; determined by HPLC (Daicel Chiralpak IB, hexane/i-PrOH 90:10); flow rate 1 mL/min; $\lambda$ = 254 nm; $t_R$ (minor) 5.34 min, $t_R$ (major) 6.38 min; EIMS: m/z : 281 (M+).

2-Morpholino-1,2-diphenylethanol (23d)

The title compound was isolated by column chromatography (hexane:ethylacetate: 90:10) as colourless oil; R$_f$ (hexane:ethylacetate: 90:10) 0.60; $[\alpha]_{D}^{25}$ -13.5 (c 1.27, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.39-2.41 (m, 2H, CH$_2$), 2.66-2.67 (m, 2H, CH$_2$), 3.56 (d, $J$ = 10.4, 1H, CH), 3.71-3.83 (m, 4H, 2 x CH$_2$), 5.05 (d, $J$ = 10.4, 1H, CH), 7.05-7.29 (m, 10H, ArH); $^{13}$C NMR (75.45 MHz, CDCl$_3$): $\delta$ 67.2 (-ve), 70.3 (+ve), 76.7 (+ve), 127.3 (+ve), 127.4 (+ve), 128.0 (+ve), 129.9 (+ve), 132.6, 141.0 enantiomeric excess 18%; determined by HPLC (Daicel Chiralpak IB, hexane/i-PrOH 90:10); flow rate 1 mL/min; $\lambda$ = 254 nm; $t_R$ (minor) 14.48 min, $t_R$ (major) 17.76 min; EIMS: m/z : 283 (M+).

2-(4’-phenylpiperazin-1-yl)cyclohexanol (24a)

The title compound was isolated by column chromatography (hexane:ethylacetate: 90:10) as colourless oil; R$_f$ (hexane:ethylacetate: 90:10) 0.54; $[\alpha]_{D}^{25}$ +1.62 (c 1.6, CHCl$_3$); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.21-1.25 (m, 4H, 2 x CH$_2$), 1.73-1.80 (m, 1H, CH$_2$), 1.83-1.87 (m, 2H, CH$_2$), 2.14 (br s, 1H, CH$_2$), 2.30 (br s, 1H, CH), 2.56-2.62 (m, 2H, CH$_2$), 2.87-2.93 (m, 2H, CH$_2$), 3.14-3.23 (m, 2H, 2 x CH$_2$), 3.41 (br s, 1H, CH), 6.86-6.95 (m, 3H, ArH), 7.26-7.30 (m, 2H, ArH); $^{13}$C NMR (75.45 MHz, CDCl$_3$): $\delta$ 22.3, 24.0, 25.4, 33.2, 48.3, 50.0, 68.6, 70.2, 110.2, 119.8, 129.1, 151.3; enantiomeric excess 6%; determined by HPLC (Daicel Chiralpak IB, hexane/i-PrOH 95:5); flow rate 1 mL/min; $\lambda$ = 254 nm; $t_R$ (minor) 18.3 min, $t_R$ (major) 20.4 min; EIMS: m/z : 260 (M+).