NOVEL BISISOQUINOLINES:

SYNTHESIS, RESOLUTION AND APPLICATION IN

ASYMMETRIC HENRY REACTION

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ABSTRACT

This research project focuses on the synthesis of bisisoquinolines and examines their application as catalysts in the Henry reaction.

*Racemic* 1,2- and 1,3-bisisoquinolines have been synthesized using the classical double Bischler-Naprialski route. Resolution of 1,2-bisisoquinoline parent compound $C_1$-$1',2',3',4'$-terahydro-1,1'-bisisoquinoline was achieved using $(S)$-(-)-$\alpha$-methylbenzyl isocyanate, while resolution of the *racemic* 1,3-bisisoquinoline parent compound 1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) was achieved via the diastereomeric salt formation using $(L)$-(-)citramalic acid. The absolute configuration of this 1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) was established by X-ray crystallographic analysis. Mono-, di- and bridged N-alkyl derivatives of $C_1$-$1',2',3',4'$-terahydro-1,1'-bisisoquinoline and 1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) were successfully synthesized to explore their chemistry.

Application of the enantiopure 1,2- and 1,3-bisisoquinolines in the asymmetric Henry reaction was examined in details. A well-defined and efficient catalytic system comprising chiral $C_1$-tetrahydro-1,1'-bisisoquinoline and CuCl in the ratio of 2:1 has been developed for the enantioselective Henry reaction. The catalytic efficiencies of the chiral $C_1$-tetrahydro-1,1'-bisisoquinolines were found to be governed to a great extent by the structural constraints and the type of substituent at the sp$^3$-$N$ atom. Aromatic and aliphatic aldehydes reacted with nitromethane to give $\beta$-nitroalcohols in very high yields (up to 95%) and enatioselectivities (up to 91% ee). The catalyst system developed was found to be simple in operation since no special precautions were taken to exclude moisture or air from the reaction flask and no additives were required for activation.
The chiral complex derived from \(N\)-methyl-\(C_1\)-tetrahydro-1,1’-bisisoquinolines and Cu(I)Cl promoted the diastereoselective Henry reaction of nitroethane with a series of aromatic and aliphatic aldehydes. The nitroalcohol adducts were obtained in excellent yields (up to 95%), moderate \textit{anti}-selectivity (up to 2.6:1) and good enantioselectivity (up to 92% \textit{ee}) without any special precautions to exclude moisture or air.

The ability of 1,2- and 1,3- bisisoquinolines to function as organocatalysts for the Henry reaction was also investigated. Both successfully catalyzed the addition of nitroalkanes to \(\alpha\)-ketoesters and aldehydes giving the corresponding nitroalcohol adducts in excellent yields under very mild conditions. Among the different bisisoquinoline types examined, \(C_1\)-symmetric bisisoquinolines (amine-imine types) were found to be more efficient than \(C_2\)-symmetric bisisoquinolines (diamine-diimine types). 1,2-bisisoquinolines were also more efficient than 1,3-bisisoquinoline. The best yields (up to 99%) were obtained using 10 mol\% \(C_1\)-1,2,3,4,-tetrohydro-1,1’-bisisoquinolines. Moderate \textit{syn/anti} diastereoselectivity of up to 2:1 was obtained in the addition of nitroethane to \(\alpha\)-ketoesters and aldehydes.

The excellent catalytic results obtained in this thesis represent a major contribution to the application of chiral bisisoquinolines as ligands in asymmetric Henry reaction.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ar</td>
<td>Aryl group</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-Binaphthol</td>
</tr>
<tr>
<td>BIQ</td>
<td>Bisisoquinoline</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>Bu₂O</td>
<td>Dibutyl ether</td>
</tr>
<tr>
<td>c</td>
<td>Concentration</td>
</tr>
<tr>
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<td>cm⁻¹</td>
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<tr>
<td>¹³C NMR</td>
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<tr>
<td>dd</td>
<td>Doublet of doublet</td>
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<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarization Transfer</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutyl aluminium hydride</td>
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<td>DMAP</td>
<td>N,N-Dimethylaminopyridine</td>
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<td>Heteronuclear multiple quantum coherence</td>
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<td>IPA</td>
<td>Isopropyl alcohol</td>
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<td>&lt;i&gt;J&lt;/i&gt;</td>
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<tr>
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<td>Nuclear Magnetic Resonance</td>
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<td>Parts per million</td>
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<td>Py</td>
<td>Pyridine</td>
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<td>Salen</td>
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<td>t</td>
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<td>(t)-BuOH</td>
<td>\textit{tert}-Butanol</td>
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<td><strong>t-BuOMe</strong></td>
<td><em>tert</em>-Butyl methyl ether</td>
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<tr>
<td><strong>TFA</strong></td>
<td>Trifluoroacetic acid</td>
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<td><strong>THF</strong></td>
<td>Tetrahydrofuran</td>
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<td><strong>TLC</strong></td>
<td>Thin layer chromatography</td>
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<td><strong>TMS</strong></td>
<td>Tetramethylsilane</td>
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<tr>
<td><strong>Ts</strong></td>
<td>Toluenesulfonyl, tosyl group</td>
</tr>
<tr>
<td><strong>UV</strong></td>
<td>Ultraviolet</td>
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<tr>
<td><strong>δ</strong></td>
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Chapter 1. Introduction

1.1. Chirality and its importance

A molecule that does not have a plane of symmetry is said to be chiral. Chirality means an object is not superimposed on its mirror image, meaning “handedness”.\(^1\) The pair of nonsuperimposable mirror-image isomers are called enantiomers. Enantiomers have identical chemical and physical properties in the absence of an external chiral influence. Chirality is very important in nature and in our bodies. Since enzymes and cell surface receptors are chiral, the two enantiomers of a \textit{racemic} drug may interact differently with a receptor leading to different pharmacological effects. For example, one enantiomer may be therapeutically effective, while the other one may be less effective, ineffective or even toxic. For example, \((R)\)-thalidomide is effective for morning sickness, however \((S)\)-thalidomide is teratogenic. Hence, chirality is of prime significance in the pharmaceutical industry. Around 56\% of the currently used drugs were chiral molecules and around 88\% of these chiral drugs are marketed as racemates.\(^2,3\) The U.S. Food and Drug Administration (FDA) announced new rules mandating that the therapeutic and toxicity effects of both enantiomers of \textit{racemic} drugs are required to be well investigated and evaluated so their effects are predictable.\(^4\)

There are three main approaches to produce compounds in enantiopure forms: (1) chiral pool synthesis (from naturally occurring chiral sources), (2) resolution of \textit{racemic} compounds, and (3) asymmetric catalysis. The first two methods suffer from potentially severe drawbacks. Compounds from the chiral pool synthesis are limited while resolution or racemic compounds can provide only up to 50\% of the desired enantiomer. Asymmetric catalysis can afford various chiral molecules in potentially quantitative yields.
Hence, asymmetric catalysis has become one of the most extensively explored research areas and approaches to chiral compounds.

The use of chiral ligands to catalyze asymmetric reactions constitutes a major research approach. To this end, many types of chiral ligands have been investigated. Specifically, application of chiral nitrogen ligands in the form of metal complexes or organocatalysts in asymmetric transformations is well documented.\textsuperscript{5-7} For example, privileged catalysts based on \textit{salen} have been extensively used in many enantioselective reactions.\textsuperscript{8-11} We\textsuperscript{12,13} and others\textsuperscript{14,15} have been interested in constructing chiral bidentate bisisoquinolines and employing them as catalysts for various enantioselective reactions. Bisisoquinolines\textsuperscript{16-19} offer structurally constrained motifs that are similar to the well-used and explored chiral 1,1'-binaphthyls.\textsuperscript{20-24}

1.2. Chemistry of bisisoquinolines

In the following sections, synthesis, resolution and application of BIQs in various asymmetric reactions will be presented.

1.2.1. Synthesis of bisisoquinolines

Bisisoquinolines have been synthesized mainly by oxidative/reductive coupling\textsuperscript{25-31} and Bischler-Napieralski reactions.\textsuperscript{32-38}

1.2.1.1. Oxidative/reductive coupling

Synthesis of 1,1'-bisisoquinolines through coupling reactions was first reported by Case in 1952.\textsuperscript{39} Coupling of 1-bromoisoquinoline 1 using copper powder under Ulmann reaction conditions gave 1,1'- bisisoquinolines 2 (Scheme 1).\textsuperscript{40,41} This method was
versatile and could also be applied to coupling of 3-bromoisoquinoline 2 to give 3,3’-bisisoquinolines 4 in 13% yield (Scheme 1).

![Scheme 1](image)

**Conditions:** i. Cu powder, 210-230 °C, 2 h; ii. Cu powder, 260-270 °C, 2 h.

In 1984, Tiecco *et. al.* reported novel nickel coupling catalyst which involves *in situ* generation of nickel (0) (by treatment of NiCl₂ with Zinc and PPh₃ in THF or DMF) to couple nitrogen containing heterocyclic halides. Thus, bisisoquinolines 2, 4 were obtained in high yields (70-83%) by the homo-coupling of haloisoquinolines 5 and 6, respectively (Scheme 2).⁴²
The same coupling approach was also adopted by Chelucci\textsuperscript{43} and Hirao\textsuperscript{44} \textit{et. al.} for the synthesis of 8,8’-dialkyl-1,1’-bisisoquinolines. The 8-alkyl-1-haloisoquinoline obtained from \textit{o}-alkylbenzaldehydes through Pomeranz-Fritsch reaction\textsuperscript{45-49} and halogenations underwent the Ullmann coupling to give the desired 1,1’-BIQ functionalized at 8,8’-positions (Scheme 3).

**Scheme 2**

4,4’-Functionalized 1,1’-bisisoquinolines were recently reported by Laschat through the oxidative coupling of 1-chloro-4-hydroxyisoquinoline \textbf{7} (and also from related biphenyl-
and phenylpyrimidine ethers) (Scheme 4). The resulting 4,4'-functionalized 1,1'-BIQs were thought to be potential precursors for metallomesogens.

**Scheme 4**

Intramolecular oxidative coupling of tethered 1-chloroisoquinolines was also used to prepare chiral 1,1'-BIQs in which complete rotation of the isoquinoline rings around the central C1-C1' bond is blocked. For example, the dioxa-bridged 1,1'-bisisoquinolines 13 and 14 were synthesized by Yamamoto et al. using Ullmann coupling (Scheme 5).
**Scheme 5**

In addition, oxidative coupling of isoquinoline \(N\)-oxide 15,\(^{57}\) lithium salts of terahydroisoquinoline\(^{58}\) 17 also provided the 1,1′-bisisoquinolines as shown in Scheme 6. The stereochemistry of compound 18 was not established.\(^{58}\)

**Scheme 6**

Several reductive coupling reagents\(^{14,15,59-62}\) to prepare BIQs have been reported in the literature. In 1970, Nielsen et. al. reported the first coupling approach\(^{60}\) where epimeric 2,2′-diacetyl-1,1’,2,2′-tetrahydro-1,1′-bisisoquinoline 20 was obtained through
bimolecular reduction of isoquinoline 19 using zinc dust in acetic anhydride. Hydrogenation of BIQ 20 gave BIQ 21 which was further transformed to 1,1’,2,2’-octahydro-1,1’-biisoquinolines 23 in two steps through BIQ 22 as shown in Scheme 7.

Conditions: i. Zinc, Acetic anhydride, 25-30 °C; ii. H₂, rhodium-charcocal Rh-C, HOAc, reflux; iii. aqueous HBr, HOAc, reflux; iv. NaOH, MeOH, THF.

Scheme 7

After a gap of three decades, a modified reductive coupling method using a mixture of zinc, 1,2-dibromoethane and chlorotriethylsilane was reported by Elliott.¹⁴ Using this method, the octahydro-1,1’-biisoquinolines 23 was obtained directly by coupling of 2-phenylethylamine thus avoiding the necessity for hydrogenation (Scheme 8).¹⁴ Later in 2005, low-valent niobium produced by NbCl₅ in the presence of zinc powder was also used to promote the homocoupling of imine 24 to BIQ 23 by Arai (Scheme 8).¹⁵
Conditions: i. EtOCHO, reflux, 12 h; ii. PPA, 160°C, 12 h; iii. Zn, BrCH2CH2Br, Me3SiCl, CH3CN; iv. NbCl5, Zn, DME-THF, r.t., 3 h.

Scheme 8

However, the biggest disadvantage of these coupling methods is the production of a mixture of racemic and meso diastereoisomers. The racemic BIQ could be separated from the racemic/meso mixture by direct recrystallization relying on the differences in solubilities and by double hydrobromide salts formation followed by recrystallization (Scheme 9).

1.2.1.2. Bischler-Napieralski approach

Bischler-Napieralski reaction (Scheme 10) involves cyclization of \( N,N' \)-bis(aryethyl) oxamides promoted by condensation reagents such as phosphoryl chloride,\(^{63-66} \) phosphorus pentoxide/phosphoryl chloride,\(^{67} \) polyphosphoric acid (PPA)\(^{14,67,68} \) or triflic anhydride/DMAP.\(^{34} \) The product of the reaction is usually a tetrahydro-BIQ (Scheme 10).

![Scheme 10](image)

**Conditions:** i. Diethyl oxalate, EtOH; ii. Dehydration reagents.

Using Bischler-Napieralski reaction and based on Scheme 10, various BIQs have been successfully prepared. Examples of these BIQs are shown in Figure 1.\(^{69} \)

![Figure 1](image)

The influence of solvents especially chlorinated solvents on the cyclization of bisoxamide, was studied by Judeh.\(^{69} \) Chlorinated solvents with higher boiling points like 1,1,2,2-tetrachloroethane and chlorobenzene afforded the products in shorter reaction time;
however, the purification process was problematic. Interestingly, when 1,2-dichloroethane was used, the desired 1,1'-BIQs were formed in good yields with fewer byproducts, but long reaction times were required for completion. Room temperature ionic liquids such as [bmim]PF$_6$ were also examined as an environmentally friendly substitute for chlorinated solvents. Bisoxamide was successfully cyclized under short reaction times to give 1,1'-BIQ in high yields (Scheme 11).

\begin{center}
\begin{tikzpicture}
\node at (-3,0) {26};
\node at (3,0) {27};
\node at (5,0) {25};
\node at (0,-1) {Conditions: i. POCI$_3$, 25, 90-100 °C, 1 h, yield 81%};
\end{tikzpicture}
\end{center}

Scheme 11

Recently, our research group reported that when bisoxamide was dehydrated by neat PPA at 190 °C for 12 h, rac-$C_1$-$1',2',3',4'$-tetrahydro-1,1'-bisisoquinoline was unexpectedly obtained (Scheme 12). The framework of $C_1$-1,1'-BIQ in which heterocyclic ring A is fully aromatic and ring B is fully saturated, has peculiar electronic and structural features (will be discussed in the results and discussion section).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {28};
\node at (3,0) {29};
\node at (0,-1) {Conditions: i. Diethyl oxalate, EtOH, 25 °C, 2 h; ii. neat PPA, 190 °C, 12 h, yield 86%};
\end{tikzpicture}
\end{center}
Scheme 12

The mechanism of formation of the unexpected BIQ 29 was explored at relatively lower temperature of 140 °C to capture the intermediate products (Scheme 13).\textsuperscript{68} From \textsuperscript{1}H NMR spectra of representative crude samples taken at various time intervals over a period of 26 days, it shows that bisoxamide 28 was undergoing a two-step cyclisation: first forming partially cyclised compound 30, then the doubly cyclised BIQ 31. After complete conversion of compound 30 to BIQ 31, BIQ 31 undergoes a disproportionation reaction to give \textit{rac}-BIQ 29.

![Scheme 12 Diagram]

\textbf{Conditions: i.} neat PPA, 140 °C

Scheme 13

Interestingly, treatment of \textit{N,N’}-Bis-(3,4-dimethoxyphenethyl)oxamide 26 with Tf2O/DMAP in CH2Cl2 provided the expected Bischler-Napieralski product 27.\textsuperscript{69} However, POCl3 in toluene\textsuperscript{68} or dry CH3CN\textsuperscript{71} afforded another three different cyclized products 32-34 (Scheme 14).

![Scheme 13 Diagram]
1.2.1.3. Reduction of bisisoquinolines

Reduction of 1,1'-bis-dihydroisoquinolines had been thoroughly studied. Racemic products can be obtained by stereoselective reduction of 1,1'-bisdihydrobisisoquinolines with NaCNBH$_3$,\textsuperscript{34,65,71-73} while catalytic hydrogenation over PtO$_2$\textsuperscript{74} or platinum catalyst\textsuperscript{60} and NaBH$_4$\textsuperscript{65,71} or LiAlH$_4$/AlCl$_3$,\textsuperscript{65} or diisobutylaluminium hydride (DIBAL-H)\textsuperscript{69} reduction all afforded \textit{meso} products. The results were explained by Cram’s rule, as the adjacent steric hindrance can determine the stereochemistry of the asymmetric center.\textsuperscript{71} Using NaCNBH$_3$\textsuperscript{34,65,71-73} as reducing reagent, BIQ 27 was easily reduced to \textit{rac}-BIQ 35 (Scheme 15).\textsuperscript{68}

\textbf{Scheme 14}

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{Scheme14.png}
\caption{Scheme 14}
\end{figure}

\textbf{Conditions:} i. Tf$_2$O/DMAP reagent, CH$_2$Cl$_2$; ii. POCl$_3$, toluene/dry CH$_3$CN, reflux.

\textbf{Scheme 15}

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{Scheme15.png}
\caption{Scheme 15}
\end{figure}

\textbf{Conditions:} i. NaBH$_3$CN, MeOH, HCl

\textit{rac-35} yield 73%
Following the same methodology, various racemic 1,1’-octahydro-BIQs have been successfully prepared under NaCNBH₃ reduction conditions (Figure 2).  

\[
\begin{array}{cccc}
R_1 & R_2 & R_3 & R_4 \\
OMe & H & H & H \\
H & OMe & H & H \\
H & H & OMe & H \\
H & OMe & OMe & OMe \\
\end{array}
\]

**Figure 2**

Similarly, C₁-1,1’-BIQ framework obtained according to Scheme 13 can easily be reduced using NaBH₄ or NaCNBH₃. For example, rac-BIQs 36 could be obtained by the reduction of BIQ 32 (Scheme 16).  

**Scheme 16**

**1.2.2. Resolution of racemic 1,1’-bisisoquinolines**

Resolution of racemic compounds can be achieved mainly through diasteromeric salt formation or covalent bond formation. The diasteromers can then be separated by crystallization or column chromatography. Many optically active amines, such as
pyridine-amine,\textsuperscript{81,82} nornicotine,\textsuperscript{83} and nicotine\textsuperscript{84} have been obtained through diastereomeric salt formation. Elliott \textit{et al.} used the diastereomeric salt formation technique to resolve \textit{rac}-BIQ-23 with chiral $\alpha$-bromocamphor-$\pi$-sulfonic acid (BCSA) ammonium salt. Crystals of (S,S)-23•BCSA salt could be obtained when \textit{rac}-23 was recrystallised with D-BCSA in EtOH and then separated.\textsuperscript{14} When L-BCSA was used, crystals of (R,R)-23•BCSA salt were obtained. Consequently, after treatment of the salts (S,S)-23•BCSA and (R,R)-23•BCSA, separately, with NaOH solution followed by extraction, enantiopure BIQs (S,S)-23 and (R,R)-23 were obtained, respectively. Later in 2005, BIQ \textit{rac}-23 was also resolved by Arai \textit{et al.} in a similar fashion using chiral camphorsulfonic acid (CSA) as resolving agent (Scheme 17).

\begin{center}
\begin{tikzpicture}
\node (rac23) at (0,0) {\includegraphics[width=1.5cm]{rac23}};
\node (ss23) at (3,0) {\includegraphics[width=1.5cm]{ss23}};
\node (rr23) at (6,0) {\includegraphics[width=1.5cm]{rr23}};
\node (reagents) at (1.5,-2) {\textbf{Reagents}: \textit{i.} D-BCSA or L-BCSA ammonium salt (1.0 equiv), recrystallization from EtOH; \textit{ii.} 5 M NaOH/CH$_2$Cl$_2$; \textit{iii.} D-CSA or L-CSA (2.0 equiv), recrystallization from i-Pr$_2$O/EtOH; \textit{iv.} 10% NaOH.};\end{tikzpicture}
\end{center}

\textbf{Scheme 17}

Similarly, \textit{rac}-BIQ 35 was resolved with D-BCSA with L-BCSA to give (S,S)-35 and (R,R)-35, respectively (Scheme 18).\textsuperscript{71}
Scheme 18

*Rac-BIQ* 29 was resolved through covalent bond formation method in our laboratory through the formation of diastereomeric ureas with (S)-(−)-α-methylbenzyl isocyanate (Scheme 19). The diastereomeric urea derivatives 37 and 38 were separated through column chromatography and fractional crystallization to give the pure diastereomers, which upon treatment with NaOBu afforded enantiopure BIQ 29.

Scheme 19
1.2.4. Bisisoquinolines and their derivatives as chiral ligands in asymmetric synthesis

Unlike the widespread use of privileged chiral $C_{2}-1,1'$-binaphthyls in asymmetric catalysis, only few examples using chiral $C_{2}-1,1'$-bisisoquinolines have emerged in the literature to date, although these chiral BIQs were thought as potential asymmetric catalysts for a long time.

The first application of BIQ ligands in asymmetric catalysis was reported by Nakajima in 1998, using $(S)$-1,1'-biisoquinoline $N,N'$-dioxide 16 which was modeled after $(S)$-1,1'-binaphthalene-2,2'-diol. It was used to catalyze the addition of allyltrichlorosilane 40 to benzaldehyde 39. Moderate results of 82% yield and 52% ee were obtained (Scheme 20).

\[
\text{Conditions: } \text{i. (S)-16 (10 mol%), CH}_2\text{Cl}_2, \text{r.t., 2 h}
\]

![Scheme 20](image)

In 2005, Arai used chiral $(R,R)$-BIQ 23 in combination with CuCl to catalyze the asymmetric oxidative coupling of ester 42 to give 3,3'-substituted BINOL 43 in moderate 60% yield and up to 48% ee (Scheme 21).
In a related work, Cavell and Elliott et al. reported the application of chiral N-heterocyclic carbene (NHC) 44, which is based upon (R,R)-BIQ 23, in the stereoselective conjugate addition of Et₂Zn to cyclohexanone 45. The alkylated ketone 46 was obtained in only 10% ee (Scheme 22).  

In 2006, NHC 44 was used by Herrmann et al. in asymmetric hydrosilylation or transfer hydrogenation to acetophenone 47, affording product 48 in unsatisfactory low 28% ee and 24% ee respectively (Scheme 23).
Scheme 23

In 2007, Hoffmann used iridium complex of NHC \( \text{49} \) in asymmetric hydrogenation of methyl 2-acetamidoacrylate \( \text{50} \) to afford product \( \text{51} \) in 67% ee (Scheme 24).\(^{92}\)

Scheme 24

Other BIQ-based NHC ligands for asymmetric catalysis have been described recently.\(^{93}\)

\(^{98}\) For example, in 2008 Seo \textit{et al.} reported asymmetric allylic alkylation of \( \text{53} \) to the \( \gamma \)
product 55 by NHC 52 Cu(I) complex (Scheme 25). Good conversion (70%) and enantioselectivity (77\% ee) were obtained.\(^9^7\)

\[
\begin{array}{c}
\text{Conditions: i. 52 (3 mol\%), CuCl (3 mol\%), n-HexMgBr (1.5 equiv), Et}_2\text{O, 0 °C, 1 h} \\
\end{array}
\]

\textbf{Scheme 25}

Later in 2011, Czekelines et al. synthesized novel class of NHC gold complexes bearing bulky substituents. With substoichiometric quantities of \(\text{AgBF}_4\), the gold complexes 56 can catalyze the desymmetrization of diynesulfonamide 57 to give the enamide product 58 in yields up to 77\% yield and enantioselectivity up to 51\% ee (Scheme 26).\(^9^8\)
Conditions: i. 56 (5 mol%), AuCl (5 mol%), AgBF₄ (3 mol%), Toluene, r.t.

Scheme 26

In 2010, structurally constrained chiral $C_1-1',2',3',4'$-tetrahydro-1,1'-bisisoquinoline 29 reported by our research group was introduced and employed for the addition of diethyl zinc to aromatic aldehydes. Yields of up to 99% and $ees$ of up to 85% were obtained. Additionally, when the same BIQs were used for the addition of Grignard reagents to cyclic enones such as 45, product 59 was obtained in 99% yield and only 35% $ee$ (Scheme 27).¹²⁻¹³,₆⁸

Conditions: i. (R)-29 (15 mol%), THF/Hexane (1:3), 0 °C, 30 h

yield 99%, 35% $ee$

Scheme 27
From the above discussion, it is clear that BIQs hold clear promise and potential in asymmetric catalysis.

1.3. Henry Reaction

Henry reaction involves the addition of nitroalkanes to carbonyl compounds such as aldehydes and ketones (Scheme 28). It can be catalyzed by hydroxides, alkoxides, amines, ammonium salts, and organo-phosphorus compounds. It generates β-nitroalcohol adducts that can be transformed into useful intermediates such as alkenes, β-aminoalcohols, β-aminoacids, and α-nitro ketones.

\[
\text{R}^1\text{HNO}_2 + \text{R}'\text{H} \rightarrow \text{cat}^* \rightarrow \text{R}\beta\alpha\text{R'}\text{O}^\text{NO}_2
\]

Scheme 28

The asymmetric version of Henry reaction was discovered first in 1992 by Shibasaki and has been developed mainly by using metal-based catalysts and to a much lesser extent by using organocatalysts.

A brief survey of the most important metal-based and organic chiral catalysts is presented in the following sections with special emphasis on nitrogen-based catalysts since our BIQs are nitrogen based ligands.
1.3.1. Metal-based chiral catalysts

As mentioned earlier, the first asymmetric Henry reaction was discovered in 1992 by Shibasaki using heterobimetallic complex 60 (Scheme 29).\textsuperscript{118}

\[
\text{Conditions: i. 60 (3.3 mol%), THF, } -42\degree\text{C, 18 h}
\]

\[
\text{yield 79-91%, ee 73-90%}
\]

Scheme 29

A number of conceptually different types of metal-catalytic systems for the asymmetric version of this reaction have been developed in recent years.\textsuperscript{9,109,123-129} By far, most catalysts developed use copper (especially Cu(II) rather than Cu(I)) due to its excellent chelating properties to bi- and poly-dentate ligands.\textsuperscript{119} Other metals such as Zn,\textsuperscript{109,123-125} Co,\textsuperscript{126,127} Cr,\textsuperscript{9,128} Pd\textsuperscript{129} and rare earth metals\textsuperscript{118,130,131} have also been examined with variable success. Majority of the ligands developed, e.g. bisoxazolines,\textsuperscript{132-138} bisoxazolidines,\textsuperscript{139,140} diamines,\textsuperscript{15,141-147} (−)-sparteine,\textsuperscript{148} sulfonyldiamines,\textsuperscript{149} sulphonimidamides,\textsuperscript{150} aminopyridines,\textsuperscript{108,151-153} tetrahydrosalens,\textsuperscript{154} and \(N,N'\)-dioxides,\textsuperscript{155} are nitrogen-based with a variety of structural features that modulate their reactivity and enantioselectivity.

Evans \textit{et al.},\textsuperscript{132} reported a very efficient Cu(II)-bis(oxazoline) (BOX) catalyst 61 for a variety of aldehydes with only 5 mol\% loading without the need for external base
(Scheme 30). The design is based on the Lewis acidic property of copper bearing moderately charged ligands which would facilitate the deprotonation of nitromethane. In the transition state 62 proposed by Evans et al. Cu(II) coordination involves a Jahn-Teller (JT) effect and both of the nitronate and the aldehyde’s carbonyl group bind with copper, producing a desired boat conformation. On the basis of steric and electronic considerations, the electrophile was positioned in one of the more Lewis acidic equatorial sites of the ligand plane, while the nucleophile was perpendicular to the ligand plane.

Scheme 30

Hong et al. reported a base-functionalized aza-bisoxazoline catalyst 64 which encompasses a chiral scaffold with a tethered tertiary amine base. This catalyst function by the dual activation concept (Scheme 31).\textsuperscript{136} Rate acceleration (2.5 times) and
improved enantioselectivity (72% ee vs. 92% ee) were achieved by the bifunctional aza-Box 64 in comparison to the unfunctionalized aza-Box 63.

\[
\begin{align*}
\text{Conditions: i. 63/64 (5 mol%), CuTC (5 mol%), 4A MS, EtOH, -20 ^\circ C, 24 h}
\end{align*}
\]

Scheme 31

Jørgensen was the first to apply Cu(II)-bis(oxazoline) catalysts, e.g. 67, in the asymmetric Henry Reaction between \( \alpha \)-ketoesters and nitromethane using Et\(_3\)N as additive (Scheme 32). This reaction afforded enantiomerically pure tertiary alcohols in up to 99% ee.\(^{133,162}\) In general, ketones are much less reactive than aldehydes and their condensation with nitroalkanes is more challenging.

\[
\begin{align*}
\text{Conditions: i. 67 (20 mol%), Et\(_3\)N (20 mol%), EtOH, r.t., 24 h.}
\end{align*}
\]
Besides Cu-BOX catalysts, other Cu-imine complexes were also applied in the catalytic asymmetric Henry Reaction. Pedro et al. employed Cu-iminopyridine complexes derived from camphor for the addition of nitromethane to o-anisaldehyde. Under similar reaction conditions developed by Evans, only modest enantioselectivities were obtained and the best result (86% ee) was obtained using ligand 68 (Figure 3). In 2007, Pedro et al. modified these types of ligands, interestingly, the two iminopyridine 69 and 70 (Figure 3) gave the products with opposite stereochemistry even though they had the same stereochemical pattern. In 2008, Pedro et al. refined the iminopyridine ligands to the new aminopyridine ligands, such as compound 71. These ligands are more flexible and the two equatorial coordination sites’ electronic differentiation is more distinct. The expected products were obtained in higher yields (up to 99%), better enantioselectivities (up to 98% ee) and diastereoselectivities (up to 82:18) (Scheme 3).
Later, a similar ligand was designed by Zhou where the pyridinyl moiety of 71 was replaced by a pyrrolidine ring to give ligand 72. This diamine-type ligand with two $N$-sp$^3$ coordinating sites exhibited outstanding catalytic efficiency for Henry reaction (Scheme 34)\cite{164}. On the basis of X-ray diffraction and HRMS analysis, a possible transition state 73 was proposed in which the nucleophilic nitronate was oriented inside, perpendicular to the ligand plane to form a strong intramolecular hydrogen bonding with the NH of the pyrrolidine ring. The electrophilic aldehyde would occupy the outside position in consideration of steric hindrance. The $Re$ face would be attacked by the nitronate thus providing the nitroaldol adduct with $S$ configuration.

Scheme 33

Conditions: i. 71 (5 mol%), Cu(OAc)$_2$ (5 mol%), DIPEA (1 equiv), EtOH, -20/-50 ºC
Scheme 34

C₂-symmetric secondary diamine ligands, derived from chiral 1,2-diphenylehylenediamine and 1,2-cyclohexanediamine, have been widely applied in various asymmetric metal-catalyzed reactions such as Henry reaction. The C₂-symmetric secondary diamine ligand 74 designed by Arai et al. gave the desired products in high yields and enantioselectivities with only 1 mol% loading (Scheme 35).

\[
\begin{align*}
\text{Conditions: i. 74 (1-5 mol%), CuCl (1-5 mol%), n-PrOH, r.t., 16-120 h} \\
\end{align*}
\]

Scheme 35

In 2007, Arai et al. developed a C₁-symmetric diamine ligand 75 with two tertiary amines to catalyze the asymmetric Henry reaction. With only 5 mol% loading, the Cu(II) complex 75 gave excellent yields (up to 99%) and enantiomeric excesses (up to 99.5% ee) (Scheme 36).
Scheme 36

One year later, Arai et al. developed a modified diamine ligand, the sulfonyldiamine ligand 76, specifically for the diastereoselective Henry Reaction. While designing ligand 76, one of the binaphthyl azepine rings in 74 was replaced by sulfonyl group to increase the acidity of this copper complex (Scheme 37) since according to Evans et al., the Lewis acidity of copper atom is crucial for activating the electrophilic aldehyde.

Scheme 37

In 2010, Bolm et al. employed another amino-functionalized sulfonimidamide 77 for the enantioselective addition of nitromethane to various aromatic aldehydes. The products were obtained in up to 95% ee and in good yields of up to 99% (Scheme 38).
Scheme 38

(-)-Sparteine 78 is well-known natural chiral diamines. Because of its conformational rigidity, its Cu(II) complexes were examined in the Henry reaction (Scheme 39). Surprisingly, while Cu(OAc)$_2$-(-)-sparteine complex give only racemic products, CuCl$_2$-(-)-sparteine complex gave good to excellent ee.

Scheme 39

In 2009, Breuning et al. investigated 9-oxabispidine 79, which carries an 2-endo, N-anellated piperidine ring showing closely related structure to (-)-sparteine 79. The CuCl$_2$ complex of 79 gave (S)-products in 91-98% ee (Scheme 40).
Recently, Noole et al. reported the application of an easily available catalyst formed by bipiperidine 80 and Cu(OAc)$_2$·H$_2$O in asymmetric Henry reaction. This catalyst system is practical, simple in operation, and afforded the products in high yields and enantioselectivities (Scheme 40). According to ESI HRMS and B3LYP/6-31+G* level calculations, the transition state 81 was proposed where the copper complex is tetra-coordinated and almost planar, and the $N$-$i$-Pr group is perpendicular to this structure. The activated nitronate is in the opposite axial position to $i$-Pr group, and fixed by hydrogen bonding, while the electrophile was oriented in the equatorial position.

\[ \text{Conditions: } i \text{. 80 (10 mol%), Cu(OAc)$_2$·H$_2$O (10 mol%), Et$_3$N (5 mol%), -25 °C} \]

Scheme 41

In 2007, Feng employed a novel copper(I)-tetrahydrosalen complex in the enantioselective Henry reaction, and extended its application in the synthesis of (S)-norphenylephrine. This chiral hydrogenated salen catalyst 82 (10 mol%), together with (CuOTf)$_2$·C$_7$H$_8$ (5 mol%) gave the nitroaldol adducts in excellent enantioselectivities.
Asymmetric reaction of \( m \)-hydroxybenzaldehyde \( 83 \) with nitromethane in presence of \( 82 \) followed by reduction of the nitro group of the product \( 84 \) gave \((S)\)-norphenylephrine \( 85 \). \((S)\)-norphenylephrine \( 85 \) is used in the treatment of pain, depression and hypertension.\(^{168}\)

\[
\begin{align*}
\text{Conditions: } & \text{i. } 82 (10 \text{ mol\%), (CuOTf)}_2 \cdot \text{C}_2 \cdot \text{H}_8 (5 \text{ mol\%), MeOH, 4A MS, 45 °C; } \\
& \text{ii. Pb/C (5 mol\%), H}_2, \text{MeOH.}
\end{align*}
\]

\textbf{Scheme 42}

In 2006, Wang has reported copper tridentate chiral Schiff-base complexes \( 86k \) and \( 86l \),\(^{169}\) and modified these ligands in 2008 (Figure 4).\(^{170}\) X-ray analysis of single crystals showed the dimeric nature of these type of catalysts. However, both the yields and the \textit{ee} values were moderate, especially with aliphatic aldehydes (almost 45-64\% \textit{ee}).
1.3.2. Organocatalytic Henry Reaction

Because of the enormous economic potential of using small organic molecules in asymmetric catalysis, organocatalysis has become one of the most extensively explored areas of research in the last few decades. Considering the mechanism of Henry reaction, there are three requirements for an organic compound to be a suitable organocatalysts: (a) should be a base or function with an external co-catalyst base; (b) should possess a unit that is capable of forming hydrogen bonding with the acceptor carbonyl oxygen; (c) should possess a unit that is capable of binding the nitronate group through electrostatic interaction or hydrogen bonding.

In 1994, Najera et al. reported the first example of enantioselective Henry reaction using chiral guanidines 87 and 88 (Figure 5), the ee values were up to 54%. Poor ee values were obtained using guanidine tetrafluoroborate salt 89 (Figure 5).
In 2005, a big breakthrough was brought by Nagasawa in the area of guanidine catalysis. He reported a novel ligand 90 which combined one quaternised guanidine moiety and one thiourea moiety into the same chiral framework. This arrangement greatly improved the efficiency of guanidine-type catalysts in Henry reactions (Scheme 43). In the proposed intermediate 91, the nitronate was paired with the guanidine unit while the carbonyl group formed hydrogen bond with the thiourea unit, and the configuration of product was controlled by the R^2 group of nitroalkane.

\[
\begin{align*}
R'CH &+ CH_3NO_2 \rightarrow R'CH(NO_2) \quad \text{yield 70-91\%, ee 55-92\%}
\end{align*}
\]

**Conditions:** i. (S,S)-90 (10 mol%), KOH (5-40 mol%), H_2O, KI (50 mol%), 0 °C, 5-45 h

Scheme 43
Organic molecules bearing both amine and thiourea moieties are also potential catalysts for Henry reactions. Hiemstra reported the application of compound 92 in Henry reaction which afforded the desired products in very good yields and ee for various aromatic aldehydes (Scheme 44). In the proposed transition model 93, nitromethane was deprotonated by the basic quinucidine nitrogen and in the meantime the aldehyde was activated by the thiourea residue through double hydrogen bonding.

\[
\begin{align*}
&\text{Conditions: i. } 92 \text{ (10 mol%), THF, } -20 \, ^\circ\text{C, 4-168 h} \\
&\text{yield 90-99%, ee 85-92%}
\end{align*}
\]

Scheme 44

In 2006, Deng reported a novel catalyst 94 which lacks both the guanidinium/amidinium moieties. It showed excellent efficiency in the asymmetric Henry reaction between nitromethane and \(\alpha\)-ketoesters 95 to yield nitroalcohol 96 (Scheme 45).
1.4. Objectives

This project focuses on the synthesis and application of bisisoquinolines at ligands for asymmetric reaction. It aims to:

1. Design, synthesize and explore the chemistry of structurally novel enantiopure bisisoquinolines.
2. Examine the application of chiral BIQ-based ligands in asymmetric Henry reaction
3. Investigate the effect of various structural features that control the efficiency in the asymmetric Henry reaction.
Chapter 2. Synthesis of novel chiral BIQs

In this chapter we will discuss the synthesis and resolution of BIQs.

2.1. Synthesis of BIQ 98

To our knowledge, all the reported chiral BIQs have the chelating nitrogens of the heterocyclic rings in a 1,2-disposition (e.g. 23, Figure 6), and would form five-membered chelating rings after coordinating with metal ions. In order to investigate the differences between a five-membered (as in 1,2-BIQs) and six-membered chelation rings we envisioned the synthesis of 1,3-BIQ (e.g. 98, Figure 6).

![Figure 6](image_url)

As mentioned in Chapter 1, there are two strategies to construct BIQ-based compounds: metal mediated coupling and Bischler-Napieralski reaction. A wide range of BIQ-based compounds using Bischler-Napieralski reaction has been prepared. We adopted a similar synthetic sequence for the synthesis of 1,3-BIQ 98 (Scheme 46). At first, the bisoxamide 100 was synthesized by condensation of phenethylamine with diethyl malonate 99. Compound 100 under Bischler-Napieralski reaction condition should provide 1,1’-methylene-bis(3,3’,4,4’-tetrahydroisoquinoline) 101, which in turn
should provide the desired 1,3-BIQ rac-1,1’-methylene-bis(1,1’,2,2’,3,3’,4,4’-octahydroisoquinoline) rac-98 upon reduction.

\[
\begin{align*}
\text{NH}_2 & \quad \text{O} \quad \text{O} \quad \text{Et} \quad \text{Et} \\
\text{NH} & \quad \text{NH} & \quad \text{O} \quad \text{O} \\
\text{NH} & \quad \text{NH} & \quad \text{O} \quad \text{O} \\
\text{N} & \quad \text{N} & \quad \text{O} \quad \text{O} \\
\end{align*}
\]

Conditions: i. Condensation; ii. Dehydration; iii. Reduction.

Scheme 46

The presence of an additional methylene moiety between the two carbonyl units in diethyl malonate 99 makes it much less reactive compared to diethyl oxalate 102 which was used to synthesize bisoxamide 28. Thus, the reaction between phenethylamine and diethyl malonate 99 proceeded at higher temperature (80 °C vs r.t.), higher concentration (neat vs Ethanol) and longer reaction time (2 days vs 4 h) in comparison with diethyl oxalate reaction (Scheme 47). The fluffy white solid obtained was confirmed to be bisoxamide 100 by various analytical tools.\textsuperscript{12,190}

\[
\begin{align*}
\text{NH}_2 & \quad \text{O} \quad \text{O} \quad \text{Et} \quad \text{Et} \\
\text{NH} & \quad \text{NH} & \quad \text{O} \quad \text{O} \\
\text{NH} & \quad \text{NH} & \quad \text{O} \quad \text{O} \\
\text{N} & \quad \text{N} & \quad \text{O} \quad \text{O} \\
\end{align*}
\]

Conditions: i. 99, 80 °C, 2 days; Conditions: i. 102, EtOH, r.t., 4 h.

Scheme 47
Following the procedure developed by Chan et al.,\textsuperscript{191} cyclization of bismalonamide 100 was achieved using a combination of phosphorus oxychloride (POCl\(_3\)) and diphosphorus pentoxide (P\(_2\)O\(_5\)) (Scheme 48). The expected 1,1’-methylene-bis(3,3’,4,4’-tetrahydroisoquinoline) 101 was obtained as a brown gum in 81% yield after column chromatography, and confirmed as structure 101 through analytical tools.

\[
\begin{align*}
\text{Conditions: } & \text{POCl}_3, \text{P}_2\text{O}_5, \text{toluene, reflux, 24 h} \\
\text{i} & \\
100 & \quad \rightarrow \quad 101
\end{align*}
\]

Scheme 48

According to the previous research on the reduction of similar bisimines 31 and 27, reductive treatment with NaCNBH\(_3\) afforded only racemic BIQs 23 and 35, respectively, while NaBH\(_4\) gave mixtures of racemic and meso isomers (See Chapter 1, Scheme 13, Scheme 15 and Figure 2).\textsuperscript{60,65,71,73,191} Therefore, we used NaCNBH\(_3\) for the reduction of 101 in anticipation to produce 99. The expected 1,1’-methylene-bis(1,1’,2,2’,3,3’,4,4’-octahydroisoquinoline) 99 was obtained as light-yellow crystals in 77% yield after recrystallization from EtOH, and the obtained product was assigned as structure 99.

The stereochemistry of 99 was examined through synthesis of derivative 103 (Scheme 49). If 99 is racemic, the N-CH\(_2\)-N’ protons of compound 103 should be in the same chemical environment, and thus these two protons would appear as one signal in the \(^1\)H NMR spectrum. While for the meso-99 isomer, these two protons would show two different, split signals.\textsuperscript{60} The \(^1\)H NMR spectrum of 103 (Figure 7) has shown only one
singlet which was found at $\delta$ 3.73 ppm corresponding to the N-CH$_2$-N’ protons. Hence, the racemic nature of the synthesized compound 99 was confirmed.

**Scheme 49**

Conditions: i. NaCNBH$_3$, MeOH, HCl, 0.5 h; ii. HCHO(37%), EtOH, 4A MS, reflux.

**Figure 7**
2.2. Resolution of BIQ 98

As mentioned in Chapter 1 (section 1.4), one of the aims of this work is to find a feasible way to obtain novel BIQ-based compounds in enantiomerically pure form. Therefore, resolution of BIQ 98 was attempted by using various techniques.

*Racemic* bases and optically active acids as well as *racemic* acids and optically active bases, can produce pairs of diastereomeric salts. Members of these pairs show different physicochemical properties like solubility, boiling point, melting point, adsorption *etc.* Out of these different physicochemical parameters, solubility is most commonly utilized for the separation of the enantiomeric pairs using fractional crystallization. Using diastereomeric salts formation approach, enantiomerically pure BIQs were obtained by various research groups.\textsuperscript{14,15,192-201} In this respect, \((D)-(+)\)-\(\alpha\)-bromocamphor-\(\pi\)-sulfonic acid \((D\text{-}BCSA)\) and \((D)-(+)\)-camphor-10-sulfonic acid \((D\text{-}CSA)\) were utilized to resolve *rac*-BIQ 23 and *rac*-BIQ 35 successfully. Hence, these two chiral acids were considered as potential resolving agents for *rac*-BIQ 98.

*Rac*-BIQ 98 was mixed separately with equimolar \(D\text{-}BCSA\) and two equivalents of \(D\text{-}CSA\) in MeOH, affording mixtures of diastereomeric salts 104/105 and 106/107 as off-white solids in quantitative yields (Figure 8) (note: different ratios of 98 and the chiral acids were also attempted). The \(^{1}\text{H}\) NMR spectra of these compounds showed the characteristic signals of the diastereomeric salts. However, recrystallization of the diastereomeric salt mixtures from different solvents like \CH\textsubscript{2}Cl\textsubscript{2}, MeOH, EtOH, EtOH-H\textsubscript{2}O, Et\textsubscript{2}O, Acetone, CH\textsubscript{3}CN, THF or EtOAc failed to produce single or enriched diasteromers.
Other diastereomeric salt mixtures were prepared by mixing \textit{rac-BIQ} \textbf{98} with different enatiopure organic acids such as (\textit{D})-(\textit{+})-mandelic acid, (\textit{R})-(\textit{-})-3-chloromandelic acid and (\textit{L})-(\textit{+})-lactic acid in MeOH. All attempts to recrystallize one single diastereomeric salt from the mixtures or obtain enriched fraction were unsuccessful. Nevertheless, the salt of (\textit{L})-(\textit{+})-citramalic acid and \textit{rac-BIQ} \textbf{98} (1:1) was found to afford one isomer in around 60\% \textit{ee} after one time recrystallization from EtOH. After optimization of the recrystallization conditions by screening different solvents and different ratios between BIQ and (\textit{L})-(\textit{+})-citramalic acid, it was found that using two equivalents of the acid in a mixed solvent of EtOH/H\textsubscript{2}O (1.5:1, v:v) gave the best separation results for diastereomeric salts \textbf{108} and \textbf{109} (Figure 9).
Figure 9

The crystals of 108 and 109 were separately treated with 10% aqueous NaOH and extracted with CH₂Cl₂ to afford enantiopure products (-)-98 and (+)-98, respectively. These enantiomeric purities of (-)-98 and (+)-98 were found to be > 99% by chiral HPLC analysis (Figure 10).

Figure 10

(Diacel Chiralcel OD-H Column, Hex/IPA/Et₃N 90/9.9/0.1, 1.0 ml/min, 256 nm)
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The mixture of (+)-98 and (L)-(+)-citramalic acid were recrystallised from EtOH, affording colorless cubic crystals which were suitable for single X-ray crystallographic analysis. From analysis of the crystal structure, we found both of the two heterocyclic rings adapted as twisted chair conformations. In addition, the absolute configuration of (+)-98 was confirmed as (R,R)-configuration and thus (-)-98 was confirmed to be (S,S)-configuration (Figure 11). The crystal structure also proved the racemic nature of compound 98 produced by NaBH₃CN in the reduction step (Scheme 49).

![Figure 11](image)

2.3. Alkylation of BIQ 98

With the enantiomerically pure BIQ 98 in hand, a range of symmetric and unsymmetric alkyl derivatives of chiral BIQ 98 (Figure 12) were designed to explore their efficiency in the asymmetric Henry reaction. The symmetric (C₂) and unsymmetric (C₁) derivatives are
expected to exhibit different selectivities and reactivities due to their distinct structural conformations. The unsymmetric $C_1$-derivatives posses two electronically different sp$^3$ nitrogens (i.e. one is alkylated $N$, the other is NH). The electronic and steric properties at the coordinating nitrogens can easily be modified in this design.$^{164}$

![Figure 12](image)

**Figure 12**

### 2.3.1. Alkylation of rac-BIQ 98

Initial attempts to prepare derivatives of 98 were examined using rac-BIQ 98. The successful approach could then be applied to enantiopure BIQ 98.

### 2.3.1.1. Synthesis of symmetric $N$-alkyl derivatives of rac-BIQ 98

Typical condensation reactions were applied for the synthesis of symmetric $N$-alkyl derivatives.$^{12,14}$ Nucleophilic rac-BIQ 98 reacted with the corresponding alkyl halides to give the desired $N$-alkyl derivatives. However, when simple alkyl halide such as iodomethane was used, ammonium salts are obtained due to multi alkylations. For example, Gao reported that when rac-BIQ 29 was reacted with iodomethane, multiple alkylation occurred to give rac-110 and rac-111 since the initially formed product rac-110 is more nucleophilic than the starting rac-29 (Scheme 50).$^{68}$
To avoid multiple alkylation problem mentioned above, \textit{rac-BIQ 98} was reacted with neat iodomethane and the final reaction mixture was treated with aqueous NaOH solution to give \textit{rac-112} in 41\% yield (Scheme 51).\textsuperscript{14} The other two symmetric alkyl derivatives \textit{rac-113} and \textit{rac-114} were synthesized using typical alkylation reaction conditions (Scheme 52). The final alkylated products were obtained in 73\%, 91\% yield, respectively.

\textbf{Scheme 50}

\textbf{Conditions:  i.} neat CH$_3$I, 12 h; 
\textbf{ii.} 10\% NaOH, H$_2$O, CH$_2$Cl$_2$.

\textbf{Scheme 51}

\textbf{Conditions:  i.} 2.2 equiv ethyl bromide/benzyl bromide, K$_2$CO$_3$, THF, 60 °C, overnight

\textbf{Scheme 52}
2.3.1.2. Synthesis of $C_1$-symmetric N-alkyl derivatives of rac-BIQ 98

Initial attempts to synthesize $C_1$-symmetric N-alkyl derivatives by directly treating rac-BIQ 98 with equimolar alkyl halides in THF failed to provide the relative mono N-alkyl products exclusively in high yields. Instead, mixtures of mono, double N-alkyl derivatives were produced along with recovered starting material (Scheme 53). This result indicated that the alkylation reaction on rac-BIQ 98 was stepwise, and the second alkylation step was faster than the first step. Consequently, the formed mono derivatives were competing for alkyl halides with the parent rac-BIQ 98. To overcome this problem, different reaction conditions were tested. Disappointingly, all attempts failed and the direct alkylation approach was thought an inappropriate route for the synthesis of mono N-alkyl derivative.

$\text{Conditions: }$ i. one equiv alkyl halides, K$_2$CO$_3$, THF, r.t., overnight

Scheme 53

Next, the reductive alkylation approach used for the synthesis of tertiary amines from secondary amines was chosen. As shown in Scheme 54, the method involved the formation of intermediate imine from condensation of a ketone or aldehyde with an amine, followed by a reduction step with suitable reducing agents (e.g. NaBH$_4$, NaCNBH$_3$, LiAlH$_4$, etc.).
Read et al. successfully applied the reductive alkylation procedure for the synthesis of various mono alkylated rac-35 in very good yields (Scheme 55). Instead of imine formation, aminal was isolated and was subjected to reduction with NaCNBH₃ to provide the desired mono N-alkylated rac-35.

Due to the structural similarities between rac-98 and rac-35, synthesis of mono N-alkyl derivatives of rac-98 utilizing the sequence of aminal formation followed by reduction was attempted (Scheme 56).
At the outset, rac-BIQ \textbf{98} was reacted with 1.3 equivalent of 37\% formaldehyde in refluxing EtOH for two days, to furnish, after workup and column chromatography purification, a yellow solid in 85\% yield (Scheme \textbf{49}). \textbf{Rac-103} was used to distinguish between the \textit{racemic} and the \textit{meso} isomers of \textbf{98} as discussed before (Figure \textbf{7}).

The resulting piperimidine \textbf{rac-103} was then subjected to reductive cleavage using NaCNBH\textsubscript{3} (Scheme \textbf{57}) to give a light yellow gum in 72\% yield after treating the reaction mixture with aqueous NaOH solution and purification by column chromatography. The product was assigned structure \textbf{rac-115} through various analytical tools.
Similar reaction conditions developed for the preparation of mono N-methyl BIQ derivative rac-115 were adapted for the preparation of other derivatives rac-117 and rac-119. Treatment of compound rac-98 with acetaldehyde in the presence of 4 Å molecular sieves in Et₂O gave a light yellow gum in 80% yield after chromatographic purification (Scheme 58). All analytical results confirmed the product’s structure as rac-116 (Scheme 58).

![Scheme 58](image)

**Conditions:** i. CH₃CHO, Et₂O, 4Å molecular sieves, r.t., overnight.

Treatment of piperimidine rac-116 with NaCNBH₃ under the same reaction conditions developed for reductive cleavage of piperimidine rac-103 afforded the final product rac-117 as a light yellow gum in 70% yield (Scheme 59).

![Scheme 59](image)

**Conditions:** i. NaCNBH₃, TFA, MeOH, r.t.

Based on the successful synthesis of mono N-ethyl derivative rac-117, another derivative with bulkier substituent (benzyl group) was attempted. Rac-BIQ 98 was firstly treated
with benzaldehyde under the reaction conditions utilized for the preparation of piperimidine rac-118, to provide a yellow fluffy solid in 90% yield after column chromatography (Scheme 60).

\[
\text{rac-98} \quad \xrightarrow{i} \quad \text{rac-118}
\]

**Conditions:** i. PhCHO, Et₂O, 4A molecular sieves, r.t., overnight

Scheme 60

Subsequently, rac-118 was subjected to the reductive cleavage by treatment with NaCNBH₃ in acidic MeOH (TFA) to afford the final product rac-119 as a light yellow gum in 80% yield (Scheme 61).

\[
\text{rac-118} \quad \xrightarrow{i} \quad \text{rac-119}
\]

**Conditions:** i. NaCNBH₃, TFA, MeOH, r.t.

Scheme 61

### 2.3.2. Alkylation of (R,R)-BIQ 98

Since the reaction conditions for the synthesis of N-substituted derivatives of rac-98 were established, we then turned our attention to the synthesis of the chiral counterparts. Therefore, the reaction conditions described for the synthesis of rac-BIQ 98 derivatives
were used to synthesize the derivatives (R,R)-112-115, 117 and 119 starting from (R,R)-98. The structures of the enantiomerically pure derivatives (R,R)-112-115, 117 and 119 were confirmed by HRMS, FTIR, \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra and by comparison with the corresponding racemic compounds. The enantiomeric purities of these derivatives were examined by HPLC using chiral columns.

2.3.2.1. Synthesis of double N-alkyl derivatives of (R,R)-BIQ 98

The alkylation conditions used for the preparation of the double N-alkyl derivatives were followed using the appropriate alkyl halide. The stereochemistry of (R,R)-98 would remain the same during the alkylation process. During the preparation of the doubly N-methyl substituted derivative (R,R)-112, only the amine salt was formed during the reaction between (R,R)-98 and neat iodomethane avoiding further multiple alkylation. Work-ups by aqueous NaOH solution gave the free enatiopure base (Scheme 62). Chiral HPLC testing using Chiralcel OD-H column proved that (R,R)-112 was obtained in >99\% ee indicating no racemization during the alkylation process. The HPLC spectra of rac-112 and (R,R)-112 are shown in Figure 13.
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Figure 13

(R,R)-113 was prepared and characterized in a similar fashion to rac-113 starting from (R,R)-98. The HPLC separation results of (R,R)-113 along with its relative racemic counterpart are shown in Figure 14. There was no evidence of racemization in the alkylation process of (R,R)-98 with ethyl bromide.
2.3.2.2. Synthesis of mono N-alkyl derivatives of (R,R)-BIQ 98

Reductive amination reaction followed by reductive cleavage was applied for the synthesis of mono alkylated derivatives (R,R)-115, (R,R)-117 and (R,R)-119. Their structures were confirmed by HRMS, FTIR, $^1$H NMR and $^{13}$C NMR spectra and by comparison with the corresponding racemic compounds. The condensation followed by aminal cleavage with NaCNBH$_3$ had no effect on the stereochemistry of the chiral carbon centre, and the configurations at the mono N-alkyl derivatives’ were unchanged. The HPLC results of the racemic and chiral mono N-benzyl derivatives 119 proved that no racemization had taken place during the reaction (Figure 15).
2.4. Synthesis of 1,2-BIQs

Several 1,2-BIQs were also prepared according to the literature\textsuperscript{68} for further investigation in the Henry reaction and to serve as comparators to the 1,3-BIQs.

2.4.1. Synthesis of 1,2-BIQs 23, 27, 29, 32, 33, 35, 36, 120, 121, 123

According to Bischler-Napieralski reaction conditions, bisoxamide 30 underwent cyclization to form tetrahydro-BIQ 31. *Racemic* 1,1'-octahydro-BIQ 23 was easily obtained by the NaCNBH\textsubscript{3} reduction of BIQ 31 (Scheme 63). All compounds were characterized by \(^1\)H and \(^{13}\)C NMR spectra and were found to be identical to those reported in the literature.\textsuperscript{68}

\[
\begin{align*}
\text{Conditions: } & \text{i. Diethyl oxalate, EtOH; ii. POCl}_{3}, \text{ P}_{2}\text{O}_{5}, \text{ toluene reflux, 24 h; iii. NaCNBH}_3.}
\end{align*}
\]

\textbf{Scheme 63}

Following Elliott’s method,\textsuperscript{14} *rac*-BIQ 23 was further reacted with neat iodomethane and the final mixture was treated with aqueous NaOH solution to give methylated derivative *rac*-BIQ 120 (Scheme 64).

\[
\begin{align*}
\text{Conditions: } & \text{i. neat CH}_3\text{l, 12 h; ii. 10\% NaOH, H}_2\text{O, CH}_2\text{Cl}_2.}
\end{align*}
\]
Scheme 64

BIQs 27, 29, 32 were readily prepared under the Bischler–Napieralski conditions (Chapter 1, Scheme 13-14), and rac-BIQs 35, 36 were obtained by reduction of BIQs 27 and 32, respectively (Chapter 1, Scheme 15-16) (Figure 16).

![Scheme 64](image)

Figure 64

Further oxidation of BIQ 27 can lead to the fully unsaturated rac-BIQ 121 (Scheme 65).

![Scheme 65](image)

**Conditions:** i. Pd/C, toluene, reflux, 3 d

Scheme 65

Synthesis of rac-BIQ 123 from rac-BIQ 35 was performed by the Judeh method.69

Urethane 122 was firstly prepared by addition of ethyl chloroformate to diamines 35, then
followed by reductive treatment using LiAlH₄/AlCl₃ in dry THF to afford rac-BIQ 123 (Scheme 66).

![Chemical Structure](image)

**Condition**: i. Ethyl chloroformate, triethylamine, CH₂Cl₂; ii. LiAlH₄, AlCl₃, dry THF.

Scheme 66

2.4.2. Resolution of rac-BIQ 23 and rac-BIQ 29

Resolution of rac-BIQ 23, was achieved using Elliott¹⁴ route with L-BCSA (Chapter 1, Scheme 17), thus affording (R,R)-23. The enantiomeric purities were found to be above 99% by chiral HPLC analysis and the configuration of the major enantiomer was confirmed to be (R,R) by comparing the sign of optical rotation values with the literature.¹⁴

For the resolution of rac-BIQ 29, (S)-(+)–α-methylbenzyl isocyanate was used to form diastereomeric urea derivatives. After column chromatography separation and fractional crystallization, pure diasteromers were obtained, which upon treatment with NaOBu afford (R)-29 (Chapter 1, Scheme 19). The FTIR, ¹H and ¹³C NMR spectra of (R)-BIQ 29 were identical to those reported in the literature, and its enantiopurity and configuration was confirmed by chiral HPLC analysis.⁶⁸
In conclusion, a new ligand framework 1,1’-methylene-bis(1,1’,2,2’,3,3’,4,4’-octahydroisoquinoline) \(^98\) and its symmetric \(^{112-114}\), asymmetric \(^{115, 117, 119}\) derivatives in both \textit{racemic} and enantiopure forms were prepared. The absolute stereochemistry of this new BIQ-based compound was established by X-Ray crystallography. The enantiomeric purities of the obtained derivatives of \((R,R)-98\) were confirmed by chiral HPLC analysis. Meanwhile, several classical 1,2-BIQs \(^{23, 27, 29, 31, 32, 35, 36, 120, 121}\) and \(^{123}\) were prepared for further exploration. Among the 1,2-BIQs, \((R,R)-23\) and \((R)-29\) were also prepared as these two BIQs were the most widely used asymmetric catalysts. The chiral BIQs and derivatives will be used as ligands in classical C-C bond forming reaction—Henry reaction (nitroaldol reaction) and the results will be discussed in detail.

(Part of this section has been published in \textit{Tetrahedron} \textbf{2011}, \textit{67}, 4086-4092, reuse and reprint in this chapter are under formal permission.)
Chapter 3. Asymmetric catalysis of Henry reaction using chiral BIQ ligands

In this chapter, asymmetric catalysis of Henry reaction will be explored using various BIQs synthesized in Chapter 2. The reaction scope will be investigated.

3.1. Enantioselective Henry reaction catalyzed by novel chiral 1,3-BIQs

As mentioned in Chapter 1, Henry (Nitroaldol) reaction is a base-catalyzed addition reaction of nitroalkanes to aldehydes or ketones. It is one of the most valuable methodologies for carbon-carbon bond formation. Its enantioselective version has been discovered in 1992.\cite{118} Asymmetric catalysis of Henry reaction using copper complexes of \(C_1/C_2\)-symmetric amines is widely applied. Due to the structural similarities between the reported amine ligands\cite{6,146,164} and our newly synthesized enantiopure \(C_2\)-symmetric 1,3-BIQs (\(R,R\)-98) and its alkyl derivatives (\(R,R\)-112-115, (\(R,R\)-117 and (\(R,R\)-119 (Figure 17), we considered using these ligands for the asymmetric Henry reaction.

![Figure 17](image-url)
In this Chapter, we will discuss the application of chiral \((R,R)-98\) and its alkyl derivatives \((R,R)-112-115\), \((R,R)-117\) and \((R,R)-119\) in the enantioselective Henry reaction. Additionally, we will examine the modular effects of the alkyl substituents attached to the chelating sp\(^3\) nitrogen atoms and the symmetry properties of ligands on the reactivity and selectivity of Henry reaction between nitromethane and benzaldehyde.

### 3.1.1. Ligand effects

We started our investigation by screening chiral ligands \((R,R)-98\), \((R,R)-112-115\), \((R,R)-117\) and \((R,R)-119\) in the enantioselective reaction between nitromethane and benzaldehyde 39. All the reactions were performed using 1 equiv benzaldehyde and 20 equiv of nitromethane in the presence of 10 mol\% ligand and 10 mol\% Cu(OAc)\(_2\) in EtOH at room temperature for 48 h. To ensure complexation between the ligands and copper, the mixture was stirred for 1 h before addition of the aldehyde and nitromethane. No special precautions were taken to exclude air or moisture from the reaction flask. The results are shown in Table 1.

**Table 1 Asymmetric nitromethane addition to benzaldehyde in the presence of \((R,R)-98\), \((R,R)-112-115\), \((R,R)-117\), and \((R,R)-119\)**

![Chemical structure](image)

**Conditions:** i. Ligand (0.1 equiv), Cu(OAc)\(_2\) (0.1 equiv), EtOH (1.5 ml), r.t., 48 h
### Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (R,R)-</th>
<th>Yield$^a$ (%)</th>
<th>ee$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98</td>
<td>90</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>112</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>113</td>
<td>68</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>114</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>115</td>
<td>82</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>117</td>
<td>78</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>119</td>
<td>70</td>
<td>10</td>
</tr>
</tbody>
</table>

$^a$ Yields of isolated products.

$^b$ Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

$^c$ The absolute configuration (S) was determined by comparing with the literature values.$^{210}$

Reactions involved the use of double alkylated (R,R)-112-114, β-nitroalcohol 123 was obtained in completely racemic form, while the other chiral ligands (R,R)-98, (R,R)-115, (R,R)-117, (R,R)-119 yielded the β-nitroalcohol (S)-123 in 9-18% ee (Table 1, entries 2-4 vs 1 and 5-7). Presumably, the lack of induction using ligands (R,R)-112-114 may be due to inability of the ligands to chelate with the copper to effectively induce chirality as shown in the proposed intermediate state (Figure 18). From the results in Table 1, the parent ligand (R,R)-98 bearing no substituent was more efficient than the other alkylated BIQs affording product (S)-124 in 90% yield and 18% ee (Table 1, entry 1). Interestingly, as the bulkiness of the alkyl group on BIQ increased, the yield of β-nitroalcohols (S)-124 dropped (Table 1, entry 2 vs 3 vs 4). Similar trend was also found from the results of
mono N-alkyl BIQs \((R,R)-115\), \((R,R)-117\) and \((R,R)-119\) (Table 1, entry 5 vs 6 vs 7). These results showed that steric effect at the copper coordination site would have a profound effect on the reactivity and enantioselectivity. Subsequently, screening of other reaction conditions was accomplished using parent ligand \((R,R)-98\).

![Intermediate state](image)

**Figure 18**

### 3.1.2. Copper sources effects

Next the influence of frequently used copper salts was examined in this enantioselective Henry reaction. The results obtained are summarized in Table 2. Copper (I) sources (Table 2, entries 4-7) were superior in both activity and selectivity, compared to copper (II) sources which are quite sluggish (Table 2, entries 2-3). Among the examined copper (I) salts, CuCl and CuI showed similar results to those with CuBr (Table 2, entries 5, 7 vs 6), while copper (I) acetate gave lower enantiomeric excess (Table 2, entry 4). These results indicated that the counter anion (e.g. halide ions) had no profound effect in the process of catalysis. Considering that the \(ee\) result obtained using copper(I) bromide was the highest, and that this metal salt was inexpensive and less toxic, it was chosen as the copper source for further optimizations of the asymmetric Henry reaction.
Table 2 Screening of copper sources for asymmetric nitromethane addition to benzaldehyde

\[
\text{苯甲醛} + \text{CH}_3\text{NO}_2 \xrightarrow{i} \text{(S)-240}
\]

**Conditions:** i. (R,R)-98 (0.1 equiv), Copper sources (0.1 equiv), EtOH (1.5 ml), r.t., 48 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu salt</th>
<th>Yield$^a$ (%)</th>
<th>ee$^b,c$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)$_2$</td>
<td>90</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)$_2$</td>
<td>43</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>CuCl$_2$</td>
<td>40</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>CuOAc</td>
<td>95</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>CuCl</td>
<td>89</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>CuBr</td>
<td>90</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>CuI</td>
<td>90</td>
<td>23</td>
</tr>
</tbody>
</table>

$^a$ Yields of isolated products.

$^b$ Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

$^c$ The absolute configuration (S) was determined by comparing with the literature values.$^{210}$

### 3.1.3. Solvent effects

Optimization of the solvents used in the enantioselective Henry reaction was carried out with solvents like alcohols, ethers and chlorinated solvents (Table 3). Generally, protic
solvents like EtOH and MeOH (Table 3, entries 1-2) were found to be more efficient than the aprotic solvents (Table 3, entries 3-9) in terms of the yield of the product (S)-124. However in terms of enantioselectivities, compared with protic solvents (Table 3, entries 1-2), ether-type solvents, toluene and chlorinated solvents, except CH₂Cl₂, (Table 3, entries 3-4, 6, 8-9) all showed better results dioxane showed optimal results in terms of ee value (38% ee) (Table 3, entry 4). Therefore, based on these results, dioxane was chosen for further optimization.

**Table 3 Screening of solvents for asymmetric nitromethane addition to benzaldehyde**

\[
\begin{array}{c}
\text{39} \quad \text{20 equiv} \\
(S)-124
\end{array}
\]

**Conditions:** i. (R,R)-98 (0.1 equiv), CuBr (0.1 equiv), Solvent (1.5 ml), r.t., 48 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield(^a) (%)</th>
<th>ee(^b,c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>90</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>89</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>80</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Dioxane</td>
<td>70</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>CH₃CN</td>
<td>45</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>65</td>
<td>30</td>
</tr>
</tbody>
</table>

\(^a\) Determined by 
\(^b\) Determined by 
\(^c\) Determined by
3.1.4. Effects of catalyst loading and ligand ratio

Other factors to be optimized were the ratio of ligand \((R,R)-98\) to CuBr and the catalyst loading (Table 4). Initially, the amount of CuBr was constantly kept at 10 mol\% (with respect to aldehyde 39) while the ligand amount was gradually increased in ratios of \((R,R)-98/CuBr\) from 1:2, 1:1, 1.5:1 to 2:1 (Table 4, entries 1-4). In terms of enantioselectivity, the optimal ratio between ligand \((R,R)-98\) and copper(I) bromide was 1:1 (Table 4, entry 2). Using the optimal ratio of ligand \((R,R)-98\) and copper(I) bromide of 1:1, attempts to decrease the catalyst loading to half provided the expected product in only 45\% yield (Table 4, entry 5 vs entry 2) whereas attempts to increase the loading from 10 to 20 mol\% afforded \(\beta\)-nitroalcohol \((S)-124\) in higher 85\% yield but unfortunately in lower enantioselectivity of 30\% ee (Table 4, entry 6 vs entry 2). BIQ \((R,R)-98\) was also applied as organocatalyst without any metal salts, expected product in racemice form is afforded in 43\% yield (Table 4, entry 8). Thus for this reaction, the optimal catalyst loading of \((R,R)-98/CuBr\) is 10 mol\%.

Table 4 Screening of the ratio of \((R,R)-98\) to CuBr and catalyst loading in the asymmetric nitromethane addition to benzaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (isolated)</th>
<th>Enantiomeric Excess (ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>65</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₃</td>
<td>75</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>ClCH₂CH₂Cl</td>
<td>50</td>
<td>26</td>
</tr>
</tbody>
</table>

\(^a\) Yields of isolated products.

\(^b\) Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

\(^c\) The absolute configuration \((S)\) was determined by comparing with the literature values.\(^{210}\)
Chapter 3  Results and Discussion

\[
\text{\(\text{PhCHO} + \text{CH}_3\text{NO}_2 \xrightarrow{i} \text{PhCH(OH)NO}_2\)}
\]

**Conditions:** i. \((R,R)-98\), CuBr, Dioxane (1.5 ml), r.t., 48 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>((R,R)-98) (mol%)</th>
<th>CuBr (mol%)</th>
<th>Yield(^a) (%)</th>
<th>ee(^b,c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>10</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>10</td>
<td>70</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>10</td>
<td>80</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>10</td>
<td>88</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>5</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>20</td>
<td>85</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>-</td>
<td>43</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Yields of isolated products.

\(^b\) Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

\(^c\) The absolute configuration \((S)\) was determined by comparing with the literature values.\(^{210}\)

Overall, the optimized reaction conditions were 10 mol\% \((R,R)-98\), 10 mol\% CuBr in dioxane at room temperature. Under these conditions, the adduct \((S)-124\) was obtained in 70\% yield and 38\% ee. These results were moderate. Hence, substrate scope of the reaction using this \((R,R)-98\) was not examined.
3.2. Enantioselective Henry reaction catalyzed by chiral 1,2-BIQs

As discussed in section 3.1, attempts to employ chiral 1,3-BIQs in the enantioselective Henry reaction furnished moderate results. This may be attributed to the flexibility of the six-membered chelating ring.

It was logical to examine 1,2-BIQs ligands (Figure 19), and investigate their catalytic ability in the asymmetric Henry reaction and compare them to 1,3-BIQs. An additional objective was also to compare the efficiencies of $C_1$ vs $C_2$ 1,2-BIQs. From the X-Ray analysis of BIQs $C_2$-symmetric 23 and $C_1$-29's major structural differences were observed. BIQ $(R,R)$-23 showed a $C_2$-symmetric structure, and the two heterocyclic rings are fully saturated. However, aromaticities of the two heterocyclic rings of BIQ $(R)$-29 are different: one ring is fully aromatic while the heterocyclic ring is saturated, hence BIQ $(R)$-29 has $C_1$-symmetry.

![Figure 19](attachment:image19.png)

3.2.1. Ligand effects

Initially the CuBr complexes with $(R,R)$-23 and $(R)$-29 were used in the enantioselective nitroaldol reaction between nitromethane and benzaldehyde 39 to examine their
reactivities and selectivities. These complexes were examined under the following reaction conditions: 10 mol% ligand and 10 mol% CuBr were stirred in THF at ambient temperature for 1.5 h followed by dropwise addition of nitromethane (20 equiv) and benzaldehyde \(39\) (1 equiv). The reaction mixture was allowed to proceed for another 36 h at room temperature. The obtained results are summarized in Table 5.

As shown in Table 5, \((R)-29\) afforded higher yield (up to 94%) and higher \(ee\) values (up to 68%) in comparison to the results obtained by \((R,R)-23\), presumably owing to the structural difference (Table 5, entry 1 \(vs\) 2). Both nitrogen atoms in the \(C_2\)-1,1'-bisisoquinolines \((R,R)-23\) are sp\(^3\) hybridized and thus were assuming a twist-boat conformation. However, the \(C_1\)-tetrahydro-1,1'-bisisoquinoline \((R)-29\) with two dissimilar nitrogen atoms demonstrated a twist-boat conformation for the sp\(^3\)-N containing ring and the sp\(^2\)-N containing ring is flat due to its aromaticity. The configuration of \((R)-29\) give better results. When the reactions are undergoing under inert conditions, similar results are obtained (Table 5, entries 3-4 \(vs\) entries 1-2). So in the following reaction process, no special precautions were taken to exclude air or moisture from the reaction tubes. And \((R)-29\) was chosen for subsequent screening and optimization.

**Table 5 Enantioselective nitromethane addition to benzaldehyde in the presence of \((R,R)-23\) and \((R)-29\)**

\[
\text{Conditions: i. Ligand (0.1 equiv), CuBr (0.1 equiv), THF (1.5 ml), r.t., 36 h}
\]
<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield$^a$ (%)</th>
<th>ee$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-23</td>
<td>90</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>(R)-29</td>
<td>94</td>
<td>68</td>
</tr>
<tr>
<td>3$^d$</td>
<td>(R,R)-23</td>
<td>89</td>
<td>59</td>
</tr>
<tr>
<td>4$^d$</td>
<td>(R)-29</td>
<td>90</td>
<td>69</td>
</tr>
</tbody>
</table>

$^a$ Yields of isolated products.

$^b$ Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

$^c$ The absolute configuration (R) was determined by comparing with the literature values.$^{210}$

$^d$ Inert conditions

### 3.2.2. Solvent effects

The effects of different types of solvents in the asymmetric Henry reaction were explored using (R)-29 and CuBr under the reaction conditions mentioned in Table 6. The results show that protic solvents like EtOH and MeOH (Table 6, entries 1-2) afforded the final product β-nitroalcohols (R)-124 in reasonable yields. However, in term of enantioselectivities, these solvents were less effective than the aprotic ones (Table 6, entries 1-2 vs 3-13). Among the tested aprotic solvents, ether-type solvents (except diethyl ether) exhibited more efficient catalytic abilities—higher yields and ees (Table 6, entries 3-7 vs entries 8-13). The highest ee value (77% ee) was obtained when this reaction was performed in 1,2-dichloroethane (Table 6, entry 10), though moderate enantioselectivities were obtained in other two chlorinated solvents. The catalyst reactivity in 1,2-dichloroethane seems sluggish as only 45% yield was achieved.
However, in consideration of the resulting optimal enantioselectivity, this chlorinated solvent was chosen for further screening to optimize the reaction conditions.

Table 6 Screening of solvents for enantioselective nitromethane addition to benzaldehyde

![Chemical Structure]

**Conditions**: i. (R)-29 (0.1 equiv), CuBr (0.1 equiv), Solvent (1.5 ml), r.t., 36 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>84</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>89</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>94</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>Dioxane</td>
<td>99</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>Bu$_2$O</td>
<td>99</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>Et$_2$O</td>
<td>35</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>t-BuOMe</td>
<td>90</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>CH$_2$Cl$_2$</td>
<td>78</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>CHCl$_3$</td>
<td>56</td>
<td>34</td>
</tr>
<tr>
<td>10</td>
<td>ClCH$_2$CH$_2$Cl</td>
<td>45</td>
<td>77</td>
</tr>
<tr>
<td>11</td>
<td>Toluene</td>
<td>91</td>
<td>29</td>
</tr>
</tbody>
</table>
## Chapter 3

### Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>CH$_3$CN</td>
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<td>55</td>
</tr>
<tr>
<td>13</td>
<td>1,2-Dimethoxyethane</td>
<td>38</td>
<td>70</td>
</tr>
</tbody>
</table>

aData yields of isolated products.

bEnantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

cThe absolute configuration ($R$) was determined by comparing with the literature values.$^{210}$

### 3.2.3. Effects of copper sources

The influence of frequently used copper salts were examined in the enantioselective catalysis of Henry reaction, and the obtained results were summarized in Table 7. Generally, copper (I) sources (Table 7, entries 5-7) showed superior catalytic ability in terms of both the activity and selectivity in comparison with the results obtained by copper (II) salts which were quite sluggish (Table 7, entry 4) or ineffective (Table 7, entries 1-3). Among the tested copper (I) salts, CuCl showed similar results to those with CuBr (Table 7, entries 5 vs 6) while CuI gave better yield but lower enantiomeric excess of only 41% $ee$ (Table 7, entry 7).

Considering both the yields and $ee$ values, copper(I) chloride will be used as the copper source of choice in the next optimization processes.

### Table 7 Screening of copper sources for asymmetric nitromethane addition to benzaldehyde
\[
\text{H}O\text{OH}
\]
\[
\text{NO}_2
\]
\[
+\text{CH}_3\text{NO}_2
\]
\[
\rightarrow
\]
\[
\text{H}O\text{OH}
\]
\[
\text{NO}_2
\]
\[
(\text{R})-\text{124}
\]

**Conditions:** i. (R)-29 (0.1 equiv), Copper sources (0.1 equiv), Cl\text{CH}_2\text{CH}_2\text{Cl} (1.5 ml), r.t., 36 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu salt</th>
<th>Yield(^a) (%)</th>
<th>ee(^b, c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(NO\textsubscript{3})\textsubscript{2}</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>CuCl\textsubscript{2}</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)\textsubscript{2}</td>
<td>21</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>CuCl</td>
<td>55</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>CuBr</td>
<td>45</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>CuI</td>
<td>70</td>
<td>41</td>
</tr>
</tbody>
</table>

\(^a\) Yields of isolated products.

\(^b\) Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

\(^c\) The absolute configuration (\textit{R}) was determined by comparing with the literature values.\textsuperscript{210}

### 3.2.4. Catalyst loading, ligand ratio and temperature effects

Other factors like the ratio between ligand (R)-29 and CuCl, the catalyst loading, and temperature were further optimized. The results are shown in Table 8. The amount of CuCl was first kept constant at 10 mol\% (with respect to aldehyde 39) while the ligand (R)-29 amount was increased gradually from 5, 10, 15 to 20 mol\% (Table 8, entries 1-4). The obtained results showed a tremendous increase in the reaction activity, yielding the
β-nitro alcohols (R)-124 in more than double yield when the amount of (R)-29 was increased from 5 to 10 mol% (Table 8, entry 1 vs entry 2). Further increase in the amount of (R)-29 did not improve the yield of product (R)-124, however a slight increase in enantiomeric excess was observed (Table 8, entries 1-4). An increase the amount of CuCl from 5, 15 to 20 mol%, while keeping the amount of (R)-29 constant at 10 mol%, resulted in a significant decrease in the reaction rates (Table 8, entries 5-7) and a drop in the ee values from 83% to 74%, to 71%, respectively, (Table 8, entry 5 vs entry 6 vs entry 7). These combined results indicated the optimal ratio between ligand (R)-29 and copper(I) chloride as 2:1 (Table 8, entry 5).

The reaction became much more sluggish after attempts to decrease the catalyst loading from 5 mol% Cu(I) and 10 mol% (R)-29 to 2.5 mol% Cu(I) and 5 mol% (R)-29. The adduct (R)-124 was produced in only 16% yield even after extending the reaction time to 120 h (Table 8, entry 8). Therefore, the optimal loading is 10 mol% ligand (R)-29 and 5 mol% CuCl.

Next, the effect of the reaction temperature was tested at 40 °C, 0 °C and -20 °C (Table 8, entries 9-11). When the reaction temperature was increased from r.t. to 40 °C, the reaction rate increased affording the product (R)-124 in 78% yield in 12 h. However, the enantioselectivity was inferior to the one obtained at room temperature (Table 8, entry 9 vs entry 5). When the temperature was decreased from r.t. to 0 °C, (R)-124 was obtained in higher enantioselectivity and comparable yield (Table 8, entry 10 vs entry 5). However, when the reaction temperature was lowered to -20 °C, the poor solubility of the catalytic copper complex made the reaction sluggish (Table 8, entry 11). Thus 0 °C was chosen as the optimal temperature for the asymmetric Henry reaction.
Table 8 Screening of the ratio of (R)-29 to CuCl, catalyst loading and temperature in the asymmetric nitromethane addition to benzaldehyde

\[
\text{Table 8 Screening of the ratio of (R)-29 to CuCl, catalyst loading and temperature in the asymmetric nitromethane addition to benzaldehyde}
\]

\[
\begin{align*}
\text{Conditions:} & \quad \text{i. (R)-29, CuCl, ClCH}_2\text{CH}_2\text{Cl (1.5 ml)} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>CuCl (mol%)</th>
<th>(R)-29 (mol%)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield(^a) (%)</th>
<th>ee(^b,c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>5</td>
<td>r.t.</td>
<td>84</td>
<td>25</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>10</td>
<td>r.t.</td>
<td>36</td>
<td>55</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>15</td>
<td>r.t.</td>
<td>36</td>
<td>56</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>20</td>
<td>r.t.</td>
<td>36</td>
<td>56</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>10</td>
<td>r.t.</td>
<td>36</td>
<td>63</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>10</td>
<td>r.t.</td>
<td>36</td>
<td>19</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>10</td>
<td>r.t.</td>
<td>36</td>
<td>13</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>2.5</td>
<td>5</td>
<td>r.t.</td>
<td>120</td>
<td>16</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>10</td>
<td>40</td>
<td>12</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>10</td>
<td>0</td>
<td>72</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>10</td>
<td>-20</td>
<td>120</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) Yields of isolated products.

\(^b\) Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

\(^c\) The absolute configuration (R) was determined by comparing with the literature values.\(^{210}\)
As the most efficient ratio of ligand \((R)-29\) to \(\text{CuCl}\) was 2:1, the solvent and copper source effects were re-tested in the hope to obtain better results (Table 9). The results shown in Table 9 were in agreement with the conclusions made from Table 6 and Table 7. Overall, the optimized reaction conditions involved using ligand \((R)-29\) (10 mol\%) and \(\text{CuCl}\) (5 mol\%) in 1,2-dichloroethane at 0 °C, furnishing final product \((R)-124\) in 60% yield and 83% ee.

Table 9 Screening of solvents and copper sources using a 2:1 ratio of \((R)-29\)-copper source for asymmetric nitromethane addition to benzaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Cu salt</th>
<th>Yield(^a) (%)</th>
<th>(ee)^(^b,c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{ClCH}_2\text{CH}_2\text{Cl})</td>
<td>(\text{CuCl})</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>(\text{MeOH})</td>
<td>(\text{CuCl})</td>
<td>90</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>(\text{CuCl})</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>(\text{CuCl})</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>(\text{CH}_3\text{CN})</td>
<td>(\text{CuCl})</td>
<td>85</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>(\text{THF})</td>
<td>(\text{CuCl})</td>
<td>90</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>(\text{ClCH}_2\text{CH}_2\text{Cl})</td>
<td>(\text{CuBr})</td>
<td>55</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>(\text{ClCH}_2\text{CH}_2\text{Cl})</td>
<td>(\text{Cu(OAc)}_2)</td>
<td>40</td>
<td>62</td>
</tr>
</tbody>
</table>

\(^i\) \((R)-29\) (0.1 equiv), Copper sources (0.05 equiv), Solvent (1.5 ml), 0 °C, 36 h
Yields of isolated products.

Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

The absolute configuration (\(R\)) was determined by comparing with the literature values.\(^{210}\)

### 3.2.5. Scope of (\(R\))-29 in the enantioselective Henry reaction

The substrate scope in Henry reaction using ligand (\(R\))-29 was then examined under the optimized reaction conditions mentioned in Table 9, entry 1. This reaction was found to be general since a wide range of aldehydes including aliphatic, conjugated, heteroaromatic and aromatic aldehydes with different electron-donating and electron-withdrawing substituents reacted smoothly with nitromethane to afford the corresponding \(\beta\)-nitroaldol products in good yields and enantioselectivities (Table 10). Interestingly, aromatic aldehydes with either electron-donating (Table 10, entries 7-13) or electron-withdrawing groups (Table 10, entries 2-6) all gave similar yields and enantioselectivities. However, the strongly electron-withdrawing nitro group was an exception as the reaction rate was accelerated and was completed in only 12 hours providing the desired product in only 64% \(ee\) (Table 10, entry 2). The lower \(ee\) value was attributed to the higher reaction rate than the other aromatic aldehydes. Meanwhile, the substitution pattern (Table 10, entries 3-5, entries 7-9 and entries 11-13) at the phenyl rings seems to have no major effect on the reactivity or enantioselectivity of the catalyst system, producing the relative adducts in moderate yields from 48-80% and with excellent enatiomeric excess ranging from 82-91% \(ee\). The reaction proceeded smoothly even with straight chain aldehydes of different length (Table 10, entries 14-16), affording comparable yields and excellent \(ee\) values (up to 91% \(ee\)). Moreover, the bulky 2-naphthylaldehyde 140, heteroaromatic 2-
furaldehyde 141 and conjugated trans-cinnamaldehyde 142 gave the expected nitro products (R)-158-160 in similar yields (78-85%) and enantiomeric excesses (80-85% ee) (Table 10, entry 17-19). In addition, no aldol side reactions or dehydration products were observed.

Table 10 Scope of (R)-29 in the asymmetric Henry reaction

\[
\begin{align*}
\text{R} \quad 
\begin{array}{c}
\text{O} \\
\text{H}
\end{array} 
\begin{array}{c}
\text{CH}_3\text{NO}_2 \\
\text{i}
\end{array} 
\begin{array}{c}
\text{OH} \\
\text{R}
\end{array} 
\begin{array}{c}
\text{NO}_2 \\
\text{(R)}
\end{array}
\end{align*}
\]

20 equiv

**Conditions:** i. (R)-29 (0.1 equiv), Cu(I)Cl (0.05 equiv), ClCH\_2CH\_2Cl (1.5 ml), 0 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time</th>
<th>Yield(^a) (%)</th>
<th>ee(^b, c) (%)</th>
</tr>
</thead>
</table>
| 1     | \begin{array}{c}
\text{O} \\
\text{H}
\end{array} 
\begin{array}{c}
\text{39}
\end{array} | \begin{array}{c}
\text{OH} \\
\text{(R)-124}
\end{array} | 72   | 60              | 85              |
| 2     | \begin{array}{c}
\text{O}\text{N} \\
\text{26}
\end{array} | \begin{array}{c}
\text{OH} \\
\text{(R)-143}
\end{array} | 12   | 95              | 64              |
| 3     | \begin{array}{c}
\text{Cl} \\
\text{27}
\end{array} | \begin{array}{c}
\text{OH} \\
\text{(R)-144}
\end{array} | 48   | 70              | 91              |
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image" alt="Compound 128" /></td>
<td><img src="image" alt="Compound (R)-145" /></td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Compound 129" /></td>
<td><img src="image" alt="Compound (R)-146" /></td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Compound 130" /></td>
<td><img src="image" alt="Compound (R)-147" /></td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Compound 131" /></td>
<td><img src="image" alt="Compound (R)-148" /></td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Compound 132" /></td>
<td><img src="image" alt="Compound (R)-149" /></td>
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<tr>
<td>9</td>
<td><img src="image" alt="Compound 133" /></td>
<td><img src="image" alt="Compound (R)-150" /></td>
<td>48</td>
</tr>
</tbody>
</table>
Chapter 3 Results and Discussion

<table>
<thead>
<tr>
<th>10</th>
<th>134</th>
<th>(R)-151</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>135</td>
<td>(R)-152</td>
</tr>
<tr>
<td>12</td>
<td>136</td>
<td>(R)-153</td>
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<tr>
<td>13</td>
<td>65</td>
<td>(R)-154</td>
</tr>
<tr>
<td>14</td>
<td>137</td>
<td>(R)-155</td>
</tr>
<tr>
<td>15</td>
<td>138</td>
<td>(R)-156</td>
</tr>
</tbody>
</table>
Chapter 3

Results and Discussion

3.2.6. Proposed mechanism

As mentioned previously, the optimum ratio between (R)-29 and CuCl was found to be 2:1 suggesting the formation of copper complex in a 2:1 ratio of (R)-29 to CuCl. When (R)-29 and CuCl were mixed in a 2:1 ratio in MeOH and the product analyzed by mass spectrometry, major molecular ion peak at m/z 584 (molecular formula C_{36}H_{32}CuN_{4} = 2 \times (R)-29 + Cu) was observed confirming the presence of a dinuclear complex.
Accordingly, chelation of copper(I) to (R)-29 is shown in Figure 22. Due to the strong coordination ability of the nitro group to soft metals, MeNO₂ is activated and deprotonated to generate the active nucleophile - nitronate in the Cu(I) transition state. In consideration of both of the stereoelectronic influences and the outcomes of this nitroaldol adduct, the Si face of the carbonyl functionality of benzaldehyde is favored for nucleophilic attack to yield the corresponding (R)-product (Figure 20).

\[
\text{Favoured} \Rightarrow \text{R-product} \quad \text{Disfavoured} \Rightarrow \text{S-product}
\]

\textbf{Figure 20}

Recently, a number of reports have demonstrated that nonlinear effects (NLEs) can shed light on the molecular interactions in the process of stereoselective catalysis, thus supplying useful mechanistic information.²¹²⁻²¹⁵

Hence, the NLEs were examined for Henry reaction of nitromethane with benzaldehyde 39 using BIQ (R)-29 with different enantiomeric purities (Table 11). Interestingly, the collected experimental data gave a double-shaped curve (Figure 23), which could be produced by Kagan’s ML₄ model system (or (ML)₄ model system).
Table 11 Nonlinear effects under 2:1 ratio of (R)-29:Cu(I)Cl in the enantioselective Henry reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>% ee Ligand, (R)-29</th>
<th>% ee Product, (R)-124&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
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</tr>
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<td>3</td>
<td>40</td>
<td>28</td>
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<tr>
<td>6</td>
<td>90</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>99</td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup> Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column. The absolute configuration (R) was determined by comparison with the literature values.\textsuperscript{132}

Kagan \textit{et al}. simplified the ML\textsubscript{4} system assuming ligands are distributed in the statistical mode, and derived equation (1) to express enantiomeric excesses of product ($ee_{prod}$) as a function of ligands’ enantiopurity ($ee_{cat}$).\textsuperscript{216} In equation (1), four basic parameters were
introduced: \( g \) and \( f \) represent reactivities of hetero complexes \((M(L_R)_3L_S)\) and hetero-meso one \((M(L_R)_2(L_S)_2)\) over homochiral complexes \((M(L_R)_4)\) \((g = k_{RRSS}/k_{RRRR}, f = k_{RRSS}/k_{RRRR})\) respectively, while \(ee_0\) defines the enantiomeric excesses of product by using enantiopure homochiral \(M(L_R)_4\) complexes and \(ee_o'\) stands for the enantiomeric excesses of the product by the use of enantiopure heterochiral \(M(L_R)_3L_S\) complexes. \(M(L_R)_2(L_S)_2\) were considered as meso complexes and assumed no additional stereoisomers involving the metal center.

\[
e e_{prod} = 8ee_o \times ee_{cat}
\]

\[
\frac{1 + ee_{cat}^2 + 2g(1 - ee_{cat}^2)e e_o'}{ee_o} \times \frac{ee_o'}{(1 + ee_{cat}^4 + (1 - ee_{cat})^4 + 8g(1 - ee_{cat}^4) + 6f(1 - ee_{cat}^2)^2)}
\]

(1)

Supposing the catalytic BIQ ligands 29 are distributed\(^{202}\) in statistical mode between the complexes, curve fitting was calculated from equation (1) with these parameters \(ee_o = 85\%\), \(K = [M(L_R)_3L_S]^2/[\{M(L_R)_4\}*[M(L_R)_2(L_S)_2]] = [M(L_S)_3L_R]^2/[\{M(L_S)_4\}*[M(L_R)_2(L_S)_2]] = 1000\), \(ee_o' = 64\%\), \(g = 0.41\) and \(K' = [M(L_R)_2(L_S)_2]^2/[\{M(L_R)_3L_S\}*[M(L_S)_3L_R]] = 1\), \(f = 2.0\). The resulting curve indicated the predominance of fairly active, moderate selective heterochiral catalyst species and more active meso complexes. This computer-drawn curve calculated by Kagan’s ML\(_4\) model system (or (ML)\(_4\) model system) was fitting well with these collected experimental data (Figure 21), and the standard deviation (S) is 0.0084565. This could be evidence for the involvement of an aggregation of dimers (with four BIQs 32 ligands) in the process of enantioselective Henry reaction by the catalytic system comprising of \((R)-32\) and CuCl in
In conclusion, the reactivities and selectivities of chiral 1,2-BIQ ligands \((R,R)-23, (R)-29\) in the Henry reaction were examined. Chiral \(C_1\)-tetrahydro-1,1’-bisisoquinoline \((R)-29\) proved to be more effective ligand in the copper(I)-catalyzed Henry reaction. The desired nitroaldol adducts were obtained in excellent yields (up to 95%) and enantioselectivities (up to 91% ee) with a broad range of aromatic and aliphatic aldehydes. Nonlinear effects have been studied, the results fit well with the Kagan’s ML\(_4\) model system.

(Reuse and reprint in this section are under formal permission.)
3.3. Enantioselective Henry reaction catalyzed by derivatives of BIQ (R)-29

Encouraged by the great results obtained using BIQ (R)-29 in the enantioselective Henry reaction (Table 10), we then turned our attention to explore the modular effects of its derivatives on the reactivity and selectivity in the asymmetric catalysis of Henry reaction.\textsuperscript{218} Based on the DFT calculation and X-ray structural analysis of (R)-29, two fully aromatic isoquinoline ring with sp\textsuperscript{2}-N atom is flat, while heterocyclic ring in the other isoquinoline moiety assumes a twist boat conformation. The dihedral angle between N\textsubscript{1}-C\textsubscript{1}-C\textsubscript{1}’-N\textsubscript{1}’ is affected by the size (bulkiness) and type (alkyl, sulfanyl, acyl etc.) of substituents attached to the sp\textsuperscript{3}-N atom of (R)-29.\textsuperscript{12,13,187}

Treatment of (R)-29 with the respective halides, isocyanate and isothiocyanate afforded its alkyl, amide, urea and thiourea derivatives (R)-161-170, respectively, in excellent yields (Figure 22). The substituents at the sp\textsuperscript{3}-N of ligands (R)-161-170 were chosen to modulate the steric bulkiness around the chelating centers and show contrasting electronic effects on the metal center.

![Chemical structures](attachment:image.png)
3.3.1. Ligand effects

Initially, ligands (R)-161-170 were examined in the enantioselective Henry reaction between nitromethane and benzaldehyde 39 to test the efficiencies of these compounds as chiral inductors. The reactions were performed under the same standard reaction conditions (10 mol% ligand, 10 mol% copper source CuBr and 20 equiv MeNO₂ in THF at r.t. developed earlier). The results are shown in Table 12.

As shown in Table 12, β-nitroalcohol (R)-124 was obtained in 98% yield and up to 83% ee using chiral ligand (R)-161, the one bearing the smallest alkyl substituent—methyl group (Table 12, entry 1). Under the same reaction conditions, other alkylated ligands (R)-162-164 afforded comparable yields (85-98%) but lower enantioselectivities (65-69% ee) than ligand (R)-161 (Table 12, entry 1 vs entries 2-4). Surprisingly, BIQ (R)-165 (with 2-hydroxy-5-nitro-benzyl group), BIQs (R)-166 and (R)-166 (with amide functional group), and BIQ (R)-168 (with urea functional group) were found to be completely inactive and the starting material benzaldehyde 39 was recovered back unchanged (Table 12, entries 5-8). The lack of reactivities may be due to the obvious steric bulkiness of these ligands, resulting in the inefficient formation of the copper complexes. Based on the analysis of these ligands’ X-Ray
crystallography shows that bulky attachments around sp$^3$-N force these chelating nitrogens to adopt an *anti* conformation preventing efficient chelation. In contrast, copper ion could coordinate with the *syn*-oriented nitrogens in the cases of alkylated BIQs with relatively smaller substituents (Table 12, entries 5-8 vs entries 1-4). However, the desired product (R)-124 was obtained in 20-30% yield and 21-24% ee by the use of ligands (R)-169 and (R)-170 with large substituents (Table 12, entries 9-10). To ensure that the catalytic induction was due to the relative formation of copper complexes, and not due to the ligands themselves, the nitroaldol reactions were repeated in the exactly same reaction conditions by the use of ligands (R)-169 and (R)-170 without metal salts, seperately. In both cases, no expected products were formed and the starting materials were recovered back, indicating ligands (R)-169 and (R)-170 themselves were inefficient organocatalysts in this addition reaction.

Based on the above results, BIQ (R)-161 was chosen for further optimization of reaction conditions (Table 12, entry 1).

**Table 12 Enantioselective nitromethane addition to benzaldehyde in the presence of (R)-161-170**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time</th>
<th>Yield$^a$ (%)</th>
<th>ee$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conditions:** i. Ligand (0.1 equiv), CuBr (0.1 equiv), THF (1.5 ml), r.t.


<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
<th>Enantiomeric Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-161</td>
<td>20</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>(R)-162</td>
<td>20</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>(R)-163</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>(R)-164</td>
<td>20</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>(R)-165</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>(R)-166</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>(R)-167</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>(R)-168</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>(R)-169</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>(R)-170</td>
<td>36</td>
<td>20</td>
</tr>
</tbody>
</table>

a Yields of isolated products.

b Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

c The absolute configuration (R) was determined by comparing with the literature values.210

### 3.3.2. Effects of copper sources

A series of frequently used copper sources were examined using (R)-161 in THF. In each case, the asymmetric nitroaldol reaction was performed at room temperature for over 20 h. The results summarized in Table 13 showed that the reaction was most sluggish by the use of Cu(II) chloride (40% yield) while the other tested copper sources all provided above 70% yield (Table 13, entry 2 vs entries 1 and 3-7). In general, copper (I) sources (Table 13, entries 3-7) are superior in reactivity in comparison to copper (II) sources (Table 13, entries 1-2). In comparison with the results obtained by copper (II) acetate, the nitroaldol adduct (R)-124 was produced in higher yields but lower ee values in the
presence of copper (I) acetate (Table 13, entry 1 vs entry 4). However, copper (I) salts with halide ions were capable of providing highest yields (up to 99%) and the best enantiomeric excesses (up to 83% $ee$) (Table 13, entries 5-7). CuCl and CuBr showed very similar reactivities to those of CuI, but higher enantioselectivities (Table 13, entries 5-6 vs entry 7). These results indicated that small counter anions (e.g. halide ions) had no prominent effect on the catalytic process of Henry reaction.

Therefore, considering CuCl was inexpensive and less toxic, so it was chosen as the copper source for the next optimizations of the asymmetric Henry reaction (Table 13, entry 5).

**Table 13 Screening of copper sources for asymmetric nitromethane addition to benzaldehyde by (R)-161**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu salt</th>
<th>Yield$^a$ (%)</th>
<th>ee$^{b,c}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)$_2$</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>CuCl$_2$</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>CuOTf</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>CuOAc</td>
<td>85</td>
<td>45</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th></th>
<th>CuCl</th>
<th>99</th>
<th>83</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>CuBr</td>
<td>98</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>CuI</td>
<td>99</td>
<td>70</td>
</tr>
</tbody>
</table>

\(^a\) Yields of isolated products.

\(^b\) Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.

\(^c\) The absolute configuration (R) was determined by comparing with the literature values.\(^{210}\)

#### 3.3.3. Solvent effects

Next, different types of solvents were also examined in combination with the copper complexe (R)-161/CuCl for the catalytic enantioselective nitroaldol reaction between benzaldehyde and nitromethane. As the results shown in Table 14, both protic solvents and the nonprotic ones were found to yield the final product β-nitro alcohols (R)-124 in similar ee values; however, ether-type solvents and alcohols gave much higher yields than the chlorinated ones (Table 14, entries 1-5 and entries 11-12 vs entries 6-8).

Surprisingly, the reaction was very sluggish in CH₃CN, and the final nitroaldol adduct (R)-124 was achieved in only 12% yield (Table 14, entry 9). Presumably, poor solubility of the forming copper complexes by (R)-161/CuCl in CH₃CN resulted in the notable sluggishness. In consideration of both the reactivity and selectivity, (i-Pr)₂O was proved to be the best solvent of choice for the enatioselective Henry reaction catalyzed by (R)-161/CuCl, providing very high yield (90%) and the highest ee value (up to 86% ee) (Table 14, entry 5).

Therefore, this ether-type solvent (i-Pr)₂O was chosen in the following optimization process of reaction conditions.
Table 14 Screening of solvents for enantioselective nitromethane addition to benzaldehyde by (R)-161/CuCl

![Chemical Structure Image]

**Conditions:** i. (R)-161 (0.1 equiv), CuCl(0.1 equiv), Solvent (1.5 ml), r.t., 20 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield(^a) (%)</th>
<th>(ee)^(b, c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>99</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>Dioxane</td>
<td>92</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>Bu(_2)O</td>
<td>70</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>Et(_2)O</td>
<td>78</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>(i-Pr)(_2)O</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>CH(_2)Cl(_2)</td>
<td>52</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>CHCl(_3)</td>
<td>65</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>ClCH(_2)CH(_2)Cl</td>
<td>62</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>CH(_3)CN</td>
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<td>10</td>
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<td>11</td>
<td>EtOH</td>
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<td>84</td>
</tr>
<tr>
<td>12</td>
<td>i-PrOH</td>
<td>89</td>
<td>85</td>
</tr>
</tbody>
</table>

\(^a\) Yields of isolated products.

\(^b\) Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column.
The absolute configuration (R) was determined by comparing with the literature values.210

3.3.4. Catalyst loading, ligand ratio and temperature effects

The impacts of other parameters like the ratio between ligand (R)-161 and CuCl, the catalyst loading, and the temperature in the asymmetric catalytic process were further explored (Table 15).

Typically, lowering the reaction temperature from r.t. to 0 °C was believed to result in improvement in the catalyst system’s enantioselectivity according to the previous reports.118,123-125,130,219,220 (R)-124 of higher enantioselectivity and comparable yield were obtained by (R)-161/CuCl catalyst system when the temperature was decreased from r.t. to 0 °C (Table 15, entry 2 vs entry 1). Thus in the optimization of other factors, the asymmetric nitroaldol reactions were performed at 0 °C.

Keeping the amount of ligand (R)-161 constant at 10 mol% (with respect to aldehyde 39), the amount of copper salt was changed gradually from 5 to 10, 15 and 20 mol% (Table 15, entries 2-5), and a range of (R)-161/CuCl ratios (from 1:1 to 1:2, 1:1.5 and 2:1) were achieved for examination. The results showed a tremendous decrease in the reaction rate, affording the β-nitro alcohols (R)-124 less than half even after extending the reaction time. The optimal ratio between ligand (R)-161 and copper source is clearly 1:1 (Table 15, entry 2).

Using the optimal ratio of these two substances, further attempts to decrease the catalyst loading from 10 mol% to 5 mol% afforded the final product (R)-124 in prominent lower yield (20%) and lower ee (80% ee) (Table 15, entry 6 vs entry 2), whereas when doubling
the catalyst loading, the reaction rate was increased and the final product \((R)-124\) with lower \(ee\) was afforded (Table 15, entry 7 vs entry 2). Therefore, the most reasonable loading of \((R)-161/\text{CuCl}\) catalyst system was 10 mol\% and 10 mol\%, respectively (Table 15, entry 2).

**Table 15** Screening of the ratio of \((R)-161\) to \(\text{CuCl}\), catalyst loading and temperature in the asymmetric nitromethane addition to benzaldehyde

\[
\begin{align*}
\text{Benzenesulfonyl chloride} & \quad \text{Chloroform} & \quad \text{CuCl} & \quad (R)-161 & \quad (R)-124 \\
\text{39} & \quad \text{20 equiv} & \quad i & \quad \text{Yield}^a (\%) & \quad \text{ee}^{b, c} (\%)
\end{align*}
\]

**Conditions**: i. \((R)-161\), \(\text{CuCl}\), \((i-\text{Pr})_2\text{O}\) (1.5 ml)

<table>
<thead>
<tr>
<th>Entry</th>
<th>CuCl (mol%)</th>
<th>((R)-161) (mol%)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield(^a) (%)</th>
<th>ee(^{b, c}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>10</td>
<td>r.t.</td>
<td>20</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>20</td>
<td>65</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>10</td>
<td>0</td>
<td>40</td>
<td>35</td>
<td>82</td>
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<td>4</td>
<td>15</td>
<td>10</td>
<td>0</td>
<td>40</td>
<td>29</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>40</td>
<td>18</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>40</td>
<td>20</td>
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<td>20</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>8(^d)</td>
<td>5</td>
<td>10</td>
<td>r.t.</td>
<td>20</td>
<td>80</td>
<td>70</td>
</tr>
</tbody>
</table>
3.3.5. Scope of (R)-161 in the enatioselective Henry reaction

With the optimal reaction conditions (Table 15, entry 2) now in hand, the substrate scope of the asymmetric Henry reaction was then evaluated. A representative selection of aldehydes of a wide scope including aliphatic, conjugated, heteroaromatic and aromatic ones were investigated by treatment with nitromethane in the presence of 10 mol% (R)-161/CuCl (1:1) complex in (i-Pr)₂O at 0 °C, producing the corresponding β-nitroalaldol adducts in moderate to excellent yields (45-99%) and enantioselectivities (63-94% ee) (Table 16).

As summarized in Table 16, whether the aromatic aldehydes are electron-poor (Table 16, entries 3-6), electron-rich (Table 16, entries 7-13) or electron-neutral (Table 16, entries 1, 22-24), the reaction proceeded smoothly, affording the desired products in similar yields and enantioselectivities (above 78% ee) using the above catalyst system. It indicated that the substituents’ electronic nature (Table 16, entries 3-6 vs entries 7-13) and position...
(Table 16, entries 4-5, entries 7-9 and entries 11-13) on the phenyl ring have no prominent effect on the reactivities and enatioselectivities. However, the most strong electron-withdrawing group (nitro substituent) was one exception, yielding the expected nitroaldol adduct (R)-143 with only 64% ee (Table 16, entry 2). The higher reaction rate than other aromatic aldehydes’ was probably the reason for that low enantiomeric excess value. Most remarkably, aliphatic straight chain aldehydes of different lengths (Table 16, entries 14-18), branched (Table 16, entries 19-20) and steric hindrance (Table 16, entry 21) could also smoothly undergo catalytic enantioselective addition of nitromethane, affording respective nitroalcohols with high yields (75-99%) and excellent ees (ranging from 90% to 94%). The higher yields for aliphatic aldehydes are presumably due to their inherently higher activities. In all the examined cases (Table 16), no aldol side reactions or dehydration were observed.

**Table 16 Scope of (R)-161/CuCl in the asymmetric Henry reaction**

![Chemical structure](image)

\[ \text{R}^\text{H} \text{O} \text{R} \text{OH} \text{NO}_2 + \text{CH}_3\text{NO}_2 \xrightarrow{i} \text{R}^\text{(R)} \text{OH} \text{NO}_2 \]

20 equiv

**Conditions**: i. (R)-161 (0.1 equiv), Cu(I)Cl (0.1 equiv), (i-Pr)\(_2\)O (1.5 ml), 0 °C

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Chapter 3

Results and Discussion

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3.3.6. Proposed Mechanism

The mixture of ligand (R)-161 and copper salt in a 1:1 ratio (the optimal ratio) was dissolved in CH₂Cl₂, and the resulting yellow solution was tested by mass spectrometry, the observed major molecular ion peaks at m/z 611 (molecular formula C₃₈H₃₆CuN₄ = 2 × (R)-161 + Cu) and at m/z 613 (molecular formula C₃₈H₃₆CuN₄ = 2 × (R)-161 + Cu + 2H⁺) proved the presence of copper complex in a 2:1 ratio of (R)-161 to CuCl. A proposed
transition state model is shown in Figure 23, nitromethane was deprotonated to the active nitronate in this copper (I) transition state. In the process of asymmetric induction, the two reaction patterns were simultaneously binding to this copper complex, the $Si$ face of the carbonyl center is favored in accordance with previously discussed steric bulkiness and electronic considerations.$^{12,13}$

![Figure 23](image)

The Non-linear effects for this substoichiometric Henry reaction of nitromethane with benzaldehyde $39$ using BIQ $(R)$-161 with copper(I) chloride was examined in Table 18.

**Table 18 The non-linear effects under 1:1 ratio of $(R)$-161/Cu(I)Cl in the enantioselective Henry reaction**

$$\text{PhCH}_2\text{O} + \text{CH}_3\text{NO}_2 \xrightarrow{i} \text{PhCH}_2\text{OH}$$(R)-124

**Conditions:** i. $(R)$-161 (0.1 equiv), Cu(I)Cl (0.1 equiv), (i-Pr)$_2$O (1.5 ml), 0 °C
Kagan et al. simplified the ML$_2$ system assuming ligands are distributed in statistical mode, and derived equation (2) to express enantiomeric excesses of product ($ee_{prod}$) as a function of ligands' enantiopurity ($ee_{cat}$).\textsuperscript{213} In equation (2), two basic parameters were introduced: $g$ represents reactivities of hetero complexes (ML$_R$L$_S$) over homochiral complexes (M(L$_R$)$_2$) ($g = k_{RS}/k_{RR}$), while $ee_o$ defines the enantiomeric excesses of product.

<table>
<thead>
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<th>Entry</th>
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<th>% ee Product, (R)-124\textsuperscript{a}</th>
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</table>

\textsuperscript{a} Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column. The absolute configuration (R) was determined by comparison with the literature values.\textsuperscript{132}
by using enantiopure homochiral $\text{M(L}_R)_2$ complexes (Table 18, entry 11). The meso complex $\text{ML}_R\text{L}_S$ were assumed no additional stereoisomers involving the metal center, affording only racemic product.

\[
\text{ee}_{\text{prod}} = \text{ee}_o \times \text{ee}_{\text{cat}} \times \frac{2}{1 + g + (1 - g)\text{ee}_{\text{cat}}} \]

(2)

The final computer-drawn curve calculated by Kagan’s $\text{ML}_2$ model system was fitting well with collected experimental data, and the standard deviation (S) is 0.0291857 (Figure 24).

![Figure 24](image-url)
The observed positive non-linear effect indicated the existence of less catalytically active heterochiral species. This could be evidence for the effective catalytic system in the process of enantioselective Henry reaction is comprising of \((R)\)-161 and CuCl in 2:1 ratio.\(^{212-215,217}\)

In conclusion, the reactivities and selectivities of chiral 1,2-BIQ 29 based derivatives in the Henry reaction were examined. Chiral \(N\)-methyl-C\(_1\)-tetrahydro-1,1’-bisisoquinoline \((R)\)-161 proved to be the most effective ligand in the copper (I)-catalyzed Henry reaction. The desired nitroaldol adducts were obtained in excellent yields (up to 99\%) and enantioselectivities (up to 94\% ee) with a broad range of aromatic and aliphatic aldehydes. Nonlinear effects have been studied, the results fit well with the Kagan’s ML\(_2\) model system. 

(\textit{Part of this section has been published in Eur. J. Org. Chem. 2011, 4892-4898, reuse and reprint in this section are under formal permission.})

**3.4. Diastereoselective Henry reaction catalyzed by BIQ \((R)\)-29 and its alkyl derivatives \((R)\)-161-164**

In the past two decades, a number of reports uncovered various metal-based catalysts, organocatalysts, and biocatalytic approaches for the asymmetric Henry reaction using nitromethane.\(^{105,119,120,184,221-224}\) However, those methods have not been examined
thoroughly or do not work with other nitroalkanes, the highly diastereo- and enantiocontrol versions of Henry reaction of other nitroalkanes still remain a challenging task.\textsuperscript{107,119} Since the first report of a syn-selective Henry reaction by Shibasaki \textit{et al.} in 1995,\textsuperscript{130,131} some other syn-diastereoselective catalyst systems such as guanidinium-thiourea,\textsuperscript{225,226} bisimadozoline,\textsuperscript{227} bisoxazolidine,\textsuperscript{139,228} brucine,\textsuperscript{109} and diamines\textsuperscript{142,149,166,229} have successfully achieved the transformation while fewer examples for the \textit{anti}-diastereoselective version\textsuperscript{111,112,129,230} has been reported. Two distinctive transition state models have been proposed: the chelation model which offers \textit{syn} products and the nonchelation one that prefers \textit{anti}-selectivity.\textsuperscript{231} Some clear limitations still remained in the diastereoselective Henry reaction like the narrow scope of aldehyde, low reaction temperatures, high catalyst loading, and long reaction times.\textsuperscript{119}

The development of novel chiral catalysts for diastereoselective (especially the \textit{anti}-selective version) Henry reaction is highly desirable. As previously discussed in this chapter, excellent results for the enatioselective Henry reaction between a wide range of aldehydes and nitromethane were obtained. Therefore, it was logical that we extend the application of these ligands such as \((R)-161-164\) (Figure 25) to the diastereoselective Henry reaction with nitroalkanes other than nitromethane.

![Figure 25](image_url)
3.4.1. Ligand and copper source effects

Effective alkylated BIQs \((R)-161-164\) and parent BIQ \((R)-29\) (Figure 25) with different levels of steric bulkiness were screened for the asymmetric Henry reaction between nitroethane and benzaldehyde \(39\), and the results are summarized in Table 19. In all cases, \textit{anti} nitroalcohols were obtained predominantly when using the above BIQs under the optimized reaction conditions (10 mol\% ligand, 10 mol\% CuCl in disopropyl ether, r.t., 48h) which was developed for the Henry reaction using nitromethane. Table 19 shows that ligands \((R)-161-164\) bearing different alkyl groups afforded the final desired product \(183\) in a little higher diastereoselectivity than the parent BIQ \((R)-29\) (Table 19, entries 2-5 \textit{vs} entry 1). BIQ \((R)-161\) with the smallest \(N\)-alkyl attachment (methyl group) was confirmed to be the most effective ligand with 64\% yield, an \textit{anti/syn} diastereoselectivity of 2:1 and \textit{ee} values of 72:78, respectively (Table 19, entry 2) while similar diastereoselectives but lower yields and enantioselectivities were achieved in the presence of other ligands \((R)-161-164\) with bigger substituents (Table 19, entries 3-5).

Using the most efficient ligand \((R)-161\), some other copper (I) and copper (II) sources were tested under the same reaction conditions (Table 19, entries 6-10). Both copper (I) and copper (II) sources yielded the expected products \(183\) in comparable diastereoselectivities, however, the copper (I) salts are superior to copper (II) ones in terms of enantioslectivities (Table 19, entries 2, 6-8 \textit{vs} entries 9-10). Among these different Cu(I) sources, CuCl was clearly the best choice for this asymmetric transformation when considering reactivity, stereoselectivity and enantioselectivity (Table 19, entry 2 \textit{vs} entries 6-8). Therefore, the optimal catalyst system formed by \((R)-161\) and
copper (I) chloride was adopted for the further screening process of diastereoselective Henry reaction (Table 19, entry 2).

Table 19 Screening of ligands (R)-29, (R)-161-164 and copper sources for the diastereoselective Henry reaction

\[
\begin{align*}
\text{Conditions:} & \quad i. \text{Ligand (0.1 equiv), Copper Salts (0.1 equiv), (i-Pr)\text{O} (1.5 ml), r.t., 48h} \\
& \quad 39 \text{ 20 equiv} \quad 183
\end{align*}
\]

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<tr>
<th>Entry</th>
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<th>Copper source</th>
<th>Yield (%)(^a)</th>
<th>anti/syn(^b)</th>
<th>ee (%)(^c)</th>
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<td>64:70</td>
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<td>CuCl</td>
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<td>2.0:1</td>
<td>72:78</td>
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<td>Cu(OAc)(_2)</td>
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<td>1.7:1</td>
<td>44:47</td>
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</table>

\(^a\) Yields of isolated products.

\(^b\) Determined by \(^1\)H NMR analysis and HPLC using Chiralpak AD-H column.

\(^c\) Enantiomeric excesses values were determined by HPLC using Chiralpak AD-H column.\(^{232}\)
3.4.2. Solvent effects

Subsequently, the effects of different types of solvents (e.g. dioxane, THF, CH₂Cl₂, EtOH, CH₃CN and toluene) were tested in the asymmetric Henry reaction using nitroethane. All the reactions were carried out smoothly by the use of (R)-161/CuCl, the results from Table 20 indicated ether-type THF solvent was the most optimal solvent of choice (Table 20, entry 3), the nitroaldol adducts 183 of acceptable yields (65%) were produced in the highest anti/syn stereoselectivity (up to 2.6:1) and the highest ee values of both products (83% ee and 90% ee, respectively). Protic solvent EtOH was found to afford the final product β-nitro alcohols 183 in the lowest anti/syn ratio (1.3:1), while the highest yield (up to 89%) was achieved (Table 20, entry 5). Moreover, the reactions were significantly slowed down in the CH₃CN or toluene solution, due to the lack of proper solubility with the formed copper complex (R)-161/CuCl (Table 20, entries 6-7).

Therefore, the following optimized of reaction conditions would be performed in THF solution by the catalyst system (R)-161/CuCl (Table 20, entry 3).

Table 20 Screening of solvents for the diastereoselective Henry reaction using ligand (R)-161

<table>
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<th>Solvent</th>
<th>Yield (%)</th>
<th>Anti/syn</th>
<th>ee (%)</th>
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<tr>
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<td>20 equiv</td>
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<tr>
<td>183</td>
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</table>

Conditions: i. (R)-161 (0.1 equiv), CuCl (0.1 equiv), solvent (1.5 ml), r.t., 48h
3.4.3. Catalyst loading, ratio effects

Next, the optimization process for the diastereoselective nitroaldol reaction was focused on the impacts of catalyst loading and ratio between ligand \((R)\text{-}161\) and CuCl (Table 21). The amount of CuCl was changed gradually while the amount of ligand \((R)\text{-}161\) was kept constant at 10 mol%, and the resulting different ratios of \((R)\text{-}161/\text{CuCl}\) showed a remarkable decrease in the yields of nitroalcohols 183 and comparable stereoselectivity. The catalyst system formed by ligand \((R)\text{-}161\) and copper source (1:1) is notably the most efficient for this diastereoselective Henry reaction (Table 21, entry 2). Surprisingly, the loading of 20 mol% copper source (2 times to the ligand \((R)\text{-}161\)’s amount) resulted in inhibition of the reaction. Applying the optimal ratio between these two substances in the catalytic system, next attempts to change the catalyst loading from 10 mol% to 5 mol% and 20 mol% yielded the expected products 183 in lower stereoselectivities and enantioselectivities (Table 21, entries 5-6 vs entry 2). Hence, the optimal amount of \((R)\text{-}161\)
161/CuCl catalyst system in the diastereoselective nitroaldol reaction was 10 mol% for each compound (Table 21, entry 2).

**Table 21** Screening of catalyst loading and ratios of (R)-161 to CuCl for the diastereoselective Henry reaction

![Chemical reaction image](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio (R)-161/CuCl</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Anti/syn&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
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<td>70</td>
<td>2.3:1</td>
<td>81:80</td>
</tr>
<tr>
<td>2</td>
<td>1:1.0</td>
<td>65</td>
<td>2.6:1</td>
<td>83:90</td>
</tr>
<tr>
<td>3</td>
<td>1:1.5</td>
<td>36</td>
<td>2.2:1</td>
<td>76:83</td>
</tr>
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<td>4</td>
<td>1:2.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>2:2.0</td>
<td>79</td>
<td>2.1:1</td>
<td>61:75</td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.5:0.5</td>
<td>17</td>
<td>2.3:1</td>
<td>84:87</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields of isolated products.

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis and HPLC using Chiralpak AD-H column.

<sup>c</sup> Enantiomeric excesses values were determined by HPLC using Chiralpak AD-H column.<sup>232</sup>

<sup>d</sup> Reaction time is 120 h.

Overall, the optimized reaction conditions were found to be 10 mol% ligand (R)-161 and 10 mol% copper (I) chloride in THF at ambient temperature, and the final product 183 was cleanly achieved in the highest stereoselectivity (2.6:1), and ee values (83% and 90% ee, respectively) with acceptable overall yield (65%).
3.4.4. Scope of (R)-161 in the asymmetric Henry reaction

With the optimal conditions in hand, the scope of Henry reaction using nitroethane and nitropropane was investigated, and the results were summarized in Table 22. For both aromatic and aliphatic aldehydes, the reaction proceeded cleanly to afford the desired nitroaldol products with predominately *anti* diastereoselectivity in good *ee* values and yields. The position of withdrawing or donating substituents on the phenyl ring has little effect on the diastereoselectivity (Table 22, entries 2-8). However, substrates with electron donating groups showed higher *ees* than the ones with electron withdrawing groups (Table 22, entries 2-5 vs entries 6-8). For the addition of nitroethane or nitropropane to aliphatic aldehydes, good yields and excellent *ee* values (up to 81% and 91%) were obtained even with relatively lower diastereoselectivities (Table 22, entries 10-14).

**Table 22 Scope of (R)-161/CuCl in the diastereoselective Henry reaction with nitroethane/nitropropane**

\[
\begin{align*}
\text{Conditions:} & i. \ (R)-161 \ (0.1 \text{ equiv}), \ CuCl \ (0.1 \text{ equiv}), \ THF \ (1.5 \text{ ml}), \ r.t. \\
R' &= H; \ R' = CH_3
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)*</th>
<th><em>Anti/syn</em>%</th>
<th><em>ee</em>%</th>
</tr>
</thead>
<tbody>
<tr>
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</table>
Chapter 3

Results and Discussion

1. 

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1.  

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<tr>
<td>O</td>
<td>H</td>
<td>39</td>
<td>O</td>
<td>H</td>
<td>48 65 2.6:1 83:90</td>
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2. 

<p>| | | | | | |</p>
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<td>O</td>
<td>H</td>
<td>126</td>
<td>O</td>
<td>H</td>
<td>48 95 1.5:1 50:66</td>
</tr>
</tbody>
</table>

3. 

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</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>184</td>
<td>O</td>
<td>H</td>
<td>48 80 2.1:1 72:86</td>
</tr>
</tbody>
</table>

4. 

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</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>187</td>
<td>O</td>
<td>H</td>
<td>48 83 1.5:1 63:86</td>
</tr>
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</table>

5. 

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</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>188</td>
<td>O</td>
<td>H</td>
<td>48 85 1.6:1 61:87</td>
</tr>
</tbody>
</table>

6. 

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</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>131</td>
<td>O</td>
<td>H</td>
<td>96 75 1.7:1 85:91</td>
</tr>
</tbody>
</table>
Chapter 3

Results and Discussion

1. 

\[
\begin{align*}
&\text{7} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & 96 & 65 & 1.6:1 & 77:87 \\
& 132 & 190
\end{align*}
\]

2. 

\[
\begin{align*}
&\text{8} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & 96 & 70 & 1.6:1 & 75:92 \\
& 133 & 191
\end{align*}
\]

3. 

\[
\begin{align*}
&\text{9} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & 48 & 70 & 0.8:1 & 40:75 \\
& 140 & 192
\end{align*}
\]

4. 

\[
\begin{align*}
&\text{10} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & 48 & 81 & 1.3:1 & 90:89 \\
& 138 & 193
\end{align*}
\]

5. 

\[
\begin{align*}
&\text{11} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & 48 & 80 & 1.3:1 & 90:91 \\
& 175 & 194
\end{align*}
\]

6. 

\[
\begin{align*}
&\text{12} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & 48 & 79 & 1.1:1 & 85:87 \\
& 138 & 195
\end{align*}
\]

7. 

\[
\begin{align*}
&\text{13} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H}
\end{array} & 48 & 77 & 1.1:1 & 86:89 \\
& 172 & 196
\end{align*}
\]
Henry reaction is known to be reversible and the obtained nitroalcohols are easily epimerized on the carbon connecting to the nitro group. Herein, the further cross-over and time-course studies on the stereochemistry of reaction were conducted.

In the cross-over reaction, treatment of a THF solution of nitroaldol adducts anti-183 and syn-183 with (R)-161/CuCl (10 mol%, 1:1) and MeNO₂ (20 mol%) resulted in the formation of benzaldehyde 39 and 1-phenyl-2-nitroethanol 123 along with anti-183 and syn-183. This result confirmed the occurrence of retro-Henry reaction. Under the optimal reaction conditions utilized, we observed that reaction time greatly affects anti:syn ratio of the nitroaldol products (Table 23, Figure 26), further confirming the retro-Henry reaction. As clearly seen from entries 1-4 (Table 23), the amount of the more thermodynamically stable anti-183 gradually decreases as the reaction proceeds and then equilibrates with the syn-183 (Table 23, entries 4-9).⁰¹³¹,¹³³ There is probably a competing kinetic vs. thermodynamic control in Henry reaction. Reaction was allowed for the formation of the more dominant and stable thermodynamically anti-183 along with the kinetically syn-183, it was a thermodynamic control. As the reaction proceeded over

---

| 14 | 175 | 48 | 73 | 1.3:1 | 86:90 |

\(^a\) Yields of isolated products.


\(^c\) Enantiomeric excess values were determined by HPLC using Chiralcel OD-H, OJ-H, Chiralpak AD-H, AS-H columns.¹²⁹,¹⁴⁶,¹⁶³,²³²

\(^d\) Reaction time is 96 h.
time, the kinetically syn-183 equilibrates with the thermodynamically stable anti-183 as a result of retro-Henry reaction and an equilibrium was established after around 30 h (Figure 26). After 62.5 h, the anti-183 slowly conversed to the syn-183 (Table 23, entries 7-9). Furthermore, the ee values of the anti- and syn-nitroalcohols are similar but with a slight bias towards the syn-product as shown in Table 22, indicating the probability of in-situ epimerization of the anti-183 adduct to the syn-183 adduct.131,230,234

Table 23 Time-course studies of diastereoselective Henry reaction of benzaldehyde with EtNO₂ catalyzed by (R)-161/CuCl.

| Entry | Time (h) | anti-183/syn-183₁³
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>3.7:1</td>
</tr>
<tr>
<td>2</td>
<td>14.5</td>
<td>3.0:1</td>
</tr>
<tr>
<td>3</td>
<td>23.5</td>
<td>2.7:1</td>
</tr>
<tr>
<td>4</td>
<td>31.5</td>
<td>2.6:1</td>
</tr>
<tr>
<td>5</td>
<td>48.5</td>
<td>2.6:1</td>
</tr>
<tr>
<td>6</td>
<td>55.5</td>
<td>2.6:1</td>
</tr>
<tr>
<td>7</td>
<td>62.5</td>
<td>2.6:1</td>
</tr>
<tr>
<td>8</td>
<td>80.5</td>
<td>2.5:1</td>
</tr>
</tbody>
</table>

Conditions: i. (R)-161 (0.1 equiv), Cu(I)Cl (0.1 equiv), THF (1.5 ml), r.t.
In conclusion, *N*-methyl BIQ (**R**)\textperiodcentered**161** was an efficient ligand in the copper (I) catalyzed diastereoselective Henry reaction of nitroethane and nitroprane, the expected nitroaldol adducts were obtained in excellent yields (up to 95%), moderate diastereoselectivities and good enantioselectivities (up to 92% *ee*). Cross-over and time-course studies suggest competition between the kinetically and thermodynamically controlled products.

(Part of this section has been published in *Tetrahedron: Asymmetry* **2011**, 22, 2065-2070, reuse and reprint in this section are under formal permission.)
Chapter 4. Organocatalytic Henry Reaction by BIQs

Application of organocatalysts in various reactions has witnessed an exponential increase due to the many advantages it offers over traditional metal-based catalysis. Nitrogen-based chiral organocatalysts such as prolines, imidazolidinones, guanidine, cinchona alkaloids, triazolium salts, urea and thioureas have seen numerous applications in asymmetric catalysis. While successful applications of BIQs as ligands for metal catalyzed reactions have been reported, their use as organocatalysts has not been documented. Given our experience in this area, it was logical to explore the applications of BIQs as organocatalysts in Henry reaction. Due to the limited number of successful organocatalysts for the asymmetric Henry reaction, there is a strong emphasis to develop robust organocatalysts with wide substrate scope that can overcome formation of the by-products due to dehydration, aldol condensation or Cannizzaro reactions. Such emphasis requires the basic understanding of the factors that control reactivity and selectivity to be considered during the design of the catalyst.

In this Chapter, the abilities of selected BIQs rac-23, 27, rac-29, 31, 32, rac-35, rac-36, rac-98, 101, rac-112, rac-120, 121-122 and rac-124 (Figure 27) to function as organocatalysts were explored for the first time. Of particular interest in this work is to examine the effect of nitrogen type (sp$^3$ vs sp$^2$) and their dispositions (1,2 vs 1,3) on the efficiency in Henry reaction, and to understand what type of N,N-organocatalyst (e.g. diamines, diimines or amine-imine) is more effective.

BIQs rac-23, 27, rac-29, 31, 32, rac-35, rac-36, rac-98, 101, rac-112, rac-120, 121-122 and rac-124 (Figure 27) were prepared according to literature procedure (Chapter 2,
Section 2.1, 2.3, 2.4). The first six BIQs (BIQs [a]) all have electron donating methoxy groups that enhance the basicity of its nitrogens through electron donation via its aromatic rings. The nitrogens in BIQs [a] and BIQs [b] are in 1,2-disposition while they are 1,3-diposed in BIQs [c]. The greatest disparity can be seen when comparing BIQs [a] and BIQs [c] since BIQ [a] is a representative of activated 1,2-\(N,N\)-ligand (with electron-donating group—methoxy group) while BIQs [c] is a representative of unactivated 1,3-\(N,N\)-ligand. Within each group of BIQs [a]-[c], there are distinct variations (degree of saturation, type of nitrogen, presence of substituents on the nitrogen and symmetry) to further elucidate the structural effects on the efficiency of these organic bases.
4.1. BIQ Screening in organocatalysis of Henry Reaction

Initially, the efficiencies of BIQs [a]-[c] were examined in the more challenging and less explored Henry reaction between α-ketoesters (ethyl pyruvate 198) and CH$_3$NO$_2$ (Table 24). The reaction was performed using 10 mol% BIQ and 20 equiv. CH$_3$NO$_2$ in THF at r.t. for 24 h. Under these condition, all BIQs gave the expected β-nitroalcohol adduct 199 cleanly. When we compare BIQs [a] (Table 24, entries 4 and 5) and BIQs [b] (Table 24, entries 9 and 10, respectively) as examples of 1,2-\(N\),\(N\)-ligands vs BIQs [c] (Table 24, entries 12 and 13, respectively) as examples of 1,3-\(N\),\(N\)-ligands we can observe a decreasing trend in the yield of 199 suggesting the superiority of 1,2-\(N\),\(N\)-ligands over 1,3-\(N\),\(N\)-ligands for this reaction. Among BIQs [a], BIQs rac-36 and rac-35 gave the highest yields (88% and 78%, respectively) due to their higher basicities which allowed them to deprotonate nitromethane effectively to form the required nucleophile – the nitronate. Similar trend was also observed in cases of BIQs [b] where BIQs rac-29 and rac-23 gave the highest yields (95% and 82%, respectively). This trend was further supported by the results obtained using BIQs [c] where BIQ rac-98 gave the highest yield of 69%. Interestingly, the BIQs with one sp$^3$ nitrogen (amine-imine type) gave better yields of rac-199 than BIQs with two sp$^3$ nitrogens (diamines) (Table 24, entry 4 vs entry
5 and entry 8 vs entry 9). This indicated the superiority of $C_1$- over $C_2$-BIQs.

Overall, BIQ rac-29 was identified as the most efficient catalyst and its scope in Henry reaction was further explored using different esters and aldehydes (Table 24).

**Table 24 Screening of bisisoquinoline organocatalysts**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bisisoquinoline</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>121</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>53</td>
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<tr>
<td>4</td>
<td>36</td>
<td>88</td>
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<td>5</td>
<td>35</td>
<td>78</td>
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<tr>
<td>6</td>
<td>124</td>
<td>66</td>
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<tr>
<td>7</td>
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<td>40</td>
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<td>8</td>
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<td>95</td>
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<tr>
<td>9</td>
<td>23</td>
<td>82</td>
</tr>
<tr>
<td>10</td>
<td>120</td>
<td>68</td>
</tr>
</tbody>
</table>

**Conditions:** i. BIQs (0.1 equiv), THF (1.5 ml), r.t., 24h
4.2. Scope of BIQ rac-29 in the organocatalysis of Henry reaction

Aromatic (Table 25, entries 1 and 2), and aliphatic (Table 25, entries 3-6) α-ketoesters reacted smoothly with CH$_3$NO$_2$ to give the corresponding β-nitro-α-hydroxyesters in excellent isolated yields ranging from 85% to 99%. Likewise, aromatic and aliphatic aldehydes reacted smoothly with CH$_3$NO$_2$ to give the expected β-nitro-α-hydroxyesters. In the case of aromatic aldehydes, the type (electron donating/withdrawing) and position of the substituents on phenyl ring were found critical for high yields. Aromatic aldehydes with electron-withdrawing groups gave better yields in comparison to those with electron-donating groups (Table 25, entries 8-12 vs 13-15) especially when the substituent was on the para- or ortho-position. Moreover, aliphatic, heteroaromatic and conjugated aldehydes (Table 25, entries 16-21, 22 and 23, respectively) also reacted with CH$_3$NO$_2$ smoothly to give the corresponding β-nitro-α-hydroxyesters in excellent yields.

Table 25 Henry reaction of nitromethane catalyzed by BIQ rac-29

<table>
<thead>
<tr>
<th>R$_1$ R$_2$</th>
<th>O</th>
<th>CH$_3$NO$_2$</th>
<th>i</th>
<th>OH R$_1$ R$_2$ NO$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R$_1$ R$_2$</td>
<td>20 equiv</td>
<td>i</td>
<td>R$_1$ R$_2$ NO$_2$</td>
</tr>
</tbody>
</table>

Conditions: i. BIQ rac-29 (0.1 equiv), THF(1.5 ml), r.t., 24h

*a* Isolated yield.
## Results and Discussion

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td>2</td>
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<td><img src="image" alt="Product 207" /></td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 198" /></td>
<td><img src="image" alt="Product 199" /></td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Substrate 202" /></td>
<td><img src="image" alt="Product 208" /></td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Substrate 203" /></td>
<td><img src="image" alt="Product 209" /></td>
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<td><img src="image" alt="Substrate 39" /></td>
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<td><img src="image15" alt="Structure 15" /></td>
<td><img src="image16" alt="Structure 16" /></td>
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<td><img src="image15" alt="Structure 15" /></td>
<td><img src="image16" alt="Structure 16" /></td>
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</tbody>
</table>
Next, we examined the efficiency of BIQ rac-29 in the diastereoselective Henry reaction (Table 26). All α-ketoesters (Table 26, entries 1 and 2), aromatic aldehydes (Table 26, entries 3-6), aliphatic aldehydes (Table 26, entries 7-9), heteroaromatic aldehyde (Table 26, entry 10) and α,β-unsaturated aldehyde (Table 26, entry 11) were found to react with EtNO₂ smoothly to give the corresponding nitroaldol adducts in excellent yields (87-99%). However, the diastereoselectivity of all the products was moderate and the best syn/anti selectivity of 2:1 was obtained in case of 2-furylaldehyde (Table 26, entry 10).

Table 26 Henry reaction of nitroethane catalyzed by BIQ rac-29

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>syn/anti&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="159.png" alt="Image" /></td>
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</tr>
<tr>
<td>23</td>
<td><img src="142.png" alt="Image" /></td>
<td><img src="160.png" alt="Image" /></td>
<td>87</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield.

**Conditions:** i. BIQ 29 (0.1 equiv), THF(1.5 ml), r.t.
Chapter 4

Results and Discussion

<table>
<thead>
<tr>
<th></th>
<th>Structure 1</th>
<th>Structure 2</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
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<td><img src="image1" alt="Structure 1" /></td>
<td><img src="image2" alt="Structure 2" /></td>
<td>48</td>
<td>1.70/1</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Structure 1" /></td>
<td><img src="image4" alt="Structure 2" /></td>
<td>48</td>
<td>1.91/1</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Structure 1" /></td>
<td><img src="image6" alt="Structure 2" /></td>
<td>24</td>
<td>1.23/1</td>
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<td>1.54/1</td>
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<tr>
<td>6</td>
<td><img src="image11" alt="Structure 1" /></td>
<td><img src="image12" alt="Structure 2" /></td>
<td>72</td>
<td>1.80/1</td>
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<tr>
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<td><img src="image13" alt="Structure 1" /></td>
<td><img src="image14" alt="Structure 2" /></td>
<td>48</td>
<td>1.20/1</td>
</tr>
</tbody>
</table>
4.3. Basicity of BIQ rac-29

The basicity of BIQ rac-29 was examined since the BIQs employed here effectively acted as organic bases to generate the nitronate nucleophile. The basicity of BIQ rac-29 was estimated by competitive NMR studies with hexafluorophosphate salt of proton sponge 218 in deuterated acetonitrile. The proton exchange between the free BIQ rac-29 base and hexafluorophosphate salt 219 was relatively slow on the NMR timescale (Scheme 67).

---

\(^{a}\) Determined by crude \(^1\)H NMR analysis.

\(^{b}\) Isolated yield.
Different molar ratios between BIQ \( \textit{rac-29} \) and hexafluorophosphate salt \( \textit{219} \) were adopted to test the competitive NMR studies. According to equations (3)-(4), the \( pK_{\text{BH}^+} \) of BIQ \( \textit{29} \) was determined to be \( 16.8 \pm 0.7 \) by equation (3)-(4).\(^{240}\)

\[
K = \frac{[\text{BIQ-PF}_6]}{[\text{Proton sponge}]} \frac{[\text{Proton sponge-PF}_6]}{[\text{BIQ}]}
\]

\[
pK_{[\text{BIQ}]} = pK_{[\text{proton sponge}]} + \log K
\]

In conclusion, both \( C_1 \)- and \( C_2 \)-symmetric BIQ acted as organocatalysts and successfully catalyzed Henry reaction where addition of nitroalkanes to \( \alpha \)-ketoesters and aldehydes proceeded cleanly under mild conditions. \( C_1 \)-symmetric BIQs (amine-imine) proved to be more efficient than \( C_2 \)-symmetric ones (diamines, diimines), \( C_1-1,2,3,4-,\text{-tetrohydro-1,1'}-\text{-bisisoquinolines} \textit{rac-29} \) proved to be the most efficient (up to 99\%). In the diastereoselective Henry reactions, excellent yields and moderate \textit{syn/anti} selectivities (up to 2.0:1) were obtained in the addition of \( \text{EtNO}_2 \) to \( \alpha \)-ketoesters and aldehydes. This study paves the way for application of chiral BIQs as organocatalysts.
4.4. Application of BIQ (R)-29 as organocatalyst in the asymmetric Henry reaction

Application of organocatalysts such as nitrogen based compounds in various reactions has witnessed an exponential increase due to the many advantages it offers over traditional metal-based catalysis.\[171-180,235-237\]

Based results obtained using BIQ rac-29 in the organocatalysis of Henry reaction, application of BIQ (R)-29 as organocatalyst to the asymmetric version of the Henry reaction was tested (Table 27).

**Table 27 Asymmetric Henry reaction of nitromethane catalyzed by (R)-29**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</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>
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<td>0</td>
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<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>95</td>
<td>0</td>
</tr>
</tbody>
</table>

**Conditions:** i. BIQ (R)-29 (0.1 equiv), THF(1.5 ml), r.t., 24h

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Based on the results obtained by the use of (R)-29 in the asymmetric Henry reaction of different substrate, only racemic products were afforded. Considering the mechanism of Henry reaction, the reason for this situation is probably because those bisisoquinoline-based catalysts are unable to forming bonding (e.g. hydrogen bonding, electrostatic interaction) with the acceptor carbonyl oxygen and nitronate group at the same time.
Chapter 5. Experimental

General

All commercial chemicals used in the whole project were obtained from Sigma-Aldrich, Merck, Alfa Aesar, Acros and Fisher Scientific, and were used as received unless otherwise indicated. The anhydrous solvents (including toluene, THF and diethyl ether) used in reaction were freshly taken from PURE SOLV PS-400-5-MD system.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F$_{254}$ precoated silica gel plate (0.2 mm thickness). The products on the TLC plate were visualized under UV light (254 nm) or by using chromogenic agent—solution of anisaldehyde in sulfuric acid EtOH (v/v/v = 2.68/0.5/50). Flash chromatography and column chromatography for purification of compounds were carried out on Merck silica gel 60 (230-400 mesh).

FTIR spectra were recorded in KBr thin film on Perkin-Elmer FTIR system Spectrum BX spectrometer. Melting points were tested by Barnstead Electrothermal 9100 melting point analytical instrument. $^1$H NMR spectra were measured at 300 MHz on a Bruker Advanced DPX 300 spectrometer. Unless otherwise specified, data refer to solutions in CDCl$_3$ with the TMS as internal reference. $^1$H NMR multiplicities were assigned as singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), triplet of doublet (td), quartet (q), multiplet (m) and broad (br). $^{13}$C NMR spectra were measured at 75.47 MHz on a Bruker Advanced DPX 300 spectrometer. C-H (HMBC, HMQC) spectra were also measured on the same apparatus using Bruker automation programs. LC-Mass spectra were recorded on Agilent LC system with
Agilent Mass selective detector. High resolution mass spectra were recorded on Finigan MAT 95*P spectrometer. X-ray single crystal diffraction data were measured on Bruker-AXS Smart Apex CCD single-crystal diffractometer. HPLC separations were performed on Agilent 1100 using Diacel chiralcel OB-H, OD-H, OJ-H and chiraopak AD-H, AS-H chiral columns. The optical rotation values were measured on JASCO P-1020 polarimeter.

5.1. Synthesis of 1,3-BIQs 98

5.1.1. N,N'-bisphenethylmalonamide 100

Diethyl malonate (3.2 mL, 0.021 mol) was added dropwise over a period of 10 minutes to phenethylamine (5.2 mL, 0.042 mol). After the addition, the resulting yellow solution was stirred at 80 °C for two days. In the reaction process, thick yellow solids were generated. After complete reaction (tested by TLC analysis), the yellow solid was separated by a Buckner funnel, washed with hexane (3×10 mL) and dried under reduced pressure. The final N,N'-bisphenethyloxamide 100 was obtained as a fluffy white solid (5.8 g, 89%), m.p. 102-104 °C. FTIR (Nujol) νmax: 3298, 1659, 1633, 1548, 1229, 747, 698, 575 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ: 2.82 (4H, t, J = 7.2 Hz, H2 and H2'), 3.04 (2H, s, H7), 4.16 (4H, t, J = 7.2 Hz, H1 and H1'), 6.93 (2H, br s, 2×NH), 7.17-7.56 (10H, m, H2", H3", H4", H5", H6" and H2"', H3"', H4"', H5"', H6'"). ¹³C NMR (75.6 MHz, CDCl₃) δ: 35.5 (C2 and C2'), 40.9 (C1 and C1'), 43.2 (C7), 126.6 (C4" and C4'"), 128.6 (C2", C6" and C2"', C6'"), 128.7 (C3", C5" and C3"', C5'"), 138.6 (C1" and C1'"), 167.2 (2×CO). Mass (ESI) calcd for C₁₀H₂₂N₂O₂: 310.15, found 311.12 (M+1).
5.1.2. 1,1'-methylene-bis(3,3',4,4'-tetrahydroisoquinoline) 101

POCl$_3$ (3.66 mL, 0.04 mol) was added dropwise over 10 min into a suspension of bisoxamide 100 (1.24 g, 0.004 mol) and P$_2$O$_5$ (5.7 g, 0.04 mol) in toluene (15 mL). After addition was complete, the mixture was heated to reflux overnight with vigorous stirring. The reaction mixture was then cooled to room temperature, the solvent was decanted and saturated NaHCO$_3$ solution (20 mL) was added into the remaining brown solid until bubbling was no longer observed. The yellow mixture was then treated by addition of saturated NaOH solution (25 mL) to adjust pH of the mixture to 10. The resulting alkaline solution was extracted with CH$_2$Cl$_2$ (4 × 30 mL) and the combined organic extracts were washed with brine, dried over MgSO$_4$ and filtered. The solvent was removed under reduced pressure, and the obtained dark brown gum was subjected to column chromatography to afford 1,1'-methylene-3,3',4,4'-tetrahydrobisisoquinoline 101 as brown gum (0.89 g, 81%). FTIR (Nujol) $\nu_{\text{max}}$: 1618, 1311, 1272, 1232, 1029, 746 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.80 (4H, t, $J = 6.6$ Hz, H$_4$ and H$_4'$), 3.60 (4H, t, $J = 6.9$ Hz, H$_3$ and H$_3'$), 5.93 (2H, s, H9), 7.17-7.19 (2H, m, H5 and H5'), 7.25-7.35 (4H, m, H6, H7 and H6', H7'), 7.72-7.77 (2H, m, H8 and H8'). $^{13}$C NMR (75.6 MHz, CDCl$_3$) $\delta$: 28.5 (C4 and C4'), 42.4 (C3 and C3'), 84.9 (C9), 124.6 (C8 and C8'), 126.7 (C5 and C5'), 127.8 (C7 and C7'), 129.2 (C8a and C8'a), 131.5 (C6 and C6'), 137.2 (C4a and C4'a), 157.8 (C1 and C1'). HRMS (ESI) calcd for C$_{19}$H$_{18}$N$_2$: 274.1548, found 275.1553 (M+1).

5.1.3. rac-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) 98

1,1'-methylene-3,3',4,4'-tetrahydrobisisoquinoline 101 (0.89 g, 3.25 mmol) was dissolved in 0.5 M HCl/MeOH solution (10 mL), and the generating brown solution was
Chapter 5

Experimental

Evaporated under reduced pressure to give a dark brown gum. The resulting residue was redissolved in MeOH (6 mL) to afford a dark brown solution which was added dropwise into a stirred suspension of NaCNBH$_3$ (0.35 g, 5.52 mmol) in 3% HCl/MeOH (2 mL) and MeOH (8 mL) solution at room temperature. After addition completion, the generated dark brown solution was stirred vigorously at room temperature for another 0.5 h. Then the solvent was removed under reduced pressure, 10% NaOH solution (20 mL) was added to adjust pH of the above mixture to 11. The alkaline solution was extracted with CH$_2$Cl$_2$ (3 × 15 mL), and the combined organic extracts were washed with brine, dried over MgSO$_4$ and filtered. After solvent removal, the obtained dark brown solid was subjected to be recrystallized from EtOH to afford rac-98 as light-yellow crystals (0.70 g, 77%). m.p. 98-102°C. FTIR (Nujol) $\nu_{\text{max}}$: 3325, 3249, 2923, 2853, 1497, 1453, 1127, 866, 767, 702 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.19 (2H, t, $J = 6.6$ Hz, 2×H9), 2.46 (2H, br s, 2×NH), 2.63-2.72 (2H, m, H$_a$4 and H$_b$4'), 2.76-2.85 (2H, m, H$_a$4' and H$_b$4), 2.19-2.99 (2H, m, H$_a$3', H$_b$3'), 3.18-3.26 (2H, m, H$_a$3 and H$_b$3'), 4.17 (2H, t, $J = 6.6$ Hz, H1 and H1'), 6.98-7.10 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'). $^{13}$C NMR (75.6 MHz, CDCl$_3$) $\delta$: 30.0 (C4 and C4'), 40.9 (C3 and C3'), 42.0 (C9), 52.9 (C1 and C1'), 125.8 (C8 and C8'), 125.9 (C7 and C7'), 126.0 (C6 and C6'), 129.4 (C5 and C5'), 135.5 (C4a and C4'a), 139.7 (C8a and C8'a). HRMS (ESI) calcd for C$_{19}$H$_{22}$N$_2$: 278.1861, found 279.1855 (M+1). $^1$H NMR and $^{13}$C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

5.1.4. Resolution of BIQ rac-98 through diastereomeric salt formation with (L)-(+-)citramalic acid
A mixture of rac-BIQ 98 (1.0 g, 3.5 mmol) and (L)-(+)citramalic acid (1.04 g, 7.0 mmol) dissolved in EtOH/H₂O (1.5/1, v/v, 15 mL) was stirred at 40 °C for 15 min. The resulting yellow solution was allowed to cool down, kept undisturbed at room temperature for several days. In total six batches of crystals were obtained, the first two batches of crystals were combined, washed by cold EtOH and dissolved in a mixture of CH₂Cl₂ (6 mL) and 10% NaOH aqueous solution (10 mL). The two layers were separated and the aqueous one was further extracted with CH₂Cl₂ (3×6 mL). The combined organic extracts were dried over MgSO₄ and filtered. The solvent was then evaporated under reduced pressure to afford (S,S)-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydrobisisoquinoline) (S,S)-98 as a light yellow solid (150 mg, 15%, >99% ee). The next three batches of crystals followed similar work-up procedure, affording (S,S)-98 as yellow solids (240 mg, 24%, 70-80% ee). The sixth batch of crystals was treated in a similar manner, producing (R,R)-98 as a white solid (30 mg, 3%, >99% ee). The remaining mother liquid was dried and treated similarly as mentioned for the above batches to afford (R,R)-98 as a white solid (540 mg, 54%, 40% ee). Melting points, FTIR, ¹H NMR, ¹³C NMR and HRMS spectra of those obtained BIQs 98 were same as those of rac-98. The ees of 99% was determined by HPLC (Chiralcel OD-H column): hexane/IPA/Et₃N = 90/9.9/0.1, 1.0 mL/min, 25 °C, 256 nm, t₁ = 12.12 min for (R,R) and t₂ = 17.72 min for (S,S). \[ \alpha_{D}^{\text{cyclohexane}} = +20.53 \] (c = 1.00, CHCl₃) for (R,R)-98; \[ \alpha_{D}^{\text{cyclohexane}} = -22.94 \] (c = 1.01, CHCl₃) for (S,S)-98.

5.2. Synthesis of racemic derivatives based on BIQ rac-98 and chiral derivatives based on BIQ (S,S)-98

5.2.1. Preparation of racemic derivatives based on BIQ rac-98
Double **N**-Alkyl derivatives

**General Procedure:** Alkyl bromides or alkyl iodides were added into a mixture of BIQ rac-98 and K$_2$CO$_3$ in dry THF under nitrogen atmosphere. The mixture was heated up to reflux and stirred for overnight. The reaction mixture was then cooled down to room temperature, filtered, and the solid was washed with CH$_2$Cl$_2$. The combined organic phases were evaporated under reduced pressure to almost dryness. The residue was allowed to be recrystallized from EtOH or subjected to column chromatography to afford pure double **N**-alkyl derivatives of BIQ rac-98.

5.2.1.1. **N,N’**-dimethyl-1,1’-methylene-bis(1,1’,2,2’,3,3’,4,4’-octahydroisoquinoline) rac-112

BIQ rac-98 (560 mg, 2 mmol) was treated with iodomethane (5 mL) in neat condition, and the reaction mixture was vigorously stirred at 50 °C for 5 h. The volatiles were evaporated under reduced pressure to afford a yellow gum. The resulting gum was then stirred in a mixture of 5 M NaOH (15 mL) aqueous solution and CH$_2$Cl$_2$ (15 mL) for 2 h at room temperature. The organic layer was separated, dried over NaOH (pellets) and filtered. After solvent removal, yellow solids were obtained to be recrystallized from EtOH solution, producing pure **rac-N,N’**-dimethyl-1,1’-methylene-bis(1,1’,2,2’,3,3’,4,4’-octahydroisoquinoline) rac-112 as light-yellow crystals (245 mg, 41%). m.p. 106-109 °C. FTIR (Nujol) $\nu_{\text{max}}$: 2924, 1448, 1378, 1284, 1116, 1031, 775, 743, 609 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 1.84 (2H, apparent t, $J = 7.2$ Hz, 2×H9), 2.40-2.47 (2H, m, H$_a$4 and H$_p$4’), 2.51 (6H, s, 2×CH$_3$), 2.88-2.98 (2H, m, H$_a$4’ and H$_p$4), 2.99-3.05 (2H, m, H$_a$3’,
Hβ3), 3.27-3.36 (2H, m, Hα3 and Hβ3'), 3.91 (2H, t, J = 6.6 Hz, H1 and H1'), 7.00-7.06 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'). 13C NMR (75.6 MHz, CDCl3) δ: 22.5 (C4 and C4'), 42.2 (2×CH3), 44.5 (C3 and C3'), 45.9 (C9), 59.9 (C1 and C1'), 125.5 (C8 and C8'), 125.8 (C7 and C7'), 128.3 (C6 and C6'), 128.7 (C5 and C5'), 134.0 (C4a and C4'a), 139.1 (C8a and C8'a). HRMS (ESI) calcd for C21H26N2: 306.2174, found 307.2166 (M+1). 1H NMR and 13C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

5.2.1.2. N,N'-diethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) rac-113

BIQ rac-98 (560 mg, 2 mmol) was treated with bromoethane (360 μL, 4.4 mmol), following the general procedure mentioned above. The resulting yellow solid was subjected to silica gel column chromatography (EtOAc/Hexane = 1/5), affording pure rac-N,N'-diethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) rac-113 as light yellow solids (490 mg, 73%). m.p. 118-121 °C. FTIR (Nujol) νmax: 2957, 1447, 1379, 1117, 1095, 1035, 768, 743, 616 cm⁻¹. 1H NMR (300 MHz, CDCl3) δ: 1.24 (6H, t, J = 7.2 Hz, 2×CH2CH3), 1.97 (2H, apparent t, J = 6.6 Hz, 2×H9), 2.41-2.50 (2H, m, Hα4 and Hβ4'), 2.66-2.85 (4H, m, 2×CH2CH3), 3.02-3.20 (4H, m, Hα4', Hβ4 and Hα3', Hβ3), 3.36-3.42 (2H, m, Hα3 and Hβ3'), 4.13 (2H, t, J = 6.6 Hz, H1 and H1'), 7.08-7.16 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'). 13C NMR (75.6 MHz, CDCl3) δ: 13.8 (2×CH2CH3), 22.3 (C4 and C4'), 41.5 (C3 and C3'), 46.0 (C9), 46.9 (2×CH2CH3), 57.8 (C1 and C1'), 125.4 (C8 and C8'), 125.7 (C7 and C7'), 128.4 (C6 and C6'), 128.8 (C5 and C5'), 134.4 (C4a and C4'a), 139.8 (C8a and C8'a). HRMS (ESI) calcd
for C\textsubscript{23}H\textsubscript{30}N\textsubscript{2}: 334.2487, found 335.2477 (M+1). \textsuperscript{1}H NMR and \textsuperscript{13}C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

\textbf{5.2.1.3. \textit{N,N'-dibenzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) rac-114}}

BIQ \textit{rac-98} (560 mg, 2 mmol) was reacted with benzyl bromide (523 \textmu L, 4.4 mmol), following the general procedure mentioned above. The resulting yellow solid was subjected to silica gel column chromatography (EtOAc/Hexane = 1/10), affording pure \textit{rac-N,N'-dibenzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) rac-114} as light yellow solids (852 mg, 93%). m.p. 159-161 °C. FTIR (Nujol) \textit{v\textsubscript{max}}: 2951, 2818, 1493, 1450, 1346, 1097, 1023, 744, 698 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \textit{\delta}: 1.87 (2H, apparent t, \textit{J} = 6.6 Hz, 2×H9), 2.27-2.34 (2H, m, H\textalpha\textsubscript{4} and H\beta\textgamma\textsubscript{4}), 2.80-2.98 (4H, m, H\textalpha\textsubscript{4}, H\beta\textgamma\textsubscript{4} and H\textalpha\textsubscript{3}, H\beta\textgamma\textsubscript{3}), 3.13-3.19 (2H, m, H\textalpha\textsubscript{3} and H\beta\textgamma\textsubscript{3}), 3.40 (2H, d, \textit{J} = 13.2 Hz, C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}), 3.66 (2H, d, \textit{J} = 12.9 Hz, C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}), 4.02 (2H, t, \textit{J} = 6.9 Hz, H1 and H1'), 6.96-7.23 (18H, m, H5, H6, H7, H8, H5', H6', H7', H8' and 2×C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}). \textsuperscript{13}C NMR (75.6 MHz, CDCl\textsubscript{3}) \textit{\delta}: 22.2 (C4 and C4'), 40.7 (C3 and C3'), 46.9 (C9), 57.5 (2×C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}), 57.5 (C1 and C1'), 125.6 (C8 and C8'), 126.0 (C7 and C7'), 126.9 (C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}), 128.2 (C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}), 128.3 (C6 and C6'), 129.0 (C5 and C5'), 129.1 (C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}), 134.3 (C4a and C4'a), 139.7 (C8a and C8'a), 140.1 (C\textsubscript{6}H\textsubscript{5}CH\textsubscript{2}). HRMS (ESI) calcd for C\textsubscript{33}H\textsubscript{34}N\textsubscript{2}: 585.2800, found 589.2808 (M+1). \textsuperscript{1}H NMR and \textsuperscript{13}C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.
Mono \(N\)-Alkyl derivatives

**General Procedure:**

Synthesis of piperimidines through condensation of \(rac\text{-}98\) with aldehydes: \(rac\text{-}98\) (560 mg, 2 mmol) was dissolved in EtOH or \(Et_2O\) (10 mL) at r.t., and then the relative aldehyde (2.7 mmol) was added dropwise into the above solution. The resulting mixture was stirred vigorously at room temperature or heated to reflux for a specific time (TLC). After reaction has completed, the mixture was filtered through Celite, then the solvent was removed under reduced pressure and the residue was subjected to column chromatography on silica gel, affording pure piperimidine products \(rac\text{-}103, 116\) and \(118\).

**Reductive cleavage of piperimidines:** Piperimidine compound (0.49 mmol) was dissolved in MeOH, the generated solution was added dropwise into a mixture of NaCNBH\(_3\) (47 mg, 0.75 mmol) and TFA (154 μL, 2 mmol) in MeOH at 0 °C. The reaction mixture was kept stirring for another 1 h at r.t., then quenched with 30% NaOH aqueous solution (10 mL) and extracted by EtOAc (3×8 mL). The obtained organic extracts were dried over MgSO\(_4\), filtered, and the volatile material was evaporated to dryness. The residue was purified by silica gel column chromatography to afford pure mono \(N\)-substituted derivatives \(rac\text{-}115, 117\) and \(119\).

**5.2.1.4. Preparation of \(N\)-methyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) \(rac\text{-}115\)**

*Reaction with formaldehyde:* \(rac\text{-}98\) (560 mg, 2 mmol) reacted with 37% formaldehyde (205 μL, 2.7 mmol, methanol solution) in EtOH solution, and the reaction mixture was heated to reflux for 2 days. Following by the general procedure, yellow solids were
obtained and purified by column chromatography on silica gel (EtOAc/Hexane, 1/1), affording pure piperimidine rac-103 as a light yellow solid (490 mg, 85%). m.p. 116-119 °C. FTIR (Nujol) \( \nu_{\text{max}} \): 1492, 1454, 1361, 1287, 1156, 1093, 1026, 750 cm\(^{-1} \). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 2.57 (2H, t, \( J = 5.7 \) Hz, 2× H9), 2.68-2.75 (2H, m, H\(_\alpha\)4 and H\(_\beta\)4'), 2.91-3.15 (4H, m, H\(_\alpha\)4', H\(_\beta\)4 and H\(_\alpha\)3', H\(_\beta\)3), 3.24-3.31 (2H, m, H\(_\alpha\)3 and H\(_\beta\)3'), 3.73 (2H, s, 2× H10), 3.90-4.05 (2H, m, H1 and H1'), 6.99-7.15 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'). \(^13\)C NMR (75.6 MHz, CDCl\(_3\)) \( \delta \): 26.6 (C4 and C4'), 32.0 (C9), 47.7 (C3 and C3'), 55.6 (C1 and C1'), 69.7 (C10), 125.6 (C8 and C8'), 126.2 (C7 and C7'), 126.3 (C6 and C6'), 129.3 (C5 and C5'), 134.9 (C4a and C4'a), 136.8 (C8a and C8'a). HRMS (ESI) calcd for C\(_{20}\)H\(_{22}\)N\(_2\): 290.1861, found 291.1860 (M+1). \(^1\)H NMR and \(^13\)C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

**Reductive cleavage of piperimidines rac-103**: Following the general procedure above, piperimidine rac-103 (142 mg, 0.49 mmol) was reduced by NaCNBH\(_3\) in acidic MeOH solution, affording pure \( N\)-methyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) rac-115 as light yellow gum (103 mg, 72%). FTIR (Nujol) \( \nu_{\text{max}} \): 3300, 2930, 1675, 1452, 1373, 1200, 1125, 1068, 1026, 745 cm\(^{-1} \). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 2.31-2.33 (2H, m, 2×H9), 2.46-2.47 (3H, m, CH\(_3\)), 2.78-2.89 (6H, m, H\(_\alpha\)4, H\(_\beta\)4, H\(_\beta\)3 and H\(_\alpha\)4', H\(_\beta\)4', H\(_\alpha\)3'), 3.01-3.32 (2H, m, H\(_\alpha\)3 and H\(_\beta\)3'), 3.73-3.80 (1H, m, H1'), 4.08 (1H, s, NH), 4.14-4.18 (1H, m, H1), 7.13-7.20 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'). \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\)) \( \delta \): 24.7 (C4'), 29.9 (C4), 40.5 (C9), 40.8 (C3), 42.2 (CH\(_3\)), 138
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47.0 (C3'), 53.8 (C1), 61.3 (C1'), 125.8 (C8), 125.96 (C7), 125.99 (C7), 126.1 (C6'), 126.2 (C6), 127.4 (C8'), 128.9 (C5'), 129.3 (C5) 134.7 (C4'a), 135.5 (C4a), 137.7 (C8'a), 139.1 (C8a). HRMS (ESI) calcd for C_{20}H_{24}N_2: 292.2018, found 293.2021 (M+1). ^1H NMR and ^13C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

5.2.1.5. Preparation of N-ethyl-1,1'-methylenbis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) rac-117

Reaction with acetaldehyde: rac-98 (560 mg, 2 mmol) reacted with acetaldehyde (151 μL, 2.7 mmol) in Et_2O solution, and the reaction mixture was then stirred vigorously at room temperature for overnight. Following the general procedure, a yellow gum was obtained and purified by column chromatography on silica gel (EtOAc/Hexane, 1/1), affording pure piperimidine rac-116 (483 mg, 80%). FTIR (Nujol) ν_max: 1490, 1452, 1376, 1161, 1074, 1032, 746 cm⁻¹. ^1H NMR (300 MHz, CDCl_3) δ: 1.31 (3H, d, J = 6.0 Hz, CH_3), 2.24-2.29 (1H, m, H9), 2.41-2.46 (2H, m, H9 and H_β^4'), 2.74-2.97 (5H, m, H_α^4, H_β^3 and H_α^4', H_α^3'), 3.12-3.20 (1H, m, H_α^3), 3.27-3.29 (1H, m, H_β^3'), 3.78-3.82 (1H, m, H1), 3.90 (1H, q, J = 7.2 Hz, H10), 4.25-4.35 (1H, m, H1'), 6.90-7.17 (7H, m, H5, H6, H7 and H5', H6', H7', H8'), 7.28 (1H, d, J = 7.2 Hz, H8). ^13C NMR (75.6 MHz, CDCl_3) δ: 18.3 (CH_3), 23.8 (C4'), 29.9 (C4), 31.8 (C9), 37.2 (C3), 47.2 (C3'), 55.4 (C1), 57.1 (C1'), 68.9 (C10), 125.6 (C8), 126.10 (C7'), 126.14 (C7), 126.3 (C6'), 126.5 (C6), 126.7 (C8'), 128.9 (C5'), 129.4 (C5), 134.6 (C4a), 135.9 (C4'a), 136.7 (C8'a), 139.2 (C8a). HRMS (ESI) calcd for C_{21}H_{24}N_2: 304.2018, found 305.2019 (M+1).
$^1$H NMR and $^{13}$C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

Reductive cleavage of piperimidines rac-116: Following the above general procedure, piperidine rac-116 (150 mg, 0.49 mmol) was reduced by NaCNBH$_3$ in acidic MeOH solution, affording pure N-ethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) rac-117 as light yellow gum (105 mg, 70%). FTIR (Nujol) $\nu_{\text{max}}$: 3251, 2930, 1676, 1490, 1452, 1378, 1270, 1200, 1118, 1034, 768, 744 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 0.92 (3H, t, $J = 7.2$ Hz, CH$_2$CH$_3$), 2.05-2.09 (1H, m, H$_9$), 2.16-2.21 (1H, m, H$_9$), 2.40-2.48 (3H, m, CH$_2$CH$_3$ and H$_\beta4'$), 2.65-2.85 (5H, m, H$_\alpha4$, H$_\beta4$, H$_\beta3$ and H$_\alpha4'$, H$_\alpha3'$), 3.14-3.29 (2H, m, H$_\alpha3$ and H$_\beta3'$), 3.70-3.73 (2H, m, H$_1'$ and NH$_N$), 4.11 (1H, d, $J = 7.8$ Hz, H$_1$), 6.91-7.04 (8H, m, H$_5$, H$_6$, H$_7$, H$_8$ and H$_5'$, H$_6'$, H$_7'$, H$_8'$). $^{13}$C NMR (75.6 MHz, CDCl$_3$) $\delta$: 13.4 (CH$_2$CH$_3$), 23.4 (C4'), 30.1 (C4), 41.2 (C9), 41.4 (C3), 42.9 (C3'), 47.0 (CH$_2$CH$_3$), 54.0 (C1), 58.0 (C1'), 125.8 (C8), 125.89 (C7'), 126.04 (C7), 126.0 (C6'), 126.1 (C6), 127.8 (C8'), 129.0 (C5'), 129.3 (C5), 134.7 (C4'a), 135.7 (C4a), 138.4 (C8'a), 139.4 (C8a). HRMS (ESI) calcd for C$_{21}$H$_{26}$N$_2$: 306.2174, found 307.2168 (M+1). $^1$H NMR and $^{13}$C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

5.2.1.6. Preparation of N-benzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) rac-119

Reaction with benzaldehyde: rac-98 (560 mg, 2 mmol) reacted with benzaldehyde (270 $\mu$L, 2.7 mmol) in Et$_2$O solution, and the reaction mixture was stirred vigorously at room
temperature for overnight. Following the general procedure, yellow solids were obtained and purified by column chromatography on silica gel (EtOAc/Hexane, 1/1), affording pure piperimidine *rac-118* as yellow fluffy solids (659 mg, 90%). m.p. 73-76 °C. FTIR (Nujol) $\nu_{\text{max}}$: 1603, 1494, 1453, 1308, 1149, 1124, 1032, 842, 743 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.14 (1H, td, $J = 11.4$, 3.6 Hz, H9), 2.46-2.53 (3H, m, H$_4$, H$_{8'}$, H$_{9'}$), 2.62-2.74 (1H, m, H9), 2.86-2.94 (3H, m, H$_{8'}$, and H$_{9'}$, H$_{3''}$), 3.08-3.17 (2H, m, H$_3$, and H$_{9'}$), 3.64 (1H, d, $J = 11.1$ Hz, H1$'$), 4.30 (1H, s, H10), 4.64-4.72 (1H, m, H1), 7.06-7.49 (11H, m, H$_5$, H$_6$, H$_7$, H$_5'$, H$_6'$, H$_7'$, H$_8'$ and C$_6$H$_5$), 7.62-7.65 (2H, m, H8 and C$_6$H$_5$). $^{13}$C NMR (75.6 MHz, CDCl$_3$) $\delta$: 24.2 (C4$'$), 29.8 (C4), 34.5 (C3), 46.5 (C9), 47.1 (C3$'$), 56.1 (C1), 57.1 (C1$'$), 80.8 (C10), 124.9 (C8), 125.6 (C7), 125.8 (C7$'$), 126.0 (C6$'$), 126.3 (C6), 126.7 (C8$'$), 128.3 (C5), 128.4 (C5$'$), 128.8 (C$_6$H$_5$), 129.1 (C$_6$H$_5$), 129.2 (C$_6$H$_5$), 129.6 (C$_6$H$_5$), 129.8 (C$_6$H$_5$), 135.3 (C4a), 135.7 (C4$'$a), 136.8 (C8$a$), 138.5 (C8a), 140.9 (C$_6$H$_5$). HRMS (ESI) calcd for C$_{26}$H$_{26}$N$_2$: 366.2174, found 367.2158 (M+1). $^1$H NMR and $^{13}$C NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

Reductive cleavage of piperimidines *rac-118*: Following the above general procedure, piperidine *rac-118* (180 mg, 0.49 mmol) was reduced by NaCNBH$_3$ in acidic MeOH solution, affording pure *N*-benzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) *rac-119* as light yellow gum (144 mg, 80%). FTIR (Nujol) $\nu_{\text{max}}$: 3340, 2930, 1651, 1490, 1453, 1360, 1201, 1118, 1023, 972, 743, 699 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 1.97-2.05 (1H, m, H9), 2.39 (1H, apparent
t, \( J = 12 \text{ Hz, H9} \), 2.62-2.70 (1H, m, H\( _{\beta} 4' \)), 2.73-2.89 (4H, m, H\( _{a} 4, H_{\beta} 4, H_{\beta} 3 \) and \( NH \)), 3.05-3.12 (3H, m, H\( _{a} 3 \) and H\( _{a} 3' \), \( H_{a} 4' \)), 3.43-3.60 (1H, m, H\( _{\beta} 3' \)), 3.69-3.81 (3H, m, H\( 1' \) and \( C_6H_5CH_2 \)), 3.87 (1H, dd, \( J = 11.1, 3.0 \text{ Hz, H1} \)), 4.30 (1H, d, \( J = 8.7 \text{ Hz, H1}' \)), 7.08-7.21 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'), 7.31-7.38 (5H, m, \( C_6H_5CH_2 \)).

\( ^{13} \text{C} \) NMR (75.6 MHz, CDCl\( _3 \)) \( \delta \): 23.0 (C\( 4' \)), 30.1 (C4), 41.4 (C3), 42.9 (C9), 43.3 (C3'), 53.1 (C1), 56.8 (C1'), 57.6 (C\( 6H_5CH_2 \)), 125.8 (C8), 125.9 (C7), 126.0 (C7'), 126.2 (C6'), 126.3 (C6), 127.4 (C8'), 128.2 (C5), 128.6 (C5'), 129.28 (C\( 6H_5CH_2 \)), 129.33 (C\( 6H_5CH_2 \)), 129.4 (C\( 6H_5CH_2 \)), 134.3 (C4a), 135.5 (C4'a), 138.3 (C8'a), 139.5 (C8a), 139.6 (C\( 6H_5CH_2 \)).

HRMS (ESI) calcd for C\( _{26}H_{28}N_2 \): 368.2331, found 369.2328 (M+1). \( ^{1} \text{H} \) NMR and \( ^{13} \text{C} \) NMR assignments were confirmed through HMQC and HMBC 2D NMR experiments at 300 MHz.

5.2.2. Preparation of chiral derivatives based on BIQ (\( R,R \))-98

The same reaction procedure for preparation of racemic derivatives \( \text{rac-112} \sim \text{rac-115} \), \( \text{rac-117} \) and \( \text{rac-119} \) were followed accordingly to prepare chiral derivatives (\( R,R \))-112 \sim (\( R,R \))-115, (\( R,R \))-117 and (\( R,R \))-119.

5.2.2.1. \( N,N' \)-dimethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (\( R,R \))-112

BIQ (\( R,R \))-98 (112 mg, 0.4 mmol) was treated with iodomethane (1 mL) in neat condition, and the reaction mixture was vigorously stirred at 50 \( ^{\circ} \text{C} \) for 5 h. The volatiles were evaporated under reduced pressure to afford a yellow gum. The resulting gum was then stirred in a mixture of 5 M NaOH (3 mL) aqueous solution and CH\( _2Cl_2 \) (3 mL) for 2 h at r.t. (\( R,R \))-112
The organic layer was separated, dried over NaOH (pellets) and filtered. After solvent removal, yellow solids were obtained to be recrystallized from EtOH solution, affording pure \((R,R)-N,N'-\text{dimethyl-1,1'}\text{-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline)}\) \((R,R)-112\) as light-yellow crystals (48 mg, 40%). The melting point, FTIR, \(^1\text{H NMR}, \text{\(^{13}\)}\text{C NMR spectra and HRMS of (R,R)-112 were identical to those of rac-112. The ee of > 99\% was tested by HPLC (Chiralcel OD-H column): n-hex/IPA/Et}_3\text{N} = 95/5/0.05, 0.4 mL/min, 25 \degree \text{C}, 254 nm, t_1 = 9.7 min for (R,R) and t_2 = 10.4 min for (S,S). [\(\alpha\)]_{D}^{25} = +16.4 (c = 1.10, CHCl}_3).\]

\[5.2.2.2. \text{ N,N'}-\text{diethyl-1,1'}\text{-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline)}\] \((R,R)-113\)

BIQ \((R,R)-98\) (112 mg, 0.4 mmol) was treated with bromoethane (72 \(\mu\)L, 0.88 mmol), following the general procedure mentioned above. The resulting yellow solid was subjected to silica gel column chromatography (EtOAc/Hexane = 1/5), affording pure \((R,R)-N,N'-\text{diethyl-1,1'}\text{-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline)}\) \((R,R)-113\) as light yellow solids (98 mg, 73\%). The melting point, FTIR, \(^1\text{H NMR}, \text{\(^{13}\)}\text{C NMR spectra and HRMS of (R,R)-113 were identical to those of rac-113. The ee of > 99\% was tested by HPLC (Chiralcel OD-H column): n-hex/IPA/Et}_3\text{N} = 95/5/0.05, 0.5 mL/min, 25 \degree \text{C}, 254 nm, t_1 = 7.4 min for (R,R) and t_2 = 7.8 min for (S,S). [\(\alpha\)]_{D}^{25} = +15.7 (c = 1.00, CHCl}_3).\]

\[5.2.2.3. \text{ N,N'}-\text{dibenzyl-1,1'}\text{-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline)}\] \((R,R)-114\)
BIQ \((R,R)-98\) (112 mg, 0.4 mmol) was reacted with benzyl bromide (105 μL, 0.88 mmol), following the general procedure mentioned above. The resulting yellow solid was subjected to silica gel column chromatography (EtOAc/Hexane = 1/10), affording pure \((R,R)-N,N'-\text{dibenzyl}-1,1'-\text{methylene-} (R,R)-114\) as light yellow solids (167 mg, 91%). The melting point, FTIR, \(^1\)H NMR, \(^{13}\)C NMR and HRMS of \((R,R)-114\) were identical to those of \textit{rac}-114. The ee of > 99% was tested by HPLC (Chiralcel OD-H column): \(n\)-hex/IPA/\(\text{Et}_3\)\(N\) = 98/2/0.02, 0.5 mL/min, 25 °C, 254 nm, \(t_1 = 9.7\) min for \((R,R)\) and \(t_2 = 11.3\) min for \((S,S)\). \([\alpha]_{D}^{25} = +145.6\) (c = 1.11, CHCl\(_3\)).

5.2.2.4. \(N\)-methyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) \((R,R)-115\)

\((R,R)-98\) (112 mg, 0.4 mmol) reacted with 37% formaldehyde (41 μL, 0.54 mmol, methanol solution) in EtOH solution, and the reaction mixture was then heated to reflux for 2 days. Following the general procedure, pure piperimidine \((R,R)-103\) was obtained and reduced by NaCNBH\(_3\) in acidic MeOH solution, affording pure \textit{N-methyl-1,1'}-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) \((R,R)-115\) as light yellow gum (80 mg, 69%). The FTIR, \(^1\)H NMR, \(^{13}\)C NMR spectra and HRMS of \((R,R)-115\) were identical to those of \textit{rac}-115. \([\alpha]_{D}^{25} = +18.1\) (c = 1.11, CHCl\(_3\)).

5.2.2.5. \(N\)-ethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) \((R,R)-117\)
(R,R)-98 (112 mg, 0.4 mmol) reacted with acetaldehyde (31 μL, 0.54 mmol) in Et₂O solution, and the reaction mixture was then stirred vigorously at r.t. for overnight. Following the general procedure, pure piperimidine (R,R)-116 was obtained and reduced by NaCNBH₃ in acidic MeOH solution, affording pure N-ethyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (R,R)-117 as light yellow gum (87 mg, 70%). The FTIR, ¹H NMR, ¹³C NMR spectra and HRMS of (R,R)-117 were identical to those of rac-117. [α]D²⁵ = +16.3 (c = 1.03, CHCl₃).

5.2.2.6. N-benzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (R,R)-119

(R,R)-98 (112 mg, 0.4 mmol) reacted with benzaldehyde (54 μL, 0.54 mmol) in Et₂O solution, and the reaction mixture was then stirred vigorously at room temperature for overnight. Following the general procedure, pure piperimidine (R,R)-118 was obtained and reduced by NaCNBH₃ in acidic MeOH (R,R)-119 solution, affording pure N-benzyl-1,1'-methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline) (R,R)-119 as light yellow gum (122 mg, 83%). The FTIR, ¹H NMR, ¹³C NMR spectra and HRMS of (R,R)-119 were identical to those of rac-119. The ee of > 99% was tested by HPLC (Chiralcel OD-H column): n-hex/IPA/Et₃N = 90/10/0.1, 0.3 mL/min, 25 °C, 254 nm, t₁ = 18.1 min for (R,R) and t₂ = 19.0 min for (S,S). [α]D²⁵ = +150.2 (c = 1.03, CHCl₃).

5.3. Synthesis of 1,2-diposed BIQs
1,2-BIQs 23, 27, 29, 31, 32, 35, 36, 120-122 and 124 were prepared according to the reported procedure, and the obtained compounds’ melting points, FTIR, $^1$H NMR, $^{13}$C NMR spectra and HRMS were same as those reported. $^{12,68,69}$ Chiral 1,2-diposed BIQs (R,R)-23, (R)-29 were obtained by the reported resolution methods. $^{12,68}$ Enantiopurity was confirmed by chiral HPLC analysis.

5.4. Synthesis of chiral derivatives based on BIQ (R)-29

Chiral derivatives based on 1’,2’,3’,4’-tetrahydro-1,1’-bisisoquinoline (R)-32 and its derivatives ((R)-161, (R)-162, (R)-164 ~ (R)-170) were prepared according to the reported methods. $^{68}$ The obtained compounds’ melting points, FTIR, $^1$H NMR, $^{13}$C NMR spectra and HRMS were same as those reported.

5.4.1. Preparation of (R)-N’-isopropyl-1’,2’,3’,4’-tetrahydro-1,1’-bisisoquinoline (R)-163

In CH$_3$CN solution (4 mL) of (R)-1’,2’,3’,4’-tetrahydro-1,1’-bisisoquinoline (R)-29 (130 mg, 0.5 mmol), 2-bromopropane (67.6 mg, 51.6 μL, 0.55 mmol) was added in the presence of K$_2$CO$_3$ (138 mg, 1.0 mmol). The reaction mixture was then heated at reflux for two days (TLC). The mixture was filtered and K$_2$CO$_3$ was washed with CH$_2$Cl$_2$ (2 × 3 mL). The combined organic filtrates were evaporated to dryness, and the obtained yellow gum was subjected to column chromatography to afford (R)-163 as white solid (84.6 mg, 56%). Enantiomeric purity (98% ee) was determined by HPLC (Daicel Chiralcel OD-H column), n-hex/i-PrOH = 98/2, 1.0 mL/min, 254 nm, $t_1 = 5.0$ min for (S)-163, $t_2 = 5.4$ min for (R)-163. $\left[\alpha\right]_{D}^{25} = +157.5$ (c = 0.86, CH$_2$Cl$_2$). FTIR (KBr)
$\nu_{\text{max}}$: 3402, 3052, 2965, 1623, 1585, 1560, 1496, 1452, 1342, 1171, 1057, 826, 734, 648 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 0.82 (3H, d, $J = 7.2$ Hz, CH$_3$), 0.89 (3H, d, $J = 7.2$ Hz, CH$_3$), 2.52-2.61 (2H, m, CH(CH$_3$)$_2$ and H$_3$'), 3.21-3.40 (1H, d, $J = 15.9$ Hz, H$_5'$), 3.16-3.27 (2H, m, H$_\beta$3' and H$_\alpha$4'), 5.47 (1H, s, H1'), 6.48 (1H, d, $J = 7.8$ Hz, H5'), 6.71 (1H, t, $J = 7.5$ Hz, H7'), 6.92 (1H, t, $J = 7.2$ Hz, H6'), 7.05 (1H, d, $J = 7.5$ Hz, H8'), 7.18 (1H, t, $J = 7.5$ Hz, H6), 7.39 (1H, t, $J = 7.5$ Hz, H7), 7.46 (1H, d, $J = 5.7$ Hz, H4), 7.61 (1H, d, $J = 8.7$ Hz, H5), 8.40 (1H, d, $J = 5.7$ Hz, H3), 8.64 (1H, d, $J = 8.7$ Hz, H8). $^{13}$C NMR (75.6 MHz, CDCl$_3$) $\delta$: 12.5 (CH$_3$), 21.3 (CH$_3$), 30.5 (C4'), 41.5 (C3'), 49.5 (NCH(CH$_3$)$_2$), 70.7 (C1'), 120.8 (C4), 125.7 (C8), 125.9 (C7'), 126.0 (C7), 126.7 (C6'), 126.8 (C5), 127.2 (C8a), 127.8 (C5'), 128.6 (C8'), 129.7 (C6), 134.5 (C4'a), 137.3 (C4a), 138.5 (C8'a), 141.0 (C3), 162.8 (C1). HRMS (ESI) calcd for C$_{21}$H$_{22}$N$_2$: 302.1861, found 303.1857 (M+1).

5.5. Catalytic enantioselective addition of nitromethane to aldehydes using ligand (R)-23 or (R)-161

Ligand (0.02 mmol, 10 mol%) and CuCl (0.01 mmol, 5 mol%) were dissolved in ClCH$_2$CH$_2$Cl/(i-Pr)$_2$O (1.5 mL), and the mixture was allowed to stir vigorously at r.t for 1 h, whereby a green/yellow solution was obtained. To the above solution, aldehyde (0.2 mmol) was added and the mixture was stirred for another 5 min before dropwise addition of CH$_3$NO$_2$ (4 mmol, 20 equiv). The reaction mixture was further stirred at the given temperature for a specific time (TLC). The $\beta$-nitroalcohol product was purified on silica gel by flash column chromatography. Enantiomeric excesses were determined by HPLC using Chiralcel OD-H, OJ-H and Chiraopak AD-H columns. The absolute configuration of the major enantiomer of product was assigned by comparing with literature precedents.$^{110,132,140}$
5.5.1. (R)-1-Phenyl-2-nitroethanol (R)-124

Benzaldehyde 39 (20 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-phenyl-2-nitroethanol (R)-124 (60%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 2.76 (1H, br s, OH), 4.39-4.56 (2H, m, CH$_2$NO$_2$), 5.37 (1H, dd, $J$ = 9.3, 9.6 Hz, CHO), 7.34-7.40 (5H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 71.0, 81.3, 126.0, 129.0, 129.1 and 138.2. The ee of 85% was determined by HPLC. HPLC (Chiralcel OD-H column): n-hex: IPA = 90:10, flow rate = 0.8 ml/min, wavelength = 215 nm, t$_1$ = 18.1 min for (R), t$_2$ = 22.2 min for (S).

5.5.2. (R)-1-(4-Nitrophenyl)-2-nitroethanol (R)-143

4-nitrobenzaldehyde 126 (30 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(4-nitrophenyl)-2-nitroethanol (R)-143 (95%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=3:7). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 3.28 (1H, br, s, OH), 4.47-4.66 (2H, m, CH$_2$NO$_2$), 5.48-5.56 (1H, m, CHO), 7.63 (2H, d, $J$ = 8.7 Hz, ArH), 8.27 (2H, d, $J$ = 8.7 Hz, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 70.0, 80.6, 124.1, 127.0, 145.4 and 148.0. The ee of 64% was determined by HPLC. HPLC (Chiralcel OD-H column): n-hex: IPA = 85:15, flow rate = 1.0 ml/min, wavelength = 215 nm, t$_1$ = 21.1 min for (R), t$_2$ = 25.5 min for (S).

5.5.3. (R)-1-(4-Chlorophenyl)-2-nitroethanol (R)-144
4-chlorobenzaldehyde 127 (23 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(4-chlorophenyl)-2-nitroethanol (R)-144 (70%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 2.89 (1H, br, s, OH), 4.47-4.62 (2H, m, CH$_2$NO$_2$), 5.44-5.47 (1H, m, CHO), 7.34-7.40 (4H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 70.3, 80.1, 127.3, 129.3, 134.9 and 136.5. The ee of 91% was determined by HPLC. HPLC (Chiralcel OD-H column): n-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 215 nm, $t_1$= 13.9 min for (R), $t_2$= 17.7 min for (S).

5.5.4. (R)-1-(3-Chlorophenyl)-2-nitroethanol (R)-145

3-chlorobenzaldehyde 128 (23 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(3-chlorophenyl)-2-nitroethanol (R)-145 (59%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 2.96 (1H, br, s, OH), 4.49-4.63 (2H, m, CH$_2$NO$_2$), 5.37-5.44 (1H, m, CHO), 7.26-7.73 (4H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 70.3, 81.0, 124.0, 126.2, 129.1, 130.3, 135.0 and 140.0. The ee of 87% was determined by HPLC. HPLC (Chiralcel OD-H column): n-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 215 nm, $t_1$= 13.6 min for (R), $t_2$= 16.8 min for (S).
5.5.5. (R)-1-(2-Chlorophenyl)-2-nitroethanol (R)-146

2-chlorobenzaldehyde 129 (23 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(2-chlorophenyl)-2-nitroethanol (R)-146 (72%, isolated yield). The \( \beta \)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \( \delta \) ppm): 3.00 (1H, br, s, O\( \text{H} \)), 4.59-4.64 (1H, m, C\( \text{H}_2\text{NO}_2 \)), 5.79 (1H, d, \( J = 9.3 \) Hz, CHOH), 7.26-7.34 (3H, m, ArH), 7.60 (1H, dd, \( J = 9.3, 2.1 \) Hz, ArH); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \( \delta \) ppm): 67.8, 79.3, 127.5, 127.6, 129.7, 129.9, 131.5 and 135.5. The ee of 87% was determined by HPLC. HPLC (Chiralcel OJ-H column): n-hex: IPA = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, \( t_1 \)= 82.0 min for (R), \( t_2 \)= 94.3 min for (S).

5.5.6. (R)-1-(4-Fluorophenyl)-2-nitroethanol (R)-147

4-fluorobenzaldehyde 130 (22 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(4-fluorophenyl)-2-nitroethanol (R)-147 (59%, isolated yield). The \( \beta \)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=3:7). \(^1\)H NMR (300 MHz, CDCl\(_3\), \( \delta \) ppm): 2.89 (1H, s, OH), 4.46-4.63 (2H, m, CH\(_2\)NO\(_2\)), 5.47 (1H, d, \( J = 7.5 \) Hz, CHOH), 7.07-7.13 (2H, m, ArH), 7.37-7.42 (2H, m, ArH); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \( \delta \) ppm): 70.3, 81.2, 115.9, 116.1, 127.7 and 127.8. The ee of 87% was determined by HPLC. HPLC
(Chiralcel OD-H column): \( n \)-hex: IPA = 90:10, flow rate = 0.8 ml/min, wavelength = 215 nm, \( t_1 \) = 15.4 min for (R), \( t_2 \) = 18.4 min for (S).

5.5.7. (R)-1-(4-Methylphenyl)-2-nitroethanol (R)-148

4-methylbenzaldehyde 131 (24 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(4-methylphenyl)-2-nitroethanol (R)-148 (65%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:8). \(^1\)H NMR (300 MHz, CDCl\(_3\), \( \delta \) ppm): 2.36 (3H, s, CH\(_3\)), 2.48 (1H, s, OH), 4.46-4.64 (2H, m, CH\(_2\)NO\(_2\)), 5.40-5.46 (1H, m, CHOH), 7.26-7.30 (4H, m, ArH); \(^1^3\)C NMR (75.6 MHz, CDCl\(_3\), \( \delta \) ppm): 21.2, 70.9, 81.3, 125.9, 129.7, 135.2 and 139.0. The ee of 88% was determined by HPLC. HPLC (Chiralcel OD-H column): \( n \)-hex: IPA = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, \( t_1 \) = 27.8 min for (R), \( t_2 \) = 35.6 min for (S).

5.5.8. (R)-1-(3-Methylphenyl)-2-nitroethanol (R)-149

3-methylbenzaldehyde 132 (23.5 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(3-methylphenyl)-2-nitroethanol (R)-149 (57%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \( \delta \) ppm): 2.38 (3H, s, CH\(_3\)), 2.81 (1H, s, OH), 4.50-4.65 (2H, m, CH\(_2\)NO\(_2\)), 5.37-5.45 (1H, m, CHOH), 7.23-7.32 (4H, m, ArH); \(^1^3\)C NMR (75.6 MHz, CDCl\(_3\), \( \delta \) ppm): 21.4, 71.1, 81.8, 123.0,
126.6, 128.9, 129.7, 138.0 and 138.9. The ee of 86% was determined by HPLC. HPLC (Chiralcel OD-H column): n-hex: IPA = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, $t_1$ = 23.9 min for (R), $t_2$ = 27.9 min for (S).

**5.5.9. (R)-1-(2-Methylphenyl)-2-nitroethanol (R)-150**

2-methylbenzaldehyde 133 (23 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(2-methylphenyl)-2-nitroethanol (R)-150 (70%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 2.40 (3H, s, CH$_3$), 2.72 (1H, d, $J$ = 3.6 Hz, OH), 4.42-4.60 (2H, m, CH$_2$NO$_2$), 5.67-5.72 (1H, m, CHO), 7.25-7.31 (3H, m, ArH), 7.51-7.56 (1H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 18.9, 68.0, 80.2, 125.6, 126.8, 128.8, 130.9, 134.4 and 136.2. The ee of 87% was determined by HPLC. HPLC (Chiralcel OD-H column): n-hex: IPA = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, $t_1$ = 23.3 min for (R), $t_2$ = 36.6 min for (S).

**5.5.10. (R)-1-(4-Phenylphenyl)-2-nitroethanol (R)-151**

4-phenylbenzaldehyde 134 (37 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(4-phenylphenyl)-2-nitroethanol (R)-151 (80%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 2.88 (1H, d, $J$ = 3.3 Hz, OH), 4.36-4.69 (2H, m, CH$_2$NO$_2$), 5.52 (1H, d, $J$ = 9.3 Hz,
CHOH), 7.34-7.64 (9H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): 70.8, 81.2, 126.4, 127.1, 127.7, 127.8, 128.9, 137.0, 140.3 and 142.0. The ee of 82% was determined by HPLC. HPLC (Chiralcel OD-H column): $n$-hex: IPA = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, $t_1$= 19.5 min for (R), $t_2$= 23.8 min for (S).

5.5.11. (R)-1-(4-Methoxyphenyl)-2-nitroethanol (R)-152

4-methoxybenzaldehyde 135 (24 µL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 µL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(4-methoxyphenyl)-2-nitroethanol (R)-152 (60%, isolated yield). The $\beta$-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 2.73 (1H, br, s, OH), 3.81 (3H, s, OCH$_3$), 4.45-4.66 (2H, m, CH$_2$NO$_2$), 5.62-5.68 (1H, m, CHO), 6.93 (2H, d, $J$ = 8.7 Hz, ArH), 7.26-7.34 (2H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): 55.4, 70.7, 81.3, 114.4, 127.3, 130.2 and 160.1. The ee of 89% was determined by HPLC. HPLC (Chiralcel OD-H column): $n$-hex: IPA = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, $t_1$= 17.0 min for (R), $t_2$= 21.8 min for (S).

5.5.12. (R)-1-(3-Methoxyphenyl)-2-nitroethanol (R)-153

3-methoxybenzaldehyde 136 (24 µL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 µL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(3-methoxyphenyl)-2-nitroethanol (R)-153 (75%, isolated yield). The $\beta$-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:4). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 2.97
1H, br, s, OH), 3.19 (3H, s, CH$_3$O), 4.72-4.84 (2H, m, CH$_2$NO$_2$), 5.42-5.48 (1H, m, CHOH), 6.88-6.97 (3H, m, ArH), 7.28-7.57 (1H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 55.3, 70.9, 81.2, 111.5, 114.4, 118.1, 130.1, 139.8 and 160.1. The ee of 90% was determined by HPLC. HPLC (Chiralcel OD-H column): n-hex: IPA = 90:10, flow rate = 0.5 ml/min, wavelength = 215 nm, t$_1$= 48.2 min for (R), t$_2$= 63.6 min for (S).

### 5.5.13. (R)-1-(2-Methoxyphenyl)-2-nitroethanol (R)-154

2-methoxybenzaldehyde 65 (24 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(2-methoxyphenyl)-2-nitroethanol (R)-154 (79%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:9). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 3.24 (1H, s, OH), 3.90 (3H, s, CH$_3$O), 4.55-4.69 (2H, m, CH$_2$NO$_2$), 5.62-5.68 (1H, m, CHOH), 6.93 (1H, d, $J = 8$ Hz, ArH), 7.03 (1H, t, $J = 7.5$ Hz, ArH), 7.35 (1H, t, $J = 8$ Hz, ArH), 7.46 (1H, d, $J = 7.5$ Hz, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 55.4, 67.8, 79.9, 110.6, 121.2, 126.0, 127.2, 129.8 and 156.0. The ee of 91% was determined by HPLC. HPLC (Chiralcel OD-H column): n-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 215 nm, t$_1$= 11.1 min for (R), t$_2$= 12.9 min for (S).

### 5.5.14. (R)-1-Nitrohexan-2-ol (R)-155

Valeraldehyde 137 (22 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-nitrohexan-2-ol (R)-155 (76%, isolated yield). The β-nitroalcohol product
was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 0.94 (3H, t, $J$ = 6.9 Hz, CH$_3$), 1.34-1.61 (6H, m, alkyl-H), 2.54 (1H, s, OH), 4.31-4.49 (3H, m, CHO, CH$_2$NO$_2$); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 13.9, 22.4, 27.3, 33.4, 68.7 and 80.6. The ee of 88% was determined by HPLC. HPLC (Chiralpak AD-H column): $n$-hex: IPA = 98:2, flow rate = 0.8 ml/min, wavelength = 215 nm, $t_1$ = 37.8 min for (R), $t_2$ = 50.5 min for (S).

5.5.15. (R)-1-Nitropentan-2-ol (R)-156

Butyraldehyde 138 (18 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-nitropentan-2-ol (R)-156 (73%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 0.98 (3H, t, $J$ = 6.9 Hz, CH$_3$), 1.50-1.59 (4H, m, alkyl-H), 2.53 (1H, br, s, OH), 4.35-4.46 (3H, m, CHO, CH$_2$NO$_2$); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 13.7, 18.4, 35.8, 68.4 and 80.7. The ee of 90% was determined by HPLC. HPLC (Chiralpak AD-H column): $n$-hex: IPA = 98:2, flow rate = 1.0 ml/min, wavelength = 215 nm, $t_1$ = 33.7 min for (R), $t_2$ = 57.2 min for (S).

5.5.16. (R)-1-Nitrodecan-2-ol (R)-157

Nonanal 139 (34.4 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-nitrodecan-2-ol (R)-157 (72%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column
chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 0.88 (3H, t, $J$ = 6.3 Hz, CH$_3$), 1.47-1.50 (14H, m, alkyl-H), 2.49 (1H, d, $J$ = 4.5 Hz, OH), 4.34-4.47 (3H, m, CHO, CH$_2$NO$_2$); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): 14.1, 22.6, 25.2, 29.2, 29.3, 29.4, 31.8, 33.7, 68.7, and 80.6. The ee of 91% was determined by HPLC. HPLC (Chiralpak AD-H column): n-hex: IPA = 98:2, flow rate = 1.0 ml/min, wavelength = 215 nm, t$_1$= 23.1 min for (R), t$_2$= 36.7 min for (S).

5.5.17. (R)-1-(2-Naphthyl)-2-nitroethanol (R)-158

2-naphthaldehyde 140 (31.2 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(2-naphthyl)-2-nitroethanol (R)-158 (85%, isolated yield). The $\beta$-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:4). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 3.04 (1H, br, s, OH), 4.54-4.82 (2H, m, CH$_2$NO$_2$), 5.61 (1H, d, $J$ = 6.9 Hz, CHO), 7.26-7.54 (3H, m, ArH), 7.84-7.88 (4H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): 71.2, 81.2, 123.2, 125.3, 126.7, 126.7, 127.8, 128.1, 129.0, 133.2, 133.4 and 135.4. The ee of 80% was determined by HPLC. HPLC (Chiralcel OD-H column): n-hex: IPA = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, t$_1$= 36.1 min for (R), t$_2$= 51.6 min for (S).

5.5.18. (R)-1-(2-Fural)-2-nitroethanol (R)-159

2-furaldehyde 141 (18 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-(2-fural)-2-nitroethanol (R)-159 (80%, isolated yield). The
\(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): 2.90 (1H, br, s, OH), 4.63-4.84 (2H, m, CH\(_2\)NO\(_2\)), 5.40-5.50 (1H, m, CHO\(_H\)), 6.38-6.40 (2H, m, ArH), 7.40-7.42 (1H, m, Ar\(_H\)); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): 64.9, 78.4, 108.2, 100.7, 143.2 and 150.7. The ee of 85\% was determined by HPLC. HPLC (Chiralcel OJ-H column): \(n\)-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 215 nm, \(t_1\) = 23.1 min for (R), \(t_2\) = 28.5 min for (S).

5.5.19. \((R, E)\)-1-Nitro-4-phenyl-3-buten-2-ol (R)-160

Trans-cinnamaldehyde 142 (26 \(\mu\)L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 \(\mu\)L, 4.0 mmol, 20 equiv) in the presence of (R)-29 (5.1 mg, 0.02 mmol, 10 mol\%) following the general procedure to give (R)-1-nitro-4-phenyl-3-buten-2-ol (R)-160 (78\%, isolated yield).

The \(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): 2.68 (1H, br s, OH), 4.51-4.61 (2H, m, CH\(_2\)NO\(_2\)), 5.02-5.08 (1H, m, CHO\(_H\)), 6.15 (1H, dd, \(J = 6.3, 15.9\) Hz, CH=CH), 6.79 (1H, d, \(J = 15\) Hz, CH=CH), 7.30-7.46 (5H, m, Ar\(_H\)); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): 69.6, 79.9, 124.9, 126.7, 128.6, 128.8, 133.7, 135.5. The ee of 81\% was determined by HPLC. HPLC (Chiralcel OD-H column): \(n\)-hex: IPA = 90:10, flow rate = 0.8 ml/min, wavelength = 215 nm, \(t_1\) = 38.6 min for (S), \(t_2\) = 42.8 min for (R).

5.5.20. \((R)\)-1-(4-bromophenyl)-2-nitroethanol (R)-177

4-bromobenzaldehyde 171 (37 \(\mu\)L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 \(\mu\)L, 4.0 mmol, 20 equiv) in the presence of (R)-161 (5.6 mg, 0.02 mmol, 10 mol\%) following the general
procedure to give \((R)-1\)-(4-bromophenyl)-2-nitroethanol \((R)\text{-}177\) (78\%, isolated yield). The \(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): 2.96 (1H, s, \(\text{O}H\)), 4.40-4.54 (2H, m, \(\text{CH}_2\text{NO}_2\)), 5.36-5.39 (1H, m, \(\text{CHOH}\)), 7.19-7.23 (2H, m, \(\text{ArH}\)), 7.45-7.48 (2H, m, \(\text{ArH}\)); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): 70.3, 80.9, 123.0, 127.6, 132.2 and 137.1. The ee of 80\% was determined by HPLC. HPLC (Chiralcel OD-H column): \(n\)-hex: IPA = 85:15, flow rate = 0.8 ml/min, wavelength = 215 nm, \(t_1\) = 13.5 min for \((R)\), \(t_2\) = 17.4 min for \((S)\).

5.5.21. \((R)\)-1-Nitrobutan-2-ol \((R)\text{-}178\)

Propionaldehyde \(172\) (14.3 \(\mu\)L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 \(\mu\)L, 4.0 mmol, 20 equiv) in the presence of \((R)\text{-}161\) (5.6 mg, 0.02 mmol, 10 mol\%) following the general procedure to give \((R)-1\)-nitrobutan-2-ol \((R)\text{-}178\) (95\%, isolated yield). The \(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): 0.94-0.98 (3H, m, \(\text{CH}_3\)), 1.46-1.61 (2H, m, alkyl-\(H\)), 2.57 (1H, br s, \(\text{OH}\)), 4.18-4.59 (3H, m, \(\text{CHOH}, \text{CH}_2\text{NO}_2\)); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): 9.6, 26.9, 69.9 and 80.4. The ee of 93\% was determined by HPLC. HPLC (Chiralpak AD-H column): \(n\)-hex: IPA = 98:2, flow rate = 1.0 ml/min, wavelength = 215 nm, \(t_1\) = 49.7 min for \((R)\), \(t_2\) = 84.6 min for \((S)\).

5.5.22. \((R)\)-1-Nitroheptan-2-ol \((R)\text{-}179\)

Hexanal \(173\) (24.6 \(\mu\)L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 \(\mu\)L, 4.0 mmol, 20 equiv) in the presence of \((R)\text{-}161\) (5.6 mg, 0.02 mmol, 10 mol\%) following the general
procedure to give (R)-1-nitroheptan-2-ol (R)-179 (94%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): 0.84 (3H, t, \(J = 6.9\) Hz, CH\(_3\)), 1.15-1.53 (8H, m, alkyl-\(H\)), 2.75 (1H, br s, OH), 4.24-4.40 (3H, m, CHO\(_2\), CH\(_2\)NO\(_2\)); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): 13.9, 22.5, 24.8, 31.5, 33.7, 68.7 and 80.7. The ee of 90% was determined by HPLC. HPLC (Chiralpak AD-H column): n-hex: IPA = 98:2, flow rate = 1.0 ml/min, wavelength = 215 nm, \(t_1\) = 23.8 min for (R), \(t_2\) = 35.6 min for (S).

5.5.23. (R)-3-Methyl-1-nitrobutan-2-ol (R)-180

Isobutyraldehyde 174 (18.3 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-3-methyl-1-nitrobutan-2-ol (R)-180 (99%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): 0.70-0.78 (6H, m, 2×CH\(_3\)), 1.66-1.81 (1H, m, CH(CH\(_3\))\(_2\)), 2.58 (1H, br s, OH), 4.00-4.11 (1H, m, CHO\(_2\)), 4.30-4.44 (2H, m, CH\(_2\)NO\(_2\)); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): 17.4, 18.4, 31.8, 73.4 and 79.3. The ee of 92% was determined by HPLC. HPLC (Chiralpak OD-H column): n-hex: IPA = 98:2, flow rate = 0.5 ml/min, wavelength = 215 nm, \(t_1\) = 40.2 min for (R), \(t_2\) = 44.6 min for (S).

5.5.24. (R)-4-Methyl-1-nitropentan-2-ol (R)-181

Isovaleraldehyde 175 (21.6 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-4-methyl-1-nitropentan-2-ol (R)-181 (99%, isolated yield). The β-nitroalcohol
product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 0.85-0.91 (6H, m, 2×CH$_3$), 1.12-1.20 (1H, m, alkyl-H), 1.39-1.49 (1H, m, alkyl-H), 1.72-1.81 (1H, m, alkyl-H), 2.53 (1H, br s, OH), 4.27-4.37 (3H, m, CH$_2$OH and CH$_2$NO$_2$); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): 21.8, 23.2, 24.3, 42.4, 67.0 and 81.0. The ee of 91% was determined by HPLC. HPLC (Chiralpak AD-H column): n-hex: IPA = 95:5, flow rate = 0.5 ml/min, wavelength = 215 nm, t$_r$ = 20.6 min for (R), t$_s$ = 29.1 min for (S).

5.5.25. (R)-1-Cyclohexyl-2-nitroethanol (R)-182

Cyclohexane carbaldehyde 176 (24.2 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of (R)-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give (R)-1-cyclohexyl-2-nitroethanol (R)-182 (70%, isolated yield). The $\beta$-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 1.00-1.23 (5H, m, alkyl-H), 1.42-1.54 (1H, m, alkyl-H), 1.60-1.70 (2H, m, alkyl-H), 1.72-1.78 (3H, m, alkyl-H), 2.38 (1H, d, $J$ = 5.1 Hz, OH), 4.02-4.04 (1H, m, CH$_2$OH), 4.36-4.44 (2H, m, CH$_2$NO$_2$); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): 25.9, 28.0, 28.8, 41.4, 72.8 and 79.3. The ee of 93% was determined by HPLC. HPLC (Chiralpak AD-H column): n-hex: IPA = 98:2, flow rate = 0.6 ml/min, wavelength = 215 nm, t$_r$ = 48.6 min for (R), t$_s$ = 51.9 min for (S).

5.6. Catalytic diastereoselective addition of nitroethane/nitropropane to aldehydes using ligand (R)-161

Ligand (0.02 mmol, 10 mol%) and CuCl (0.01 mmol, 5 mol%) were dissolved in THF (1.5 mL) and the mixture was allowed to stir vigorously at r.t. for 1 h, whereby a yellow
solution was obtained. To the above solution, aldehyde (0.2 mmol) was added and the mixture was stirred for another 5 min before dropwise addition of CH\(_3\)CH\(_2\)NO\(_2\)/CH\(_3\)CH\(_2\)CH\(_2\)NO\(_2\) (4 mmol, 20 equiv). The reaction mixture was further stirred at room temperature for a specific time (TLC). The \(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography. Diastereomeric ratios were determined by \(^1\)H NMR and HPLC. Enantiomeric excesses were determined by HPLC using Chiralcel OD-H and OB-H columns, Chiralpak AD-H and AS-H columns. The absolute configuration of the major enantiomer of product was assigned by comparing with literature precedents.\(^{107,129,146,232}\)

5.6.1. 1-Phenyl-2-nitropropan-1-ol 183

Benzaldehyde 39 (20 \(\mu\)L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 \(\mu\)L, 4.0 mmol, 20 equiv) in the presence of \((R)\)-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-phenyl-2-nitropropan-1-ol 183 (65\%, isolated yield). The \(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): \textit{anti isomer}—1.48 (3H, d, \(J = 6.9\) Hz, CH\(_3\)), 3.05 (1H, s, OH), 4.65-4.82 (1H, m, CHNO\(_2\)), 5.33-5.39 (1H, m, CHO\(_2\)), 7.31-7.42 (5H, m, Ar\(\text{H}\)); \textit{syn isomer}—1.30 (3H, d, \(J = 6.9\) Hz, CH\(_3\)), 3.05 (1H, s, OH), 4.65-4.82 (1H, m, CHNO\(_2\)), 5.01 (1H, d, \(J = 9.0\) Hz, CHO\(_2\)), 7.31-7.42 (5H, m, Ar\(\text{H}\)); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): \textit{anti isomer}—12.1, 73.9, 87.4, 125.9, 128.6, 128.8, 138.4; \textit{syn isomer}—16.5, 76.3, 88.4, 126.9, 129.0, 129.2, 138.3. Diasteromeric ratios (\textit{anti/syn}, 2.6:1) were determined by \(^1\)H NMR and HPLC. \textit{antilsyn} = 83%/90% \(ee\) was determined by HPLC. HPLC (Chiralpak AD-H column): \(n\)-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength =
210 nm, \( t_1 = 8.4 \) min for \( \text{anti}_{\text{minor}}(1S, 2R) \), \( t_2 = 9.2 \) min for \( \text{anti}_{\text{major}}(1R, 2S) \), \( t_3 = 10.7 \) min for \( \text{syn}_{\text{minor}}(1S, 2S) \), \( t_4 = 11.8 \) min for \( \text{syn}_{\text{major}}(1R, 2R) \).

5.6.2. 1-(4-Nitrophenyl)-2-nitropropan-1-ol 185

4-nitrobenzaldehyde 126 (30 mg, 0.2 mmol, 1 equiv) was treated with nitroethane (285 \( \mu L \), 4.0 mmol, 20 equiv) in the presence of \((R)-161\) (5.6 mg, 0.02 mmol, 10 mol\%) following the general procedure to give 1-(4-nitrophenyl)-2-nitropropan-1-ol 185 (95\%, isolated yield). The \( \beta \)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:4). \(^1\)H NMR (300 MHz, CDCl\(_3\), \( \delta \) ppm): \textit{anti} isomer-1.49 (3H, d, \( J = 6.9 \) Hz, \( CH_3 \)), 3.10 (1H, s, \( OH \)), 4.68-4.82 (1H, m, \( CHNO_2 \)), 5.55-5.59 (1H, m, \( CHOH \)), 7.58-7.62 (2H, m, \( ArH \)), 8.24-8.28 (2H, m, \( ArH \)); \textit{syn} isomer-1.39 (3H, d, \( J = 6.9 \) Hz, \( CH_3 \)), 3.10 (1H, s, \( OH \)), 4.58-4.82 (1H, m, \( CHNO_2 \)), 5.20 (1H, d, \( J = 9.0 \) Hz, \( CHOH \)), 7.58-7.62 (2H, m, \( ArH \)), 8.24-8.28 (2H, m, \( ArH \)); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \( \delta \) ppm): \textit{anti} isomer-11.9, 72.9, 86.8, 124.0, 127.0, 145.6, 148.5; \textit{syn} isomer-16.1, 75.0, 87.8, 124.1, 127.9, 145.6, 148.0. Diasteromeric ratios (\textit{anti}/\textit{syn}, 1.5:1) were determined by \(^1\)H NMR and HPLC. \textit{anti/syn} = 50%/66% \textit{ee} was determined by HPLC. HPLC (Chiralcel OD-H + Chiralpak AD-H column): \( n\)-hex: IPA = 80:20, flow rate = 1.0 ml/min, wavelength = 210 nm, \( t_1 = 17.0 \) min for \( \text{anti}_{\text{major}}(1R, 2S) \), \( t_2 = 18.7 \) min for \( \text{anti}_{\text{minor}}(1S, 2R) \), \( t_3 = 21.6 \) min for \( \text{syn}_{\text{major}}(1R, 2R) \), \( t_4 = 24.8 \) min for \( \text{syn}_{\text{minor}}(1S, 2S) \).

5.6.3. 1-(2-Fluorophenyl)-2-nitropropan-1-ol 186

2-Fluorobenzaldehyde 184 (24 \( \mu L \), 0.2 mmol, 1 equiv) was treated with nitroethane (285 \( \mu L \), 4.0 mmol, 20 equiv) in the presence of \((R)-161\) (5.6 mg, 0.02 mmol, 10 mol\%) following the general procedure to give 1-(2-
fluorophenyl)-2-nitropropan-1-ol 186 (80%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): *anti isomer*: 1.49 (3H, d, $J = 6.9$ Hz, CH$_3$), 2.91 (1H, d, $J = 6.9$ Hz, OH), 4.79-4.88 (1H, m, CHNO$_2$), 5.70-5.76 (1H, m, COH), 7.03-7.13 (1H, m, ArH), 7.19-7.59 (3H, m, ArH); *syn isomer*: 1.41 (3H, d, $J = 6.9$ Hz, CH$_3$), 2.77 (1H, s, OH), 4.79-4.88 (1H, m, CHNO$_2$), 5.38-5.39 (1H, m, COH), 7.03-7.13 (1H, m, ArH), 7.19-7.59 (3H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): *anti isomer*: 11.9, 68.3, 85.2, 115.4, 124.6, 125.4, 127.8, 130.1, 157.5; *syn isomer*: 16.2, 70.0, 87.9, 115.8, 125.0, 125.6, 128.3, 130.6, 160.8. Diasteromeric ratios ($^{anti}$/syn, 2.1:1) were determined by $^1$H NMR and HPLC. $^{anti}$/syn = 72%/86% ee was determined by HPLC. HPLC (Chiralpak AD-H column): n-hex: IPA = 95:5, flow rate = 1.0 ml/min, wavelength = 210 nm, $t_1$= 11.5 min for *anti$_{minor}$* (1S, 2R), $t_2$= 14.1 min for *anti$_{major}$* (1R, 2S), $t_3$= 18.9 min for *syn$_{minor}$* (1S, 2S), $t_4$= 22.6 min for *syn$_{major}$* (1R, 2R).

### 5.6.4. 1-(4-Chlorophenyl)-2-nitropropan-1-ol 187

4-Chlorobenzaldehyde 127 (23 μL, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL, 4.0 mmol, 20 equiv) in the presence of (R)-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(4-chlorophenyl)-2-nitropropan-1-ol 187 (83%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): *anti isomer*: 1.49 (3H, d, $J = 6.0$ Hz, CH$_3$), 2.82 (1H, s, OH), 4.62-4.75 (1H, m, CHNO$_2$), 5.62-5.68 (1H, m, COH), 7.30-7.40 (4H, m, ArH); *syn isomer*: 1.33 (3H, d, $J = 6.0$ Hz, CH$_3$), 2.71 (1H, s, OH), 4.62-4.75 (1H, m, CHNO$_2$), 5.39 (1H, d, $J = 8.1$ Hz, COH), 7.30-7.40 (4H,
m, ArH; $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): anti isomer- 12.0, 73.2, 87.2, 127.4, 129.0, 134.4, 136.9; syn isomer- 16.4, 75.5, 88.2, 128.3, 129.2, 135.1, 136.8. Diasteromeric ratios (anti/syn, 1.5:1) were determined by $^1$H NMR and HPLC. anti/syn = 63%/86% ee was determined by HPLC. HPLC (Chiralpak AD-H column): n-hex: IPA = 95:5, flow rate = 1.0 ml/min, wavelength = 210 nm, $t_1$ = 16.1 min for anti$_{\text{minor}}$ (1S, 2R), $t_2$ = 17.3 min for anti$_{\text{major}}$ (1R, 2S), $t_3$ = 22.8 min for syn$_{\text{major}}$(1R, 2S), $t_4$ = 25.4 min for syn$_{\text{minor}}$(1S, 2S).

### 5.6.5. 1-(4-Bromophenyl)-2-nitropropan-1-ol 188

4-Bromobenzaldehyde 171 (37 $\mu$L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 $\mu$L, 4.0 mmol, 20 equiv) in the presence of (R)-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(4-bromophenyl)-2-nitropropan-1-ol 188 (85%, isolated yield). The $\beta$-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): anti isomer- 1.40 (3H, d, $J = 6.9$ Hz, CH$_3$), 2.89 (1H, d, $J = 3.9$ Hz, OH), 4.53-4.69 (1H, m, CHNO$_2$), 5.25-5.31 (1H, m, CHO$_\text{OH}$), 7.16-7.20 (2H, m, ArH), 7.42-7.47 (2H, m, ArH); syn isomer- 1.24 (3H, d, $J = 6.9$ Hz, CH$_3$), 2.83 (1H, d, $J = 3.9$ Hz, OH), 4.53-4.69 (1H, m, CHNO$_2$), 4.90-4.94 (1H, m, CHO$_\text{OH}$), 7.16-7.20 (2H, m, ArH), 7.42-7.47 (2H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): anti isomer- 12.0, 73.3, 87.2, 122.5, 127.7, 131.9, 137.6; syn isomer- 16.3, 75.5, 88.2, 123.2, 128.6, 132.1, 137.4. Diasteromeric ratios (anti/syn, 1.6:1) were determined by $^1$H NMR and HPLC. anti/syn = 61%/87% ee was determined by HPLC. HPLC (Chiralpak AD-H column): n-hex: IPA = 90:10, flow rate = 1.0 ml/min,
wavelength = 210 nm, \(t_1= 9.8\) min for \(anti_{\text{minor}} (1S, 2R)\), \(t_2= 10.5\) min for \(anti_{\text{major}} (1R, 2S)\), \(t_3= 13.3\) min for \(syn_{\text{major}} (1R, 2S)\), \(t_4= 15.3\) min for \(syn_{\text{minor}} (1S, 2S)\).

5.6.6. 2-Nitro-1-\(p\)-tolypropan-1-ol 189

4-methylbenzaldehyde 131 (24 \(\mu\)L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 \(\mu\)L, 4.0 mmol, 20 equiv) in the presence of (\(R\))-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-nitro-1-\(p\)-tolypropan-1-ol 189 (75%, isolated yield). The \(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): \(anti\) isomer- 1.51 (3H, d, \(J = 6.9\) Hz, CH\(_3\)), 2.36 (3H, s, Ar-CH\(_3\)), 2.62 (1H, br s, OH), 4.67-4.79 (1H, m, CH\(\text{NO}_2\)), 5.32-3.39 (1H, m, CHOH), 7.21-7.28 (4H, m, ArH); \(syn\) isomer- 1.31 (3H, d, \(J = 6.9\) Hz, CH\(_3\)), 2.36 (3H, s, Ar-CH\(_3\)), 2.49 (1H, br s, OH), 4.67-4.79 (1H, m, CH\(\text{NO}_2\)), 5.06 (1H, d, \(J = 8.1\) Hz, CHOH), 7.21-7.28 (4H, m, ArH); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): \(anti\) isomer- 12.3, 21.1, 73.9, 87.5, 125.9, 129.4, 135.4, 138.4; \(syn\) isomer- 16.5, 29.7, 76.2, 88.5, 126.8, 129.7, 133.4, 139.2. Diasteromeric ratios (\(anti/syn\), 1.7:1) were determined by \(^1\)H NMR and HPLC. \(anti/syn = 85%\)/91% \(ee\) was determined by HPLC.

HPLC (Chiralpak AD-H column): \(n\)-hex: IPA = 95:5, flow rate = 1.0 ml/min, wavelength = 210 nm, \(t_1= 14.6\) min for \(anti_{\text{minor}} (1S, 2R)\), \(t_2= 16.4\) min for \(anti_{\text{major}} (1R, 2S)\), \(t_3= 22.5\) min for \(syn_{\text{minor}} (1S, 2S)\), \(t_4= 26.7\) min \(syn_{\text{major}} (1R, 2R)\).

5.6.7. 2-Nitro-1-\(m\)-tolypropan-1-ol 190

3-methylbenzaldehyde 132 (23.5 \(\mu\)L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 \(\mu\)L, 4.0 mmol, 20 equiv) in the presence of (\(R\))-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give
Chapter 5

Experimental

2-nitro-1-\textit{m}-tolypropan-1-ol \textbf{190} (65\%, isolated yield). The \(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): \textit{anti isomer}- 1.44 (3H, d, \(J = 6.9\) Hz, CH\(_3\)), 2.29 (3H, s, Ar-CH\(_3\)), 2.63 (1H, d, \(J = 3.6\) Hz, OH), 4.54-4.57 (1H, m, CHNO\(_2\)), 5.50-5.56 (1H, m, CHOH), 7.05-7.11 (3H, m, ArH), 7.17-7.24 (1H, m, ArH); \textit{syn isomer}- 1.23 (3H, d, \(J = 6.9\) Hz, CH\(_3\)), 2.30 (3H, s, Ar-CH\(_3\)), 2.58 (1H, d, \(J = 3.6\) Hz, OH), 4.54-4.57 (1H, m, CHNO\(_2\)), 5.50-5.56 (1H, m, CHOH), 7.05-7.11 (3H, m, ArH), 7.17-7.24 (1H, m, ArH); \(^13\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): \textit{anti isomer}- 12.1, 21.4, 74.0, 87.5, 123.0, 126.6, 128.6, 129.3, 138.5, 138.6; \textit{syn isomer}- 16.5, 21.5, 76.3, 88.5, 124.1, 127.5, 128.9, 130.0, 138.3, 138.9. Diasteromeric ratios (\textit{anti}/\textit{syn}, 1.6:1) were determined by \(^1\)H NMR and HPLC. \textit{anti}/\textit{syn} = 77\%/87\% \textit{ee} was determined by HPLC. HPLC (Chiralpak AS-H column): \(n\)-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 210 nm, \(t_1\) = 8.7 min for \textit{anti}_{\text{minor}} (1S, 2R), \(t_2\) = 9.7 min for \textit{anti}_{\text{major}} (1R, 2S), \(t_3\) = 10.4 min for \textit{syn}_{\text{minor}} (1S, 2S), \(t_4\) = 12.9 min \textit{syn}_{\text{major}} (1R, 2R).

5.6.8. 2-Nitro-1-\textit{o}-tolypropan-1-ol \textbf{191}

2-methylbenzaldehyde \textbf{133} (23 \(\mu\)L, 0.2 mmol, 1 equiv) was treated with nitroethane (285 \(\mu\)L, 4.0 mmol, 20 equiv) in the presence of (\textit{R})-\textbf{161} (5.6 mg, 0.02 mmol, 10 mol\%) following the general procedure to give 2-nitro-1-\textit{o}-tolypropan-1-ol \textbf{191} (70\%, isolated yield). The \(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): \textit{anti isomer}- 1.43 (3H, d, \(J = 6.9\) Hz, CH\(_3\)), 2.29 (3H, s, Ar-CH\(_3\)), 2.58 (1H, s, OH), 4.54-4.57 (1H, m, CHNO\(_2\)), 5.50-5.56 (1H, m, CHOH), 7.08-7.19 (3H, m, ArH), 7.46 (1H, d, \(J = 7.2\) Hz, ArH); \textit{syn isomer}-
1.22 (3H, d, $J = 6.9$ Hz, $CH_3$), 2.36 (3H, s, Ar-$CH_3$), 2.48 (1H, s, OH), 4.77-4.80 (1H, m, CHNO$_2$), 5.27-5.30 (1H, m, CHO), 7.08-7.19 (3H, m, ArH), 7.29-7.32 (1H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): *anti* isomer - 11.5, 18.9, 70.9, 85.4, 126.0, 126.4, 128.4, 130.8, 134.3, 136.7; *syn* isomer - 16.1, 19.6, 72.2, 88.8, 126.5, 126.8, 128.8, 131.0, 135.9, 136.6. Diasteromeric ratios (*anti*/*syn*, 1.6:1) were determined by $^1$H NMR and HPLC. *anti*/*syn* = 75%/92% ee was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 95:5, flow rate = 1.0 ml/min, wavelength = 210 nm, $t_1$ = 11.4 min for *anti*$_{\text{minor}}$ (1S, 2R), $t_2$ = 12.8 min for *anti*$_{\text{major}}$ (1R, 2S), $t_3$ = 15.6 min for *syn*$_{\text{minor}}$ (1S, 2S), $t_4$ = 19.4 min *syn*$_{\text{major}}$ (1R, 2R).

5.6.9. 1-(Naphthyl-2-yl)-2-nitropropan-1-ol 192

2-naphthaldehyde 140 (31.2 mg, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL, 4.0 mmol, 20 equiv) in the presence of (R)-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(naphthyl-2-yl)-2-nitropropan-1-ol 192 (70%, isolated yield). The $\beta$-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): *anti* isomer - 1.52 (3H, d, $J = 6.9$ Hz, $CH_3$), 2.84 (1H, s, OH), 4.79-4.93 (1H, m, CHNO$_2$), 5.54-5.62 (1H, m, CHO), 7.43-7.55 (3H, m, ArH), 7.84-7.94 (4H, m, ArH); *syn* isomer - 1.33 (3H, d, $J = 6.9$ Hz, $CH_3$), 2.69 (1H, s, OH), 4.79-4.93 (1H, m, CHNO$_2$), 5.20 (1H, d, $J = 9.3$ Hz, CHO), 7.43-7.55 (3H, m, ArH), 7.84-7.94 (4H, m, ArH); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): *anti* isomer - 12.0, 74.0, 87.3, 123.3, 125.3, 126.5, 126.6, 127.7, 128.09, 128.7, 133.11, 133.2, 135.7; *syn* isomer - 16.6, 76.5, 88.4, 123.8, 126.7, 126.74, 126.8, 127.8, 128.07, 129.1, 133.09, 133.6, 135.6. Diasteromeric ratios (*anti*/*syn*, 0.8:1)
were determined by $^1$H NMR and HPLC. *anti/syn* = 40%/75% ee was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 90:10, flow rate = 1.0 ml/min, wavelength = 210 nm, $t_1$= 11.6 min for *anti*$_{\text{minor}}$ (1S, 2R), $t_2$= 13.9 min for *anti*$_{\text{major}}$ (1R, 2S), $t_3$= 18.0 min for *syn*$_{\text{minor}}$ (1S, 2S), $t_4$= 20.6 min *syn*$_{\text{major}}$ (1R, 2R).

5.6.10. 2-Nitrohexan-3-ol 193

Butyraldehyde 138 (18 µL, 0.2 mmol, 1 equiv) was treated with nitroethane (285 µL, 4.0 mmol, 20 equiv) in the presence of (R)-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-nitrohexan-3-ol 193 (81%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): *anti* isomer- 0.87-0.92 (5H, m, alkyl-H), 1.34-1.40 (2H, m, alkyl-H), 1.46 (3H, d, $J = 6.9$ Hz, CH$_3$), 2.13 (1H, br s, OH), 4.12-4.15 (1H, m, CHNO$_2$), 4.45-4.50 (1H, m, CHO); *syn* isomer- 0.87-0.92 (5H, m, alkyl-H), 1.34-1.40 (2H, m, alkyl-H), 1.49 (3H, d, $J = 6.9$ Hz, CH$_3$), 2.22 (1H, br s, OH), 3.75-3.85 (1H, m, CHNO$_2$), 4.45-4.50 (1H, m, CHO); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): *anti* isomer- 13.8, 16.3, 18.4, 35.1, 72.7, 86.4; *syn* isomer- 12.4, 13.9, 19.0, 29.7, 71.8, 87.7. Diasteromeric ratios (*anti/syn*, 1.3:1) were determined by $^1$H NMR and HPLC. *anti/syn* = 90%/89% ee was determined by HPLC. HPLC (Chiralpak AD-H column): *n*-hex: IPA = 98:2, flow rate = 0.8 ml/min, wavelength = 220 nm, $t_1$= 25.4 min for *anti*$_{\text{minor}}$ (1S, 2R), $t_2$= 27.9 min for *anti*$_{\text{major}}$ (1R, 2S), $t_3$= 31.6 min for *syn*$_{\text{major}}$ (1R, 2R), $t_4$= 35.1 min *syn*$_{\text{minor}}$ (1S, 2S).

5.6.11. 5-Methyl-2-nitrohexan-3-ol 194

Isovaleraldehyde 175 (21.6 µL, 0.2 mmol, 1 equiv) was treated with nitroethane (285 µL, 4.0 mmol, 20 equiv) in the presence of (R)-161 (5.6
mg, 0.02 mmol, 10 mol%) following the general procedure to give 5-methyl-2-nitrohexan-3-ol 194 (80%, isolated yield). The \(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): anti isomer- 0.86-0.91 (6H, m, 2×CH\(_3\)), 1.15-1.23 (1H, m, alkyl-\(H\)), 1.48 (3H, d, \(J = 6.6\) Hz, CH\(_3\)), 1.76-1.80 (2H, m, alkyl-\(H\)), 2.28 (1H, br s, OH), 4.20 (1H, d, \(J = 6.6\) Hz, CHNO\(_2\)), 4.40-4.46 (1H, m, CHOH); syn isomer- 0.86-0.91 (6H, m, 2×CH\(_3\)), 1.06-1.14 (1H, m, alkyl-\(H\)), 1.30-1.39 (2H, m, alkyl-\(H\)), 1.49 (3H, d, \(J = 6.9\) Hz, CH\(_3\)), 2.28 (1H, br s, OH), 3.86-3.90 (1H, m, CHNO\(_2\)), 4.40-4.46 (1H, m, CHOH); \(^1\)^\(^3\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): anti isomer- 16.3, 21.7, 23.6, 24.3, 42.0, 71.2, 86.7; syn isomer- 12.4, 21.4, 23.3, 24.5, 41.8, 70.2, 88.2. Diasteromeric ratios (anti/syn, 1.3:1) were determined by \(^1\)H NMR and HPLC. anti/syn = 90%/89% ee was determined by HPLC. HPLC (Chiralpak AD-H column): n-hex: IPA = 98:2, flow rate = 0.8 ml/min, wavelength = 220 nm, \(t_1\) = 20.2 min for \(anti_{\text{minor}}\) (1S, 2R), \(t_2\) = 21.7 min for \(anti_{\text{major}}\) (1R, 2S), \(t_3\) = 26.1 min for \(syn_{\text{major}}\) (1R, 2R), \(t_4\) = 28.0 min \(syn_{\text{minor}}\) (1S, 2S).

### 5.6.12. 3-Nitroheptan-4-ol 195

Butyraldehyde 138 (18 \(\mu\)L, 0.2 mmol, 1 equiv) was treated with nitropropane (360 \(\mu\)L, 4.0 mmol, 20 equiv) in the presence of (\(R\))-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 3-nitroheptan-4-ol 195 (79%, isolated yield). The \(\beta\)-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) ppm): anti isomer- 0.85-0.95 (6H, m, alkyl-\(H\)), 1.32-1.49 (4H, m, alkyl-\(H\)), 1.80-1.85 (1H, m, alkyl-\(H\)), 2.00-2.06 (2H, m, alkyl-\(H\) + OH), 3.90-4.00 (1H, m, CHNO\(_2\)), 4.30-4.39 (1H, m, CHOH); syn isomer- 0.85-0.95 (6H, m, alkyl-\(H\)), 1.32-1.49
(4H, m, alkyl-\(H\)), 1.80-1.85 (1H, m, alkyl-\(H\)), 2.00-2.06 (2H, m, alkyl-\(H\) + \(OH\)), 3.81-
3.88 (1H, m, \(CHNO_2\)), 4.30-4.39 (1H, m, \(CHOH\)); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): \(anti\) isomer-10.5, 13.7, 18.8, 21.5, 35.2, 72.0, 93.9; \(syn\) isomer-10.2, 13.8, 18.5, 23.9, 
35.5, 71.6, 94.4. Diasteromeric ratios (\(anti/syn\), 1:1:1) were determined by \(^1\)H NMR and 
HPLC. \(anti/syn\) = 85%/87% \(ee\) was determined by HPLC. HPLC (Chiralpak AD-H column): \(n\)-hex: IPA = 99.5:0.5, flow rate = 1.0 ml/min, wavelength = 215 nm, \(t_1\) = 27.4 
min for \(anti\)\(_{\text{minor}}\) (1\(S\), 2\(R\)), \(t_2\) = 29.2 min for \(anti\)\(_{\text{major}}\) (1\(R\), 2\(S\)), \(t_3\) = 38.7 min for \(syn\)\(_{\text{minor}}\) (1\(S\), 
2\(S\)), \(t_4\) = 40.7 min \(syn\)\(_{\text{major}}\) (1\(R\), 2\(R\)).

5.6.13. 3-Nitrohexan-4-ol 196

Propionaldehyde 172 (14.3 \(\mu\)L, 0.2 mmol, 1 equiv) was treated with 
nitropropane (360 \(\mu\)L, 4.0 mmol, 20 equiv) in the presence of (\(R\))-161 
(5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 
3-nitrohexan-4-ol 196 (77%, isolated yield). The \(\beta\)-nitroalcohol product was purified on 
silica gel by flash column chromatography (EA/Hexane=1:5). \(^1\)H NMR (300 MHz, 
CDCl\(_3\), \(\delta\) ppm): \(anti\) isomer- 0.96-0.99 (6H, m, alkyl-\(H\)), 1.26-1.41 (2H, m, alkyl-\(H\)), 
1.65-1.91 (2H, m, alkyl-\(H\)), 2.33-2.60 (1H, m, \(OH\)), 3.77-3.83 (1H, m, \(CHNO_2\)), 4.16-
4.21 (1H, m, \(CHOH\)); \(syn\) isomer- 0.96-0.99 (6H, m, alkyl-\(H\)), 1.26-1.41 (2H, m, alkyl-
\(H\)), 1.65-1.91 (2H, m, alkyl-\(H\)), 2.33-2.60 (1H, m, \(OH\)), 3.60-3.75 (1H, m, \(CHNO_2\)), 
4.16-4.21 (1H, m, \(CHOH\)); \(^{13}\)C NMR (75.6 MHz, CDCl\(_3\), \(\delta\) ppm): \(anti\) isomer-10.0, 10.5, 
21.5, 26.3, 73.6, 93.7; \(syn\) isomer- 9.6, 10.2, 24.0, 26.5, 73.1, 94.1. Diasteromeric ratios 
(\(anti/syn\), 1:1:1) were determined by \(^1\)H NMR and HPLC. \(anti/syn\) = 86%/89% \(ee\) was 
determined by HPLC. HPLC (Chiralpak OB-H column): \(n\)-hex: IPA = 98:2, flow rate =
0.6 ml/min, wavelength = 215 nm, t₁= 18.7 min for antiₘᵣᵢₜₒᵢᵦ (1S, 2R), t₂= 22.1 min for antiₘᵢⱼₒᵢᵦ (1R, 2S), t₃= 28.0 min for synₘᵢⱼₒᵢᵦ (1R, 2R), t₄= 32.2 min synₘᵢᵦᵢᵦ (1S, 2S).

5.6.14. 2-Methyl-5-Nitroheptan-4-ol 197

Isovaleraldehyde 175 (21.6 μL, 0.2 mmol, 1 equiv) was treated with nitropropane (360 μL, 4.0 mmol, 20 equiv) in the presence of (R)-BIQ rac-161 (5.6 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-methyl-5-nitroheptan-4-ol 197 (73%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). ¹H NMR (300 MHz, CDCl₃, δ ppm): anti isomer- 0.84-0.96 (9H, m, 3× CH₃), 1.11-1.23 (2H, m, alkyl-H), 1.34-1.41 (1H, m, alkyl-H), 1.76-1.84 (2H, m, alkyl-H), 2.02-2.19 (1H, m, OH), 4.08-4.13 (1H, m, CHNO₂), 4.25-4.30 (1H, m, CHOH); syn isomer- 0.84-0.96 (9H, m, 3× CH₃), 1.11-1.23 (2H, m, alkyl-H), 1.34-1.41 (1H, m, alkyl-H), 1.76-1.84 (2H, m, alkyl-H), 2.02-2.19 (1H, m, OH), 3.89-3.92 (1H, m, CHNO₂), 4.25-4.30 (1H, m, CHOH); ¹³C NMR (75.6 MHz, CDCl₃, δ ppm): anti isomer-10.5, 21.3, 21.5, 23.5, 24.5, 42.0, 70.4, 94.2; syn isomer-10.2, 21.5, 23.4, 23.9, 24.3, 42.5, 70.0, 94.8. Diasteromeric ratios (anti/syn, 1.3:1) were determined by ¹H NMR and HPLC. anti/syn = 86%/90% ee was determined by HPLC. HPLC (Chiralpak AD-H column): n-hex: IPA = 99:1, flow rate = 0.6 ml/min, wavelength = 210 nm, t₁= 22.1 min for antiₘᵢⱼₒᵦᵢᵦ (1S, 2R), t₂= 25.0 min for antiₘᵢⱼₒᵦᵢᵦ (1R, 2S), t₃= 30.8 min for synₘᵢⱼₒᵦᵢᵦ (1S, 2S), t₄= 32.1 min synₘᵢⱼₒᵦᵢᵦ (1R, 2R).

5.7. Catalytic addition of nitromethane/nitroethane to α-esters and aldehydes using BIQ rac-29

BIQ (0.02 mmol, 10 mol%) was dissolved in THF (1.5 mL) and nitromethane (205 μL, 4 mmol, 20 equiv)/nitroethane (285 μL, 4 mmol, 20 equiv) was added and the mixture was
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stirred for another 5 mins before dropwise addition of α-ketoester/aldehyde (0.2 mmol).
The reaction mixture was further stirred at r.t. for a certain time (TLC). The solvent was
then removed under vacuum and the residue was purified on silica gel by flash column
chromatography. Diastereomeric ratios were determined by $^1$H NMR.

5.7.1. 2-Hydroxy-3-nitro-2-(4-nitro-phenyl)-propanoic Acid Ethyl Ester 206

Ethyl 4-nitrophenyl glyoxylate 200 (44.6 mg, 0.2 mmol, 1 equiv)
was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in
the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%)
following the general procedure to give 2-Hydroxy-3-nitro-2-(4-
nitro-phenyl)-propanoic Acid Ethyl Ester 206 (99%, isolated yield). The β-nitroalcohol
product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H
NMR (300 MHz, CDCl$_3$, δ ppm): 1.35 (3H, t, $J = 7.2$ Hz), 4.34-4.46 (2H, m), 4.54 (1H,
s), 4.70 (1H, d, $J = 13.5$ Hz), 5.32 (1H, d, $J = 13.5$ Hz), 7.83-7.87 (2H, m), 8.23 (2H, d, $J$
= 8.7 Hz); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 13.8, 64.3, 76.0, 80.4, 123.9, 126.8,
143.3, 148.3, 170.6.

5.7.2. 2-Hydroxy-2-Nitromethyl-4-Phenyl-butanoic Acid Ethyl Ester 207

Ethyl 2-oxo-4-phenylbutyrate 201 (38 μL, 0.2 mmol, 1 equiv)
was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in
the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%)
following the general procedure to give 2-hydroxy-2-nitromethyl-4-phenyl-butanoic acid
ethyl ester 207 (90%, isolated yield). The β-nitroalcohol product was purified on silica
gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ
ppm): 1.36 (3H, t, $J = 7.2$ Hz), 1.98-2.06 (2H, m), 2.52-2.56 (1H, m), 2.83-2.87 (1H, m),
3.96 (1H, s), 4.32-4.39 (2H, m), 4.61 (1H, d, $J = 13.6$ Hz), 4.86 (1H, d, $J = 13.5$ Hz), 7.18-7.35 (5H, m); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): 14.1, 29.0, 38.2, 63.2, 75.0, 80.8, 126.4, 128.3, 128.6, 140.2, 172.6.

5.7.3 2-Hydroxy-2-methyl-3-nitro-propanoic Acid Ethyl Ester 199

Ethyl pyruvate 198 (23 $\mu$L, 0.2 mmol, 1 equiv) was treated with nitromethane (205 $\mu$L, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-hydroxy-2-methyl-3-nitro-propanoic acid ethyl ester 199 (95%, isolated yield). The $\beta$-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 1.26 (3H, t, $J = 7.2$ Hz), 1.39 (3H, s), 3.77 (1H, s), 4.19-4.35 (2H, m), 4.50 (1H, d, $J = 13.5$ Hz), 4.78 (1H, d, $J = 13.8$ Hz); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): 14.0, 23.9, 63.1, 72.4, 81.0, 173.4.

5.7.4 2-Hydroxy-2-nitromethyl-butanoic Acid Ethyl Ester 208

Ethyl 2-oxobutanoate 202 (26 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 $\mu$L, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-hydroxy-2-nitromethyl-butanoic acid ethyl ester 208 (90%, isolated yield). The $\beta$-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$ ppm): 0.84 (3H, t, $J = 7.5$ Hz), 1.26 (3H, t, $J = 6.9$ Hz), 1.47-1.75 (2H, m), 3.79 (1H, s), 4.20-4.35 (2H, m), 4.51 (1H, d, $J = 13.5$ Hz), 4.78 (1H, d, $J = 13.5$ Hz); $^{13}$C NMR (75.6 MHz, CDCl$_3$, $\delta$ ppm): 6.9, 13.9, 30.0, 62.9, 75.6, 80.6, 172.8.

5.7.5 2-Hydroxy-4-methyl-2-nitromethyl-pentanoic Acid Ethyl Ester 209
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Ethyl 4-methyl-2-oxopentanoate 203 (31 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-hydroxy-4-methyl-2-nitromethyl-pentanoic acid ethyl ester 209 (88%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 0.83 (3H, d, $J = 6.6$ Hz), 0.93 (3H, d, $J = 6.6$ Hz), 1.29 (3H, t, $J = 7.2$ Hz), 1.49-1.61 (2H, m), 1.69-1.80 (1H, m), 3.80 (1H, s), 4.20-4.24 (2H, m), 4.50 (1H, d, $J = 13.5$ Hz), 4.71 (1H, d, $J = 13.6$ Hz); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 13.9, 23.3, 23.7, 24.0, 44.5, 62.9, 75.4, 81.5, 173.3.

5.7.6. 2-Hydroxy-2-nitromethyl-octanoic Acid Ethyl Ester 210

Ethyl 2-oxooctanoate 204 (37 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-hydroxy-2-nitromethyl-octanoic acid ethyl ester 210 (85%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300MHz, CDCl$_3$, δ ppm): 0.80 (3H, t, $J = 6.9$ Hz), 1.06-1.19 (1H, m), 1.20-1.29 (9H, m), 1.38-1.52 (1H, m), 1.55-1.63 (2H, m), 3.81 (1H, s), 4.22-4.40 (2H, m), 4.50 (1H, d, $J = 13.5$ Hz), 4.77 (1H, d, $J = 13.5$ Hz); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 13.8, 13.9, 22.3, 22.4, 28.9, 31.4, 36.4, 62.8, 75.3, 80.8, 172.9.

5.7.7. 1-(2-Nitrophenyl)-2-nitroethanol 211
2-Nitrobenzaldehyde 205 (30 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(2-nitrophenyl)-2-nitroethanol 211 (96%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=3:7). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): 3.64 (1H, s), 4.42-4.49 (1H, m), 4.71-4.77 (1H, m), 5.89-5.93 (1H, m), 7.43-7.48 (1H, m), 7.63-7.68 (1H, m), 7.84 (1H, d, $J = 7.2$ Hz), 7.95 (1H, d, $J = 7.6$ Hz); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): 66.8, 80.2, 125.0, 128.7, 129.7, 134.3, 134.5, 147.1.

5.7.8. 2-Hydroxy-2-nitromethyl-4-phenyl-pentanoic Acid Ethyl Ester 212

Ethyl 2-oxo-4-phenylbutyrate 201 (38 μL, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-hydroxy-2-nitromethyl-4-phenyl-pentanoic acid ethyl ester 212 (92%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): anti isomer-1.24-1.30 (3H, m), 1.55 (3H, d, $J = 6.9$ Hz), 1.88-1.90 (1H, m), 2.05-2.17 (1H, m), 2.25-2.37 (1H, m), 2.69-2.79 (1H, m), 3.79 (1H, s), 4.21-4.29 (2H, m), 4.74-4.85 (1H, m), 7.06-7.20 (5H, m); syn isomer-1.24-1.30 (3H, m), 1.55 (3H, d, $J = 6.9$ Hz), 1.84-1.93 (2H, m), 2.25-2.37 (1H, m), 2.69-2.79 (1H, m), 3.60 (1H, s), 4.21-4.29 (2H, m), 4.74-4.85 (1H, m), 7.06-7.20 (5H, m); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): anti isomer-12.8, 15.0, 29.5, 37.7, 63.3, 77.1, 89.0, 126.3, 128.4, 128.6, 140.4, 140.5, 172.4; syn isomer- 14.1, 14.2, 29.6, 37.9, 63.0, 76.7, 87.2, 126.4, 128.3, 128.5, 140.44, 140.6, 173.2.
5.7.9. 2-Hydroxy-2-methyl-3-nitro-butanoic Acid Ethyl Ester 213

Ethyl pyruvate 198 (23 μL, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-hydroxy-2-methyl-3-nitro-butanoic acid ethyl ester 213 (96%, isolated yield). \(^1\)H NMR (300 MHz, CDCl\(_3\), δ ppm): \textit{anti isomer}- 1.22-1.31 (3H, m), 1.43 (3H, s), 1.55-1.65 (3H, m), 3.70 (1H, s), 4.18-4.33 (2H, m), 4.75 (1H, q, \(J = 7.0\) Hz); \textit{syn isomer}- 1.22-1.31 (3H, m), 1.35 (3H, s), 1.55-1.65 (3H, m), 3.54 (1H, s), 4.18-4.33 (2H, m), 4.84 (1H, q, \(J = 7.0\) Hz); \(^13\)C NMR (75.6 MHz, CDCl\(_3\), δ ppm): \textit{anti isomer}- 14.0, 14.9, 23.3, 63.1, 74.9, 88.8, 173.2; \textit{syn isomer}- 12.6, 13.9, 23.4, 62.9, 74.8, 86.7, 174.2.

5.7.10. 1-(2-Nitrophenyl)-2-nitropropan-1-ol 214

2-Nitrobenzaldehyde 205 (30 mg, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(2-nitrophenyl)-2-nitropropan-1-ol 214 (99%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane = 1:1). \(^1\)H NMR (300 MHz, CDCl\(_3\), δ ppm): \textit{anti isomer}- 1.53-1.57 (3H, m), 3.30-3.36 (1H, br s), 4.97-5.10 (1H, m), 6.05-6.13 (1H, m), 7.55-7.58 (1H, m), 7.93-8.12 (3H, m); \textit{syn isomer}- 1.53-1.57 (3H, m), 3.30-3.36 (1H, br s), 4.97-5.10 (1H, m), 5.69-5.80 (1H, m), 7.55-7.58 (1H, m), 7.93-8.12 (3H, m); \(^13\)C NMR (75.6 MHz, CDCl\(_3\), δ ppm): \textit{anti isomer}- 11.9, 69.3, 84.8, 125.0, 128.9, 129.4, 134.0, 134.2, 147.1; \textit{syn isomer}- 16.4, 70.5, 87.6, 125.2, 129.3, 129.7, 134.1, 134.3, 148.3.

5.7.11. 2-Nitroheptan-3-ol 215
Chapter 5

Experimental

Valeraldehyde 137 (22 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 2-nitroheptan-3-ol 215 (94%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane = 1:5) to give a colorless oil (94% yield); ¹H NMR (300 MHz, CDCl₃, δ ppm): anti isomer- 0.83-0.87 (3H, m), 1.28-1.40 (6H, m), 1.46-1.49 (3H, m), 2.43 (1H, br s), 4.11-4.19 (1H, m, anti-CHOH), 4.42-4.52 (1H, m); syn isomer- 0.83-0.87 (3H, m), 1.28-1.40 (6H, m), 1.46-1.49 (3H, m), 2.43 (1H, br s), 3.75-3.90 (1H, m, syn-CHOH), 4.42-4.52 (1H, m); ¹³C NMR (75.6 MHz, CDCl₃, δ ppm): anti isomer- 13.9, 16.2, 22.4, 27.2, 32.7, 72.9, 86.4; syn isomer- 12.3, 16.1, 22.5, 27.9, 32.6, 72.1, 87.8.

5.7.12. 1-(2-Furyl)-2-nitropropan-1-ol 216

2-Furaldehyde 141 (18 μL, 0.2 mmol, 1 equiv) was treated with nitromethane (205 μL, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give 1-(2-furyl)-2-nitropropan-1-ol 216 (94%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane = 1:5). ¹H NMR (300 MHz, CDCl₃, δ ppm): anti isomer- 1.56-1.60 (3H, m), 3.21 (1H, br s), 4.85-5.02 (1H, m), 5.29-5.33 (1H, m), 6.38-6.42 (2H, m), 7.40-7.44 (1H, m); syn isomer- 1.34-1.39 (3H, m), 3.21 (1H, br s), 4.85-5.02 (1H, m), 5.06-5.09 (1H, m), 6.38-6.42 (2H, m), 7.40-7.44 (1H, m); ¹³C NMR (75.6 MHz, CDCl₃, δ ppm): anti isomer- 13.1, 68.9, 85.0, 108.2, 110.6, 142.8, 150.8; syn isomer- 16.2, 69.5, 86.3, 109.3, 110.5, 143.2, 151.3.

5.7.13. (E)-2-Nitro-5-phenyl-4-buten-3-ol 217
Trans-cinnamaldehyde 142 (26 μL, 0.2 mmol, 1 equiv) was treated with nitroethane (285 μL, 4.0 mmol, 20 equiv) in the presence of BIQ rac-29 (5.1 mg, 0.02 mmol, 10 mol%) following the general procedure to give (E)-2-nitro-5-phenyl-4-buten-3-ol 217 (92%, isolated yield). The β-nitroalcohol product was purified on silica gel by flash column chromatography (EA/Hexane=1:5). $^1$H NMR (300 MHz, CDCl$_3$, δ ppm): anti isomer- 1.44-1.52 (3H, m), 2.66 (1H, d, $J$ = 3.9 Hz), 4.47-4.50 (1H, m), 4.69-4.77 (1H, m), 5.96-6.05 (1H, m), 6.60-6.69 (1H, d, $J$ = 15 Hz), 7.24-7.29 (5H, m); syn isomer- 1.44-1.52 (3H, m), 2.66 (1H, d, $J$ = 3.9 Hz), 4.47-4.50 (1H, m), 4.50-4.56 (1H, m), 5.96-6.05 (1H, m), 6.60-6.69 (1H, d, $J$ = 15 Hz), 7.24-7.29 (5H, m); $^{13}$C NMR (75.6 MHz, CDCl$_3$, δ ppm): anti isomer- 13.0, 73.3, 86.1, 125.1, 126.7, 128.4, 128.7, 133.8, 135.6; syn isomer-16.2, 74.7, 87.2, 125.2, 126.8, 128.6, 128.8, 134.9, 135.8.
Chapter 6. Future Work

6.1. Application of chiral BIQs in asymmetric aza-Henry reaction

Bearing close resemblance to three of the most fundamental carbon-carbon bond forming reactions (aldol, Mannich and Henry), nitro-Mannich coupling allows access to synthetically useful $\beta$-nitroamine products. Also known as aza-Henry reaction, it involves the addition of nitro compounds to azomethine functions.\(^{116}\) This reaction is a highly valuable C-C bond forming process, as the $\beta$-nitroamine products 219 can be transformed into 1,2-diamines 220/221 via reduction or $\alpha$-amino acids by a Nef oxidation (Scheme 68). Diamines are of particular interest as they can be employed as biologically active natural products, drug candidates and chiral ligands for asymmetric reactions. Hence, the stereocenters in the products must be controlled to give the required configuration.

Scheme 68

Nonetheless, development for the enantioselective version for this reaction is challenging.\(^{238-239}\) The catalyst must be able to activate the imine to a nucleophilic attack, but not be hindered by strong Lewis basic amine products. Based on the great results afforded from BIQ (R)-29 and its alkyl derivatives in the Henry reaction (Chapter 3), future work can be focused to explore these BIQs for the asymmetric catalysis of aza-Henry reaction.
REFERENCES


45 Gensler, W. J. *Organic reactions* 1951, 6, 191-206.


67 Gao, Q., PhD, **2009**, Nanyang Technoogical University.

68 GAO, Q. Novel 1,1′-Bisisoquinolines: Synthesis, Resolution and Application in Asymmetric Catalysis, **2010**, NANYANG TECHNOLOGICAL UNIVERSITY.

69 Judeh, Z. M. A. Design and Synthesis of Bis-isoquinoline Derivatives for use as Cleft-like Host Molecules, PhD thesis, **2000**, The University of New South Wales.


75 *CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation* CRC Press LLC: Boca Raton, **2000**.

76 Newman, P. In *optical resolution for chemica compounds*; Manhattan College: Riverdale, New York, **1976**: Vol. 1, p 10471.
References

86 *Homogeneous Transition Metal Catalyzed Reactions*; American Chemical Society, **1992**; Vol. 230.
90 Cavell, K. J.; Elliott, M. C.; Nielsen, D. J.; Paine, J. S. *Dalton Trans.* **2006**, *4922-4925.*


101 Shibasaki, M.; Groger, H.; Kanai, M. *In Comprehensive Asymmetric Catalysis*; Springer: Heidelberg, Germany, **2004**.

102 Shibasaki, M.; Groger, H. *In Comprehensive Asymmetric Catalysis*; Springer: Berlin, Germany, **1999**.


Ono, N. *The Nitro Group in Organic Synthesis*; Wiely-VCH: New York, **2001**.


References


References


References


APPENDIX

$^1$H, $^{13}$C NMR, FTIR and Mass spectra results of 100

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$^1$H, $^{13}$C NMR, spectra and HPLC results of (R)-143

$^1$H, $^{13}$C NMR, spectra and HPLC results of (R)-144
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\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-145} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-146} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-147} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-148} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-149} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-150} \]

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\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-152} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-153} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-154} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-155} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-156} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-157} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-158} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-159} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-160} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-177} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-178} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-179} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-180} \]

\[ {^1}H, \ {^{13}}C \text{ NMR, spectra and HPLC results of (R)-181} \]

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$^1$H, $^{13}$C NMR, spectra and HPLC results of 187 246
$^1$H, $^{13}$C NMR, spectra and HPLC results of 188 247
$^1$H, $^{13}$C NMR, spectra and HPLC results of 189 248
$^1$H, $^{13}$C NMR, spectra and HPLC results of 190 249
$^1$H, $^{13}$C NMR, spectra and HPLC results of 191 250
$^1$H, $^{13}$C NMR, spectra and HPLC results of 192 251
$^1$H, $^{13}$C NMR, spectra and HPLC results of 193 252
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\[ \text{HN} \]
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100

$\text{\textsuperscript{1}H NMR}$

$\text{\textsuperscript{13}C NMR}$

$\text{FTIR}$

$\text{Mass}$
ract-98

\[ \text{rac-98} \]

\[ \text{H NMR} \]

\[ \text{13C NMR} \]

\[ \text{FTIR} \]

\[ \text{HRMS} \]
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min

Hexane/IPA/Et₃N = 90/10/0.1

Column: Chiralcel OD-H column
Appendix

rac-112

\[ \text{FTIR} \quad \text{HRMS} \]

\[ \text{1H NMR} \quad \text{13C NMR} \]
HPLC results:

Separation conditions: Flow rate = 0.4 mL/min

$$\text{Hexane/IPA/Et}_3\text{N} = 95/5/0.05$$

Column: Chiralcel OD-H column
Appendix

rac-113

$^1$H NMR

$^{13}$C NMR

FTIR

HRMS
HPLC results:

Separation conditions: Flow rate = 0.5 mL/min

Hexane/IPA/Et$_3$N = 95/5/0.05

Column: Chiralcel OD-H column
Appendix

\[ \text{rac-114} \]

\[ \text{\textsuperscript{1}H NMR} \quad \text{\textsuperscript{13}C NMR} \]

\[ \text{FTIR} \quad \text{HRMS} \]
HPLC results:

Separation conditions: Flow rate = 0.5 mL/min

Hexane/IPA/Et₃N = 98/2/0.02

Column: Chiralcel OD-H column
Appendix

rac-115

\[ \text{\( ^1\text{H NMR} \)} \quad \text{\( ^{13}\text{C NMR} \)} \quad \text{FTIR} \quad \text{HRMS} \quad \text{HMQC} \quad \text{HMBC} \]
Appendix

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\text{rac-117}
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Appendix

rac-118

1H NMR

13C NMR

FTIR

HRMS

HMOC

HMBC
Appendix

rac-119

$^1$H NMR

$^{13}$C NMR

FTIR

HRMS
HPLC results:

Separation conditions: Flow rate = 0.3 mL/min

Hexane/IPA/Et$_3$N = 90/10/0.1

Column: Chiralcel OD-H column
(R)-163

**1H NMR**

**13C NMR**

**FTIR**

**HRMS**
HMQC  
HMBC

HPLC results:

Separation conditions: Flow rate = 1.0 mL/min

Hexane/IPA/Et$_3$N = 98/2

Column: Chiralcel OD-H column
**HPLC results:**

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 90/10

Column: Chiralcel OD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 85/15
Column: Chiralcel OD-H column
Appendix

\[
\text{OH} \quad \text{NO}_2 \quad (R)-144
\]

\[
\begin{align*}
\text{HPLC results:} \\
\text{Flow rate} &= 1.0 \text{ mL/min}, \quad \text{Hexane/IPA} = 90/10 \\
\text{Column:} &\quad \text{Chiralcel OD-H column}
\end{align*}
\]
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10
Column: Chiralcel OD-H column
\( \text{OH} \)

\[
\begin{align*}
\text{Cl} & \quad \text{NO}_2 \\
(\text{R})-146
\end{align*}
\]

**HPLC results:**

Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 90/10

Column: Chiralcel OJ-H column
HPLC results:

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 90/10

Column: Chiralcel OD-H column
**HPLC results:**

Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 90/10

Column: Chiralcel OD-H column
Appendix

\[
\text{(R)-149}
\]

\[
\begin{align*}
\text{HPLC results:} \\
\text{Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 90/10} \\
\text{Column: Chiralcel OD-H column}
\end{align*}
\]
HPLC results:

Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 90/10
Column: Chiralcel OD-H column
HPLC results:

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 85/15

Column: Chiralcel OD-H column
HPLC results:

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 85/15

Column: Chiralcel OD-H column
HPLC results:

Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 90/10

Column: Chiralcel OD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10
Column: Chiralcel OD-H column
HPLC results:

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 98/2

Column: Chiralpak AD-H column
$\text{OH}$

$\text{NO}_2$

$\text{(R)-156}$

$\text{H NMR}$

$\text{13C NMR}$

HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 98/2

Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 98/2

Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 85/15
Column: Chiralpak OD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10

Column: Chiralpak OJ-H column
Appendix

\[ \text{(R)-160} \]

HPLC results:

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 90/10

Column: Chiralpak OD-H column
HPLC results:

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 85/15
Column: Chiralpak OD-H column
OH
\[\text{NO}_2\]

(R)-178

HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 98/2

Column: Chiralpak AD-H column
$\text{OH}$

$\text{NO}_2$

$(R)-179$

$\text{H NMR}$

$\text{C NMR}$

HPLC results:

$(R)-179$

$\text{rac}-179$

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 98/2

Column: Chiralpak AD-H column
Appendix

\[
\begin{align*}
\text{OH} & \quad \text{NO}_2 \\
(R)-180
\end{align*}
\]

HPLC results:

\text{Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 98/2}

Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 0.5 mL/min, Hexane/IPA = 98/2
Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 0.6 mL/min, Hexane/IPA = 98/2
Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10

Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 80/20
Column: Chiralcel OD-H + Chiralpak AD-H columns
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 95/5
Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 95/5
Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10
Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 95/5
Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10
Column: Chiralpak AS-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 95/5

Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 90/10

Column: Chiralpak AD-H column
OH
\[\text{NO}_2\]

193

\[\text{H NMR} \quad \text{C NMR}\]

HPLC results:

nonracemic-193

rac-193

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 98/2

Column: Chiralpak AD-H column
Appendix

HPLC results:

Separation conditions: Flow rate = 0.8 mL/min, Hexane/IPA = 98/2
Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 1.0 mL/min, Hexane/IPA = 99.5/0.5

Column: Chiralpak AD-H column
HPLC results:

Separation conditions: Flow rate = 0.6 mL/min, Hexane/IPA = 98/2
Column: Chiralpak OB-H column
HPLC results:

Separation conditions: Flow rate = 0.6 mL/min, Hexane/IPA = 99/1
Column: Chiralpak AD-H column
Appendix

OH
O
O
O
2N
O
OH
O
O
2N

1H NMR

13C NMR

1H NMR

13C NMR
Appendix

\[
\begin{align*}
\text{1H NMR} & \\
\text{13C NMR} & \\
\end{align*}
\]
Appendix

211

212

$^{1}H \text{ NMR}$  

$^{13}C \text{ NMR}$
Appendix

213

$\text{H NMR}$  $\text{C NMR}$

214

$\text{H NMR}$  $\text{C NMR}$
Appendix

\[
\begin{align*}
\text{OH} & \quad \text{NO}_2 \\
\end{align*}
\]

\[217\]

\begin{align*}
\text{H NMR} & \quad \text{C NMR} \\
\end{align*}

\[1^H \text{ NMR} \quad 13^C \text{ NMR}\]