SYNOPSIS

The thesis entitled “Synthesis and Applications of Pyrrolidine Based Amino acids and Hydroxylamine Derivatives” has been divided into three chapters.

CHAPTER-I: Chapter I describes the Asymmetric synthesis of 3-hydroxyproline: The constituent of several bioactive compounds.

CHAPTER-II: Chapter II is further divided into two sections (Section-A and Section-B).

Section-A: This section describes the development of a new chiral pyrrolidine-pyrazole catalyst for enantioselective Michael addition of carbonyls to nitroolefins and Mechanistic insight.

Section-B: This section describes the development of a new hydroxylphthalimide allied triazole-pyrrolidine catalyst for asymmetric Michael additions in water.

CHAPTER-III: Chapter III is divided into two sections (Section-A and Section-B).

Section-A: This section describes the application of hydroxylamine derivatives as nucleophiles in Ferrier glycosylation: Synthesis of aminooxy pseudoglycals.

Section-B: This section describes the application of hydroxylamine derivatives in click chemistry: Synthesis of novel triazoles and oxime ethers.

CHAPTER-I

This chapter describes the synthesis of 3-hydroxyproline: The constituent of several bioactive compounds.

3-Hydroxyprolines are one of the significant members of $\beta$-hydroxy-$\alpha$-amino acids, which are found as key structural components in biologically active compounds. Specifically, (2S,3S)-3-hydroxyproline ($\textit{trans}$-3-hydroxy-$\textit{L}$-proline) 1, was found in various pharmaceutically important compounds such as antibiotic Telomycin, polyhydroxylated alkaloids, cyclopeptide alkaloids and also serve as valuable chiral building block in organic synthesis. It is a natural product first isolated from hydrolysates of Mediterranean sponge and later from collagen hydrolysates of various sources. In association with our work on synthesis of peptides with unusual amino acids we aimed at
asymmetric synthesis of 1 and its enantiomer employing Sharpless asymmetric epoxidation and reductive cyclisation as the key steps. From the retrosynthetic perspective, we envisioned (2S,3S)-3-hydroxyproline 1 can be derived from compound 2, which could be obtained by reductive cyclisation followed by Boc protection of azidoeoxide 3. The azidoeoxide 3 can be attained from a known epoxy alcohol 4, which in turn can be easily synthesized from commercially available 3-butyne-1ol 6 (Scheme 1).

![Scheme 1 Retrosynthesis of (2S,3S)-3-hydroxyproline 1.](attachment:image)

**Synthesis of (2S,3S)-3-hydroxyproline 1:**

The synthesis of (2S,3S)-3-hydroxyproline 1 was achieved starting from commercially available 3-butyne-1-ol 6 as summarized in scheme-2. Accordingly, 6 was protected as para-methoxybenzyl ether (PMB) with NaH/PMB-Br in THF and further homologated to 7 under EtMgBr/formaldehyde conditions. Compound 7 was reduced with LiAlH₄ in THF to give allylic alcohol 8 in good yield. Sharpless asymmetric epoxidation of 8 with L (+) DET and TBHP afforded the enantiomerically enriched epoxide 5 in 72% yield. The tert-butyldimethylsilyl protection of the free hydroxyl group of 5 produced compound 9 in 92% yield. The subsequent deprotection of the PMB group with DDQ followed by tosylation with TsCl/Et₃N in CH₂Cl₂ resulted in compound 10 (in 80% yield), which was further subjected to nucleophilic displacement using NaN₃ in DMF at 70 °C to furnish the azidoeoxide 3 in 60% yield. The conversion of compound 6 to the desired hydroxy pyrrolidine 2 was achieved in a one-pot operation. The reduction of azide 3 with Pd/C-H₂ in MeOH to amine followed by subsequent epoxide opening (a 5- endo- tet ring closure) by amine, *insitu* cyclisation and Boc-protection resulted in the
required hydroxy pyrrolidine 2 in 45% yield. The compound 2 was converted to 1 by tert-butyldimethylsilyl protection of secondary hydroxyl group followed by selective deprotection of primary silyl ether with HF.Py/THF and subsequent oxidation of primary alcohol 11 in to acid 12 using TEMPO/BAIB followed by deprotection of Boc group under HCl/EtOH conditions. (Scheme 2) The other enantiomer of 1, (2R,3R)-3-hydroxyproline ent-1 was synthesized in a procedure analogous to scheme 2, from 8 by performing Sharpless asymmetric epoxidation using D (-) DET instead of L (+) DET.

Scheme 2 Synthesis of (2S,3S)-3-hydroxyproline 1.

In conclusion, we have achieved the enantioselective synthesis of (2S,3S)-3-hydroxyproline 1 and (2R,3R)-3-hydroxyproline ent-1 using Sharpless asymmetric epoxidation and reductive cyclisation as the key steps.
CHAPTER-II, Section-A:

This section describes the development of a new A chiral pyrrolidine-pyrazole catalyst for enantioselective Michael addition of carbonyls to nitroolefins and mechanistic insight.

Asymmetric Michael addition is one of the widely used basic C-C bond forming reactions to test the efficiency of new organocatalysts. Since the discovery of L-proline catalysed asymmetric transformations, various proline based organocatalysts have been employed for asymmetric Michael reactions with various levels of success. With continued our interest in organocatalysis, we have developed a new chiral pyrrolidine-pyrazole catalyst for asymmetric Michael reaction of carbonyls to nitroolefins. The chiral pyrrolidine-pyrazole 1 employed for this work was easily obtained by coupling pyrazole with tosylated-L-Boc prolinol 3. Compound 3 could be easily obtained from L-proline 4 (Scheme 1 & 2).

Scheme 1 Retrosynthesis of pyrrolidine-pyrazole catalyst 1.

Scheme 2 Synthesis of pyrrolidine-pyrazole catalyst 1.
Evaluation of the catalyst:

After the successful synthesis of the organocatalyst 1, initial experiments were performed with the reaction between cyclohexanone 8a and nitrostyrene 9a to test the efficiency of the catalyst 1. Firstly, the reaction was carried out in CH₂Cl₂ at room temperature by using 10 mol% of catalyst 1. To our delight, the reaction proceeded well to give the corresponding Michael adduct 10a in 80% yield with 94:6 (syn/anti) diastereoselectivity and 89% enantiomeric excess in 24 h. In order to establish the optimized reaction conditions, we have screened a variety of solvents, interestingly the best yields (96%) along with high stereoselectivities (syn/anti = 98:2, ee = 94%) were observed in the case of solvent-free reaction conditions (for 24 h). After the solvent screening experiments, we then examined the effect of various additives and the best result was found with TFA (2 mol%), giving the product in 98% yield with (syn/anti = 98:2, ee = 95%) in 15 h reaction time. In addition, we have also tested the effect of catalyst loading in the Michael addition of cyclohexanone 8a onto nitroolefin 9a. The decrease in catalyst loading had no profound effect on selectivities but took very long reaction times, whereas the increase in catalyst loading to 20 mol% produced similar results (Scheme 3).

![Scheme 3](image)

Having established the optimal conditions, we then explored the generality of this reaction with a variety of nitroolefins 9b-j using cyclohexanone 8a as the Michael donor (Scheme 4) (Table 1). The present catalytic system is tolerant to a broad range of nitroolefins derived from aromatic aldehydes bearing electron-donating as well as electron-withdrawing groups (entries 1 to 6, Table 1) and heteroaromatic aldehydes providing a series of γ-nitro carbonyl compounds in high yields with good to high selectivities (entries 7 to 9, Table 1). To further expand the scope of the newly prepared catalyst, the reaction of β-nitrostyrene 9a with different carbonyl compounds 8b-h has also been examined (Scheme 5) (Table 2).
After the above successful experiments we decided to study the mechanistic pathway and the transition state involved in the reaction. On the basis of our experimental findings, we propose a possible mechanism for asymmetric Michael reaction catalysed by pyrrolidine-pyrazole catalyst 1 (Figure 1), which was supported by the ESI-MS of the reaction mixture showing peaks at m/z 232 (M+H)⁺ & 381(M)⁺ corresponding to the reaction intermediates 11 and 12 respectively. Further, the reaction was also investigated by computational studies.

Figure 1 Possible reaction mechanism.
<table>
<thead>
<tr>
<th>entry</th>
<th>nitro olefin</th>
<th>time (h)</th>
<th>product</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>syn/anti&lt;sup&gt;c&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
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<tr>
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<td>O₂N-CH=N-NO₂</td>
<td>15</td>
<td>O₂N-CH=N-NO₂</td>
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<td>92</td>
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<td>MeO-CH=N-NO₂</td>
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<td>MeO-CH=N-NO₂</td>
<td>97</td>
<td>96:4</td>
<td>98</td>
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<tr>
<td>3</td>
<td>Me-CH=N-NO₂</td>
<td>15</td>
<td>Me-CH=N-NO₂</td>
<td>93</td>
<td>97:3</td>
<td>99</td>
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<td>95</td>
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<td>18</td>
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<td>90</td>
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<tr>
<td>9</td>
<td>CH=N-NO₂</td>
<td>18</td>
<td>CH=N-NO₂</td>
<td>93</td>
<td>94:6</td>
<td>86</td>
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</tbody>
</table>

<sup>a</sup> Reaction conditions: Nitrostyrene (1 mmol), cyclohexanone (5 mmol), catalyst (10 mol%) solvent-free, rt  
<sup>b</sup> Isolated yields  
<sup>c</sup> Determined by <sup>1</sup>H NMR and HPLC analysis  
<sup>d</sup> Determined by chiral HPLC using chiral pak-IA, IC or OD-H columns
In conclusion, we have developed a new chiral pyrrolidine-pyrazole catalyst for asymmetric Michael reaction of carbonyls to nitroolefins. The reactions were best performed with 10 mol% of the catalyst, in combination with TFA under solvent-free conditions giving rise to the products in high yields and high stereoselectivities. Further the mechanistic insights of the reaction were also demonstrated using mass spectral studies and computational studies.
CHAPTER-II, Section-B:

This section describes the development of a new hydroxyphthalimide allied triazole-pyrrolidine catalyst for asymmetric Michael additions in water.

With our continued interest on organocatalysts, we have developed a new hydroxyphthalimide linked triazole-pyrrolidine catalyst 13 from L-proline 4 using the Huisgen 1,3- dipolar cycloaddition, ‘click reaction’. We envisioned that N-propargyloxyphthalimide 14 could participate in a click reaction with Boc-protected proline azide 15 to afford Boc protected catalyst, which on deprotection of Boc group would yield the desired organocatalyst 13 (Scheme 6 & 7).

Scheme 6 Retrosynthesis of organocatalyst 13.

Scheme 7 Synthesis of organocatalyst 13.

Evaluation of the catalyst:

The efficiency of the catalyst 13 was evaluated in a model reaction of cyclohexanone 8a with β-nitrostyrene 9a. Initially, the reaction was performed in THF with 10 mol% of the catalyst 13 at room temperature and found that the reaction proceeded well to give the Michael product 10a in 65% yield, syn/anti = 7:3, ee = 72% for 24 h. To further improve the yield as well as stereoselectivity we have investigated
the effect of different solvents and the best result was observed when H₂O was used as the solvent (92% yield, syn/anti = 9:1, ee = 88% for 18 h). With the hope of improving the yield and selectivity we next examined the effect of various acid additives. From these experiments we found that the use of PhCOOH (5 mol%) as an additive improved the selectivity as well as the yield (Scheme 8).

![Scheme 8](image)

**Scheme 8**

Having the established reaction conditions, a series of nitroolefins 9a-d & 9i-l (Michael acceptors) with ketones 8a, 8b & 8f (Michael donors) were examined to expand the substrate scope of the catalyst 13 (Scheme 9). All β-nitrostyrenes 9a-d & 9i-l irrespective of the nature of substituents on aryl group were reacted smoothly with cyclohexanone 8a to give the corresponding Michael adducts 10a-d & 10i-l in good yields with high diastereoselectivity and enantioselectivity (Table 3). The reaction of β-nitrostyrenes 9a & 9d with cyclopentanone 8a was also equally good resulting in the corresponding Michael products 10k & 10r respectively with good yields and selectivities (entries 1 and 2, Table 4). Whereas the reaction of β-nitrostyrenes 9a & 9b with acetone 8f was very sluggish and afforded the desired products 10o & 10s respectively in low yield with low selectivity even after prolonged reaction times (entry 3 and 4, Table 4).

![Scheme 9](image)

**Scheme 9**
<table>
<thead>
<tr>
<th>entry</th>
<th>nitroolefin</th>
<th>time (h)</th>
<th>product</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>syn/anti&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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</table>

<sup>a</sup> Isolated yields.

<sup>b</sup> Determined by <sup>1</sup>H NMR and HPLC analysis.

<sup>c</sup> Determined by chiral HPLC using chiral pak-IA, IC or OD-H columns.

Table 3
Based on the above experimental results, we propose two potential transition states to rationalize the stereochemical outcome of the asymmetric Michael addition reaction performed by organocatalyst 13 (Figure 2).

![TS 1](image1.png)

**TS 1**

![TS 2](image2.png)

**TS 2**

In conclusion, we have developed a new pyrrolidine-triazole organocatalyst by employing click reaction conditions for the asymmetric Michael addition of ketones to nitroolefins. The reactions were performed in water with the aid of an acid co-catalyst leading to the desired products in good yield and high selectivity.
CHAPTER-III, Section-A:

This section describes the application of hydroxylamine derivatives as nucleophiles in Ferrier glycosylation: Synthesis of aminoxy pseudoglycals.

Aminoxy functionality has gained importance in chemistry as well as in biology. This functionality was found in many compounds such as carbohydrates, peptides, steroids, glycoproteins and also in a large number of biologically active molecules. Further the carbohydrates bearing aminoxy group are used as intermediates for the synthesis of several bioactive compounds. These aspects along with our interest in Ferrier glycosylation as well as in the exploration of hydroxylamine derivatives, prompted us to develop a new method in Ferrier glycosylation by employing hydroxylamine derivatives as nucleophiles.

Initially the reaction was performed with tri-O-acetyl-D-glucal 1a using N-hydroxysuccinimide 2a as the nucleophile in dichloromethane at room temperature employing Lewis acid catalysts to give the corresponding pseudoglycal 3a in good yields and selectivities. Among the catalysts tested, ZnCl₂ (2 mol%) was found to be more effective than others in terms of yield, reaction profile and selectivity (Scheme 1).

Encouraged by this observation, we performed the Ferrier glycosylation of tri-O-acetyl-D-glucal 1a using N-hydroxysuccinimide 2b as the nucleophile in dichloromethane at room temperature employing ZnCl₂ (2 mol%). The reaction proceeded well to give the corresponding pseudoglycal 3b in 90% yield with 20:1(α/β) selectivity (Scheme 2).
With the above successful results, we then explored the scope of this reaction by replacing the tri-\(O\)-acetyl-D-glucal 1a with other tri-\(O\)-protected-D-glucals. In this process various tri-\(O\)-protected-D-glucals, such as tri-\(O\)-benzyl-D-glucal 1b, tri-\(O\)-allyl-D-glucal 1c and tri-\(O\)-methyl-D-glucal 1d were reacted independently with \(N\)-hydroxyphthalimide 2a as well as with \(N\)-hydroxysuccinimide 2b under the optimized reaction conditions and the results of these experiments are summarized in Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Glucal</th>
<th>Hydroxylamine derivative</th>
<th>time (h)</th>
<th>Pseudoglycal</th>
<th>Yield (%)(^a)</th>
<th>Anomeric ratio ((\alpha/\beta))(^b)</th>
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<td>3c</td>
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<td>2b</td>
<td>4</td>
<td>3d</td>
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<tr>
<td>3</td>
<td>1c</td>
<td>2a</td>
<td>3</td>
<td>3e</td>
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<td>3f</td>
<td>82</td>
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<td>5</td>
<td>1d</td>
<td>2a</td>
<td>4</td>
<td>3g</td>
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<td>6</td>
<td>1d</td>
<td>2b</td>
<td>4.5</td>
<td>3h</td>
<td>78</td>
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</table>

\(^a\)Isolated yields as anomeric mixtures after purification
\(^b\)The anomeric ratio was determined on the basis of the integration of the anomeric hydrogen in the \(^1H\) NMR spectra

Table 1
Having developed a useful Ferrier glycosylation, we next examined the transformations of the product 3a. Accordingly, the product 3a was subjected to the deprotection of phthalimide group using hydrazine hydrate to give the aminoxo compound 4 in 65% yield, which was then transformed to 5 and 7 as described in Scheme 3. The aminoxo compounds 4 and 5 can be used as intermediates for the synthesis of bioactive compounds.

Scheme 3. Transformations from 3a.

In conclusion, we have described the use of hydroxylamine derivatives as the oxygen atom nucleophiles in Ferrier glycosylation. This transformation, efficiently catalyzed by ZnCl$_2$, affords aminoxo pseudoglycal product in good yields and with high $\alpha$-selectivity. The products were also successfully transformed to the useful oxime derivatives and may find use in organic synthesis.

CHAPTER-III, Section-B:

This section describes the application of hydroxylamine derivatives in click chemistry: Synthesis of novel triazoles and oxime ethers.

Since the discovery of click chemistry, 1,2,3-triazoles have become one of the most important heterocycles in medicinal, material and biological research. 1,2,3-
Triazoles have been widely used in synthetic intermediates and industrial applications, such as dyes, anticorrosive agents, photo stabilizers, agrochemicals etc. These compounds also display numerous biological activities like anti-HIV activity, antimicrobial activity against Gram positive bacteria, anti-allergic, anti-convulsant, anti-fungal, β-lactamase inhibitory etc. With our interest in click chemistry as well as in exploration of hydroxylamine derivatives we have synthesized several structurally divergent 1,4-disubstituted-1,2,3-triazoles 10a-h possessing imido functionality, from N-propargyloxyphthalimide 8 and different organic azides 9a-h using Huisgen 1,3-dipolar cycloaddition ‘click reaction’ (Scheme 4) (Figure 1). Further the triazole 10a was transformed to aminoxyl compound 11, which was used for the synthesis of triazole based oxime ethers 12a-l on reaction with various carbonyl compounds (Scheme 5) (Figure 2).
Figure 1 Structures of 1,4-disubstituted-1,2,3-triazoles 10a-h.
In conclusion, we have achieved the synthesis of novel 1,4-disubstituted-1,2,3-triazoles and triazole based oxime ethers from N-propargyloxyphthalimide and different organic azides by employing Huisgen 1,3-dipolar cycloaddition ‘click reaction’.

**Figure 2** Structures of triazole based oxime ethers 12a-l.