ABSTRACT

The thesis entitled “Asymmetric Synthesis towards Bioactive Molecules: Linezolid, Eperezolid, Moprolol, Toliprolol, Bunitrolol via Nitroaldol reaction and Organic transformation over Copper Fluorapatite” is divided into four chapters.

The title of the thesis clearly specify the objective to synthesize an enantiomerically pure bioactive molecules Linezolid, Eperezolid, Moprolol, Toliprolol, Bunitrolol and the development of synthetic methodologies over heterogeneous recyclable copper fluorapatite catalyst. Chapter 1 deals with an enantioselective synthesis of Linezolid and Eperezolid via nitroaldol reaction over copper fluorapatite catalyst in the presence of $C_2$-symmetric chiral piperazine ligand. Chapter 2 describes an enantioselective synthesis of three β-blockers namely (S) Moprolol, (S)-Toliprolol and (S)-Bunitrolol via nitroaldol reaction over copper fluorapatite catalyst in the presence of chiral trianglamine ligand. Chapter 3 deals with the synthetic methodologies for the synthesis of diaryl ethers over heterogeneous, reusable copper fluorapatite catalyst. Chapter 4 describes the synthetic methodologies for the synthesis of β-nitroalcohols and amides from aldehydes using copper fluorapatite as heterogeneous and reusable catalyst.

Chapter 1

Enantioselective synthesis of Linezolid and Eperezolid via nitroaldol reaction over copper fluorapatite catalyst in the presence of chiral $C_2$-symmetric piperazine ligand

The chapter includes the preparation of copper fluorapatite catalyst and details about biological action and comprehensive literature on synthesis of Linezolid and Eperezolid. Both Linezolid and Eperezolid are the new class of the antibacterial agents that can
inhibit the bacterial growth by a novel mechanism involving the early inhibitions of bacterial protein synthesis prior to chain initiation (Fig. 1).

Fig. 1. Structure of Linezolid 1 and Eperezolid 2.

The 3-aryl-2-oxazolidinones are a relatively new class of synthetic antibacterial agents having a new mechanism of action which involves early inhibition of bacterial protein synthesis. Linezolid 1, the first and only oxazolidinone belongs to a new class of synthetic antibacterial drugs and is available for intravenous or oral treatment of gram-positive infections caused by bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant *Enterococcus faecalis* (VRE). However, Linezolid 1 displays modest activity against RTI-causative gram-negative bacteria such as *Haemophilus influenzae*, and resistance against Linezolid has already been observed in gram-positive bacteria such as *S. aureus* and *Enterococcus faecium*.

**Enantioselective synthesis of Linezolid**

The synthesis was started with the 3-fluoro, 4-morpholinyl aniline 3 (scheme 1), which was prepared from 3,4-difluoronitrobenzene with excess amount of morpholine under nucleophilic aromatic displacement at the para position, selectively gave the p-substituted nitrobenzene followed by reduction of nitro group using 10 % Pd/C as catalyst and ammonium formate as hydrogen donor gave amine 3. 3-fluoro, 4-morpholinyl aniline 3
was treated with 2-chloroethanol in an \( n \)-butanol in the presence of molecular iodine catalyst and then followed by the protection of amine with Cbz-Cl in a DCM solvent at room temperature provided amine protected alcohol 4. Amine protected alcohol 4 on Swern oxidation to give an aldehyde 5 as intermediate, which on an asymmetric nitroaldol reaction with nitromethane catalysed by copper fluorapatite in the combination with chiral \( C_2 \)-symmetric piperazine ligand gives \( \beta \)-nitro alcohol 6 as a key step product for the synthesis of Linezolide. The \( \beta \)-nitroalcohol 6 under goes cyclisation with anhydrous \( K_2 CO_3 \) in a methanol solvent to give nitro oxazolidinone product 7. The nitro oxazolidinone product 7 was reduced to amine by \( H_2 \) in the presence of Pd/C catalyst and acylated with acetic anhydride to give Linezolide 1.

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\begin{align*}
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Enantioselective synthesis of Eperezolid

The synthesis was started with the 3-fluoro-4-[4- (t-butoxycarbonyl)-piperazinyl] aniline 8 (scheme 2), which was prepared from 3, 4-difluoronitrobenzene with excess amount of piperazine under nucleophilic aromatic displacement at the para position, selectively gave the \( p \)-substituted nitrobenzene. The protection of secondary amine of piperazine with BOC- anhydride gave the protected amine followed by reduction of nitro group using 10 % Pd/C as catalyst and ammonium formate as hydrogen donor gave amine 8.

![Scheme 2](image)

**Scheme 2:** *Reagents and reactions conditions: (i) 2-Chloroethanol, I\(_2\), butanol, Reflux 8 h, 93 %; (ii) Cbz–Cl, NaHCO\(_3\), DCM, 95 %; (iii) (COCl)\(_2\), DMSO, Et\(_3\)N, CH\(_2\)Cl\(_2\), -78 to -60 °C, 93 %; (iv) CuFAP, Ligand, nitromethane, 24 h, 85 %; (v) K\(_2\)CO\(_3\), dry methanol, 0-RT, 12 h, 88 %; (vi) 10 % Pd/C, H\(_2\) (1 atm), EtOAc, 12 h then Ac\(_2\)O, Py, 92 %; (vii)(a)TFA, RT, 8 h (b) HOCH\(_2\)COCl, TEA, DCM, 0-RT, 4 h, 86 %.

3-fluoro-4-[4- (t-butoxycarbonyl)-piperazinyl]aniline 8 was treated with 2-chloroethanol in a \( n \)-butanol in the presence of molecular iodine catalyst gives 9 and then followed by
the protection of amine 9 with Cbz-Cl in a DCM solvent at room temperature provided amine protected alcohol 10. Amine protected alcohol 10 by Swern oxidation to give an aldehyde 11 as intermediate, which on an asymmetric nitroaldol reaction with nitromethane catalysed by copper fluorapatite in the combination with chiral C$_2$-symmetric piperazine ligand gives β-nitro alcohol 12 as a key step product for the synthesis of eperezolid. The β-nitroalcohol 12 under goes cyclisation with anhydrous K$_2$CO$_3$ in a methanol solvent to give nitro oxazolidinone product 13. The nitro oxazolidinone product 13 was reduced to amine by H$_2$ in the presence of Pd/C catalyst and acylated with acetic anhydride to give Boc protected eperezolid 14. Deprotection of Boc and finally acetylation of amine with 2-hydroxy acetyl chloride to gave Eperezolid 2.

Chapter 2

Enantioselective synthesis of (S)-Moprolol, (S)-Toliprolol and (S)-Bunitrolol via nitroaldol reaction over copper fluorapatite catalyst in presence of chiral trianglamine ligand

This chapter includes the details about biological action and comprehensive literature on synthesis of (S)-Moprolol, (S)-Toliprolol and (S)-Bunitrolol (Fig. 2). All three β-adrenergic blocking agents are (S)-Moprolol, (S)-Toliprolol and (S)-Bunitrolol, which posses antihypertensive, antianginal and sympatholytic properties. 

These β-Adrenergic blocking agents are important drugs widely used for the treatment of hypertension, angina pectoris, glaucoma, anxiety and obesity. The three fundamental goals of cardiovascular drugs are lowering of blood pressure (antihypertensive), return of the heart to rhythmic beating (antiarrhythmics) and the general improvement of the heart
muscle tone (cardiotonics). Biochemically, the mechanism of action involves the adrenergic system in which the hormonal system provides the communication link between the sympathetic nervous system and involuntary muscle.

Fig. 2. Structure of (S)-Moprolol 15, (S)-Toliprolol 16 and (S)-Bunitrolol 17

Enantioselective synthesis of (S)-Moprolol

Scheme 3: Reagents and reactions conditions: (i) NaOH, 3-chloro,1-2-propanediol, reflux, 8 h, 90 % (ii) NaIO₄, H₂O 0-5 °C, 90 % (iii) CuFAP, nitromethane, chiral trianglamine ligand, 84 % (iv) (a) H₂, Pd/C, methanol (b) isopropyl bromide, reflux, 88 %.
The synthesis was started with the commercially available guaiacol 18 (scheme 3). Guaiacol 18 was treated with 3-chloro, propane-1, 2-diol in a 10 % NaOH solution at refluxed condition for 8 h provided diol compound 19. The oxidation of diol 19 with NaIO₄ at 0-5 °C, gives aldehyde 20. The aldehyde 20 was subjected to nitroaldol reaction using CuFAP catalyst in the presence of chiral trianglamine ligand, gives β-nitro alcohol 21 as a key step product. Finally, the nitro group of 21 was reduced using H₂ in the presence of Pd/C catalyst in a methanol to provide amine and then followed by alkylation with isopropyl bromide at refluxed condition gives (S)-Moprolol 15.

**Enantioselective synthesis of (S)-Toliprolol**

**Scheme 4:** 
*Reagents and reactions conditions:* (i) NaOH, 3-chloro,1-2-propanediol, 8 h, 94 % (ii) NaIO₄, H₂O 0-5 °C, 93 % (iii) CuFAP, nitromethane, chiral trianglamine ligand, 84 % (iv) (a) H₂, Pd/C methanol (b) isopropyl bromide, reflux, 83 %.

The synthesis was started with the commercially available m-Cresole 22 (scheme 4). The m-Cresole 22 was treated with 3-chloro, propane-1,2-diol in a 10 % NaOH solution at refluxed condition for 8 h, provided diol compound 23. The oxidation of diol 23 with NaIO₄ at 0-5 °C, gives aldehyde 24. The aldehyde 24 was subjected to nitroaldol reaction
using CuFAP catalyst in the presence of chiral trianglamine ligand, gives β-nitro alcohol 25 as a key step product. Finally, the nitro group of 25 was reduced using H₂, in the presence of Pd/C catalyst in a methanol to provide amine and then followed by alkylation with isopropyl bromide at refluxed condition gives (S)-Toliprolol 16.

**Enantioselective synthesis of (S)-Bunitrolol**

The synthesis was started with the commercially available o-cynophenole 26 (scheme 5). The o-cynophenole 26 was treated with 3-chloro, propan-1, 2-diol in a 10 % NaOH solution at refluxed condition provided diol compound 27. The oxidation of diol 27 with NaIO₄ at 0-5 °C, gives aldehyde 28. The aldehyde 28 was subjected to nitroaldol reaction using CuFAP catalyst in the presence of chiral trianglamine ligand, gives β-nitro alcohol 29 as a key step product. Finally, the nitro group of 29 was reduced using H₂, in the presence of Pd/C catalyst in a methanol to provide amine and then followed by alkylation with tert-butyl bromide at refluxed condition gives (S)-Bunitrolol 17.

![Chemical structures]

**Scheme 5:** Reagents and reactions conditions: (i) NaOH, 3-chloro,1-2-propanediol, 8 h, 92 % (ii) NaIO₄, H₂O, 0-5 °C, 96 % (iii) CuFAP, nitromethane, chiral trianglamine ligand, 90 % (iv) (a) H₂, Pd/C methanol (b) tert-Butyl bromide, reflux, 79 %.
Chapter 3

Copper fluorapatite catalysed ligand-free synthesis of diaryl ethers

The chapter describes introduction, literature survey and the applications of heterogeneous reusable copper fluorapatite catalyst for synthesis of diaryl ethers. The chapter is divided into two sections.

Section I: Synthesis of diaryl ethers from phenols and aryl halides

Diaryl ether motifs are presents in the natural products and medicinally important compounds. Diaryl ethers molecules are not only important in biological systems but also key moieties in pharmaceutical, agricultural, polymer, industrial and life science. The classical copper catalysed Ullmann coupling reaction for ether synthesis has been extensively used for the formation of diaryl ether on industrial scale in polar solvents. However application on industrial scale synthesis has been limited due to harsh reaction conditions such as high reaction temperature (125-300 °C), longer reaction time at which many functional groups are unstable hence lower yield to desire product. In addition, requirement of excess or stoichiometric quantities of copper complexes leads to problem of waste disposal.

\[ \text{R, } R' = \text{H, Me, OMe, NO}_2, \text{t-Bu, Ph, Naphthyl, Halogen, etc} \]

Scheme 6: Reagents and reactions conditions: (i) Haloarenes (1 mmol), substituted potassium phenoxide (1.1 mmol), CuFAP (100 mg), NMP (1 mL), 120 °C, 5-12 h.
Abstract

Developed, a novel ligand free, highly efficient, an inexpensive and general method for the synthesis of diaryl ethers in a good to excellent yield from the cross coupling reactions of a wide range of electron-deficient, electronically neutral and electron-rich aryl halides with the various substituted potassium salts of phenols over ecofriendly, heterogeneous reusable copper fluorapatite (CuFAP) catalyst in the presence of N-Methyl-2-pyrrolidone as a solvent at 120 °C (Scheme 6).

Section II: Base promoted synthesis of diaryl ethers by cross-coupling of phenols with arylboronic acids

This section describes highly efficient synthesis of diaryl ethers from phenols and arylboronic acids over copper fluorapatite using Cs₂CO₃ as a base and methanol as a solvent at ambient reaction temperature.

\[ \text{PhOH} + \text{PhB(OH)₂} \xrightarrow{\text{i}} \text{PhOPh} \]

R & R' = H, Me, OMe, NO₂, Ph, Naphthyl, Halogen, etc

[49-94 % Yield]

Scheme 7: Reagents and reactions conditions: (i) Phenols (1 mmol), arylboronic acid (1.1 mmol), CuFAP (100 mg), methanol (1 mL), RT, 5-12 h.

A mild, general, and highly efficient protocol has been developed for the synthesis of diaryl ethers in good to excellent yield under mild and ligand-free conditions. This is first example using recyclable, heterogeneous copper fluorapatite catalyzed arylation of substituted phenols with substituted arylboronic acids at room temperature in the presence of Cs₂CO₃ as base and methanol as a solvent. The catalyst was recovered and reused several time without loss of catalytic activity (Scheme 7).
Chapter 4

Synthesis of β-nitroalcohols and amides over copper fluorapatite catalyst

The chapter describes introduction, detail literature survey on β-nitroalcohols, amides and their industrial applications. The chapter is divided into two sections.

Section I: Base-free synthesis of β-nitroalcohols from aldehydes and nitroalkanes at ambient reaction temperature

The Henry reaction is one of the most useful carbon-carbon bond forming reactions and has wide synthetic applications in organic synthesis by which β-nitroalcohols were synthesized on treatment of carbonyl derivatives with nitroalkanes in the presence of a basic catalyst. From last few decades various methods has been developed for the synthesis of β-nitroalcohols using varieties of reagent and catalysts in combination with the various ligands such as organic, inorganic bases like metal hydroxides or alkoxides\(^{12,13}\) are reported. Other catalysts such as phosphonium salts,\(^{14}\) phosphine-metal complexes,\(^{15}\) ionic liquid,\(^{16}\) simple amines,\(^{17}\) ammonium salts,\(^{18}\) guanidine derivatives,\(^{19}\) lithiumaluminum hydride,\(^{20}\) Mg-Al-HT,\(^{21}\) and Amberlyst-21\(^{22}\) also have been reported. All the above mentioned methods can be applied for the synthesis of β-nitroalcohols but still suffering from limitations and drawbacks such as harsh reaction conditions, moisture sensitive and toxic catalyst and also the formation of the side product with poor yield to desired product. In this respect, there is still a need to develop mild and efficient methods for the synthesis of β-nitroalcohols. Hence, we developed a heterogeneous, highly efficient, eco-friendly and base-free catalyst system for Henry reaction by using CuFAP catalyst under neat reaction conditions (Scheme 8).
Scheme 8: \textit{Reagents and reactions conditions:} (i) Aldehyde (1 mmol), nitromethane (1 mL), CuFAP (100 mg), RT, 5-18 h.

**Section II: A direct synthesis of amides from aldehydes and hydroxylamine hydrochloride in solvent free conditions**

Amides are key intermediates in organic synthesis as well as raw material in industrial applications such as detergents, lubricants and pharmaceuticals. Amides are commonly synthesized by the reaction of acid chlorides, acid anhydrides, or esters with amines. However, due to generation of waste and toxic material in the process, the synthesis of amide with high atom economical is great challenge in pharmaceutical industry. Beckmann rearrangement has been recognized as versatile method for the preparation of amides at high temperature using a strong Bronsted or Lewis acids as catalyst. The various methods for the synthesis of amides from aldehyde using varieties of reagent and catalysts with the precious metal compounds such as Ir, Rh, Ru, Ag/ Au, Pd, anhydrous oxalic acid, chloral, sulfamic acid, cyanuric chloride/DMF, ethyl chloroformate/boron trifluoride etherate, and chlorosulfonic acid have been reported.

Although, so far reported protocols have their own drawbacks and limitations such as the use of toxic solvents, expensive reagents, and formation of unwanted side products, prolonged reaction timings, tedious workup procedures and low yields to desire product.
We developed a one pot, an efficient, simple, general and convenient protocol for the synthesis of amides in good to excellent yields from various substituted aldehydes and utilizing readily available inexpensive hydroxylamine hydrochloride in a solvent-free condition at 100 °C (Scheme 9).

\[
\text{R-CHO} + \text{NH}_2\text{OH.HCl} \xrightarrow{\text{i}} \text{R-CONH}_2
\]

\(\text{R= Aromatic, Heteroaromatic, Aliphatic, etc.} \quad \text{Yield= 85-96 %}\)

**Scheme 9:** *Reagents and reactions conditions:* (i) Aldehyde (1 mmol), hydroxylamine hydrochloride (1.2 mmol), CuFAP (100 mg), 100 °C.

**References**


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