Chapter 5

CLAY SUPPORTED CHIRAL DIPEPTIDE METAL COMPLEX CATALYSTS: PREPARATION, CHARACTERIZATION AND APPLICATION IN AZA-DIELS ALDER REACTION

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5.2 Results and Discussion
5.3 Experimental

Development of new catalysts for enantiomerically pure compounds in organic synthesis is an important area of research. Heterogeneous versions of chiral catalysts are limited, inspite of a number of advantages. Peptides are cheaper sources of chiral inducing agents. In this chapter, preparation of clay supported dipeptide catalysts of Cu and Ti, characterization and application for the synthesis of Pyrano[3,2,c] and Furo[3,2,c] quinolines via Aza Diels Alder reaction are discussed in detail.

5.1 Introduction

Naturally occurring alkaloids play an important role in numerous areas of modern chemical industry, such as in medicine, cosmetics, agriculture and nutrition science. These compounds were often originally found in nature and have later prepared by synthetic methods.
The development of a method to synthesize optically active compounds has always received much attention in various areas of organic and biological chemistry [1]. Enantiomerically pure compound consists of only one of its mirror image isomers (enantiomers). There are numerous examples of structures where the two enantiomers express different biological activity in living organism. One such example, which highlights the importance of enantiomeric purity, is naproxen (Fig.5.1), where the (S)-enantiomer is the active ingredient in an anti-inflammatory drug, while the (R)-enantiomer is a liver toxin.

![Fig.5.1](image)

**Fig.5.1** The enantiomers of naproxen show dramatic difference in biological activity.

Preparation of optically active compounds is important for drug development. Various strategies have been developed to prepare enantiomer enriched compounds and can be divided into three subgroups: resolution methods where a racemic mixture is separated; use of chiral pool thereby starting with a chiral substrate and asymmetric synthesis.

Different methodologies can be applied to induce stereoselectivity via asymmetric synthesis. One way is the attachment of a chiral auxiliary to the substrate that directs new transformations to give the desired stereoisomer. After the reaction, the chiral auxiliary is cleaved from the molecule. A drawback with this approach is the requirement of additional synthetic steps for attachment and cleavage of the auxiliary and the need for stoichiometric
amounts of the enantiomerically pure entity. Asymmetric catalysis is another opportunity that allows the use of substoichiometric amounts of chiral inductor such as chiral Lewis acids or an enzyme. This approach allows better atom efficiency, since, only a small amount of the catalyst is required in the catalytic cycle and this catalyst induces stereoselectivity.

5.1.1 Lewis acids in organic synthesis

In 1923 G.N. Lewis broadened the acid base theory considerably by proposing that acids could be defined as electron-pair acceptors and bases as electron pair donors [2]. The number of organic reactions like Friedel-Crafts-, ene, and Diels Alder reaction which make use of Lewis acids as catalysts such as AlCl₃, TiCl₄, BF₃.OEt₂ and SnCl₄ is still increasing. Choosing an appropriate Lewis acid is a delicate task and optimizations are generally required since many of them, especially chiral ones are substrate dependent. However supported Lewis acid catalysts in organic synthesis are limited.

5.1.2 Aza Diels Alder reaction

A useful method for the synthesis of six-membered rings is the Diels Alder reaction. The Aza-Diels Alder reaction provides a useful method for the incorporation of a nitrogen atom in the ring structure with the possibility to control regio, diastereo- and enantio-selectivity [3-5]. The hetero Diels Alder reaction of imines with dienes forming nitrogen-containing cycloadducts is therefore an important field of research [6, 7]. The reactivity of the imines can be increased by activating groups such as sulphonyls or carbonyls and are commonly used to promote imine reactivity in Diels-Alder reactions. These activating groups may be attached either to the imine carbon or the nitrogen atom or to both. MO calculations have suggested that carbonyl substituents are more activating than sulfonyl ones, with a more pronounced effect for electron withdrawing substituents bound to the imine carbon atom than those bound to...
nitrogen [8]. A Diels-Alder reaction involving an azirine is shown in Fig 5.2 (a) by the reaction between 3-phenyl-2H-azirine and Danishefsky’s diene. (b) The symmetry allowed Diels-Alder reaction can take place either by a normal electron-demand HOMO diene-controlled process (b) or through an inverse electron-demand LUMO diene-controlled reaction(c) [9].

![Fig.5.2 Basic concepts of Diels-Alder reaction](image)

### 5.1.3 Aim of this study

The development of a method to synthesize optically active compounds has always received much attention in various areas of organic and biological chemistry [10]. The design of chiral metal complexes as catalysts for asymmetric organic reactions has been widely studied with the metal complex derivatives of binaphthol, tartaric acid and semicorrin [11-13]. In the area of organic synthesis, α-amino acids are one of the most frequently used sources of chirality. The use of both natural and unnatural α-amino acids and their derivatives as chiral reagent auxiliaries and ligands for asymmetric catalysis is wide-spread [14-16]. In contrast, peptides and their complexes have rarely been reported as effective ligands of metallic species in asymmetric reactions [17]. Peptide titanium complex was reported as catalyst for asymmetric hydrocyanation under homogeneous conditions [18-19]. The development of chiral lewis acid catalysts for carbon-carbon bond forming reactions is one of the most challenging formidable goals in organic synthesis [20]. The catalytic
asymmetric reaction with imine, can open a wide variety of possibilities for the synthesis of natural product of alkaloid family [21]. Generally these compounds are prepared by Aza-Diels Alder reactions of imines derived from aldehydes and amines with dihydropyran or dihydrofuran. Chiral lanthanide Lewis acids [22], various transition metal complexes as catalysts were reported for the synthesis [23-25]. However there are very few reports on supported catalysts for asymmetric organic synthesis [26, 27]. In the present work, an attempt was made to prepare clay supported chiral dipeptide catalysts, revealing that peptide metal complex if effectively designed and supported on a cheap support, can be potentially useful chiral auxiliaries because enzymes, natural peptides, exhibit remarkably high stereo specificities and stereoselectivity in biochemical reactions.

5.2 Results and Discussion

The peptides used were acyclic dipeptide esters whose amino terminal was modified to Schiff bases derived from naphthaldehyde or salicylaldehyde derivatives to facilitate complexation with metal ions [28]Titanium isopropoxide and CuCl₂ were used as metallic species. Synthesis of dipeptides bearing naphthaldehyde Schiff base were carried by a procedure described in the literature [29], which involved the coupling of an amino acid, whose amino group was modified to Schiff base by condensation with 2-hydroxy-1-naphthaldehyde, with another amino acid methyl ester by using dicyclohexylcarbodiimide (DCC) in dichloromethane.

5.2.1 Preparation of L-Phenylalanine methyl ester

The carboxyl group of the amino acid was esterified with methanol in the presence of SOCl₂. The product obtained was purified by recrystallisation. The synthesis of methyl esters of phenyl alanine and tyrosine are shown in scheme 5.1 and 5.2. The amino acid methyl esters were prepared reacting the L-amino acids with methanol in the presence of thionylchloride. Pure amino
acid methyl esters were obtained by fractional precipitation from methanol solution using dry ether.

Scheme 5.1 Preparation of Phenylalanine methyl ester

5.2.2 Preparation of Tyrosine methyl ester

The excess thionyl chloride was distilled off under vacuum. The amino acid methyl ester was extracted with hot methanol and recrystallised and or fractionally precipitated from methanol.

5.2.3 Preparation of amino acid Schiff base

Schiffs bases are commonly used for the synthesis of metal complexes for various catalytic applications. Schiff base ligands are able to coordinate metals through imine nitrogen and another group, usually linked to the aldehyde. Modern chemists still prepare Schiff bases, and nowadays active and well-designed Schiff base ligands are considered “privileged ligands”[30]. In fact, Schiff bases are able to stabilize many different metals in various oxidation states, controlling the performance of metals in
a large variety of useful catalytic transformations. Stereogenic centres or other elements of chirality (planes, axes) can be introduced in the synthetic design.

The Schiff bases of amino acids were synthesized by reacting equimolar mixture of amino acid and 2-hydroxy-1-naphthaldehyde in a mixture of ethanol and methanol. The product obtained was washed with diethyl ether to give the corresponding amino acid Schiff base (Scheme 5.3).

Scheme 5.3 Synthesis of valine - naphthaldehyde Schiff base

The product was characterized by IR and $^1$HNMR spectra. The amino acid stereochemistry was maintained after the reaction.

5.2.4 Synthesis of dipeptides

Dipeptides of amino acids were synthesized by reacting equimolar mixture of schiffs base of amino acids and amino acid methyl esters at 0°C for 24h. DCC was used as the coupling agent. Phenylalanine methyl ester and tyrosine methyl ester were used for preparing the dipeptides using valine-naphthaldehyde Schiff base. The crude product was filtered through celite. Pure products were obtained by column chromatography using silica gel column and hexane: dichloromethane as eluent (8:2v/v). Scheme 5.4 & 5.5
Scheme 5.4 Synthesis of valine-naphthaldehyde phenylalanine methyl ester dipeptide (Naph val-phe-OMe) (DP2)

Scheme 5.5 Synthesis of valine-naphthaldehyde tyrosine methyl ester dipeptide (Naph-val- tyr OMe) (DP3)

The dipeptides 2 & 3 were characterized by determining melting points, IR, $^1$HNMR and mass spectra. Attempts to get sufficiently large crystals suitable for recording X-ray diffraction patterns failed. NMR spectra indicated the absence of racemization.
5.2.5 Preparation of dipeptide metal complexes of Copper and Titanium

The metal complexes of dipeptides DP$_2$ and DP$_3$ were prepared by reacting equimolar mixture of dipeptide and metal salt in dichloromethane under N$_2$ atm. Yellow colored solid was obtained for complex of titanium and green coloured solid was obtained for copper complexes of dipeptides. The tentative structures of the complexes are shown in fig. 5. 3. The metal complexes were characterized by FT IR spectroscopy.

![Fig. 5.3 Tentative structures of dipeptide metal complexes](image-url)
5.2.6 Characterisation of dipeptide metal complexes

5.2.6.1 FT-IR spectra of complexes

Fig. 5.4 FT-IR Spectra of DP3, DP3Cu and DP3TiP
IR spectra of the complexes and free ligand exhibited a broad band in the region 3300-3400 cm\(^{-1}\), which can be attributed to the stretching vibration of the OH group \[31\]. The C=N imine stretching vibration was observed in the region 1619-1655 cm\(^{-1}\) for the free ligand, clearly indicating the formation of Schiff bases. When the spectra of the complexes are compared with those of the free Schiff base ligands, the \(\nu(C=N)\) band observed at 1650 cm\(^{-1}\) was shifted to a lower frequency (1620 cm\(^{-1}\)), indicating that the imino nitrogen has coordinated to the metal ion. The negative shift of 30 cm\(^{-1}\) for the band indicated weakening of the C-N bond \[32\].

In the FT-IR spectra of complexes, the asymmetric and symmetric carbonyl stretching vibration bands are shifted to higher frequency indicating the formation of a linkage between a metal ion and the carbonyl oxygen \[33\]. Other sets of characteristic absorption bands appear in the region 1223 and 1521 cm\(^{-1}\). These can be assigned to phenolic C-O and amide N-H stretching vibrations for the free ligand respectively. The phenolic stretching C-O and amide N-H stretching are shifted to a higher frequency upon complexation, implying that the phenolic oxygen and amide nitrogen on the dipeptide form coordinate bond with the metal ions \[34-35\]. Conclusive evidence regarding the bonding of the nitrogen and oxygen is provided by the occurrence of bands at 587-515 cm\(^{-1}\)(M-N) and 507-424 cm\(^{-1}\)(M-O) \[36\] (fig.5.4).

5.2.6.2 Electronic spectra

The electronic absorption spectra of the metal complexes were recorded in methanol. The divalent metal complex absorption bands of strong intensity corresponding to C=N chromophore occur at 200-300 nm. These bands are attributed to \(\pi-\pi^*\) transitions of the extended conjugation system formed by the benzene ring, phenolic oxygen and imino nitrogen confirming the formation of Schiff base metal complexes \[37\]. From the Fig.5.5 it can be seen that only complexes of copper shows peak in this region. The band at,
353, 388, 413 nm have been assigned to $n-\pi^*$ transitions of the C=N chromophore, coupled with the secondary band of the benzene ring [38].

5.2.7 Preparation of clay supported dipeptide – metal ion complexes

Activated K10 clay swollen in water was stirred with 2M solution of NaNO$_3$ overnight. The sodium exchanged clay so obtained was washed with deionized water repeatedly till the filtrate was free from nitrate ions; the clay was dried in air oven for 2h at 150$^\circ$C. Sodium exchanged clay was stirred with 20 wt% of the dipeptide metal complexes in CH$_2$Cl$_2$ under N$_2$ atmosphere and dried at 100$^\circ$C for 2h. Tentative structure of the Cu and Ti complexes supported on clay are given in fig. 5.6.
5.2.7.1 Characterization of the catalyst

The thermal stability of the selected catalyst was studied using thermogravimetric analysis. The catalyst was subjected to thermogravimetric analysis in the temperature range 50-800°C using a linear temperature programme at a heating rate of 10°C/min. Thermogram of the samples shows a weight loss around 230°C which may be due to the loss of organic part. The TG/DTA profiles of K10DP3Cu is shown in (Fig 5.7)
Table 5.1 EDX data of K10DP3Cu

<table>
<thead>
<tr>
<th>Element</th>
<th>(keV)</th>
<th>Mass%</th>
<th>Atom%</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>C K</td>
<td>0.27</td>
<td>3.86</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>O K</td>
<td>0.53</td>
<td>39.4</td>
<td>52.07</td>
<td>1.30</td>
</tr>
<tr>
<td>Na K</td>
<td>1.041</td>
<td>0.05</td>
<td>0.05</td>
<td>0.97</td>
</tr>
<tr>
<td>Mg K</td>
<td>1.2</td>
<td>1.24</td>
<td>1.08</td>
<td>0.94</td>
</tr>
<tr>
<td>Al K</td>
<td>1.48</td>
<td>9.35</td>
<td>7.33</td>
<td>0.98</td>
</tr>
<tr>
<td>Si K</td>
<td>1.74</td>
<td>40.21</td>
<td>30.28</td>
<td>1</td>
</tr>
<tr>
<td>K K</td>
<td>3.31</td>
<td>1.13</td>
<td>0.61</td>
<td>1.48</td>
</tr>
<tr>
<td>Fe L</td>
<td>0.70</td>
<td>4.57</td>
<td>1.73</td>
<td>4.80</td>
</tr>
<tr>
<td>Cu K</td>
<td>8.04</td>
<td>0.19</td>
<td>0.06</td>
<td>4.87</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 5.8 EDX spectra of K10DP3Cu

The metal content of the catalysts was estimated using electron dispersive X-ray microscope (EDX) connected to a JOEL microscope. The presence of copper was confirmed in the catalyst. The results are shown in table 5.1 and fig 5.8
The amount of copper present in the catalyst was also estimated by ICP-AES. The results are shown in table 5.2. The K10DP3Cu catalyst contains 0.2% of copper.

<table>
<thead>
<tr>
<th></th>
<th>Al</th>
<th>Ca</th>
<th>Cu</th>
<th>Mg</th>
<th>Si</th>
<th>K</th>
<th>Fe</th>
<th>Na</th>
</tr>
</thead>
<tbody>
<tr>
<td>K10DP3Cu</td>
<td>12.1</td>
<td>2.9</td>
<td>0.2</td>
<td>2.7</td>
<td>62.2</td>
<td>4.1</td>
<td>7.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

**Fig 5.9** UV-DRS spectra of catalysts derived from DP3

The UV-DRS spectra of the parent Montmorillonite K10, supported copper complex and supported titanium complex catalysts are shown in Fig 5.9. UV-DRS Spectra of the catalysts are characterized by broad absorption band centered around 400-500nm in the copper catalysts and 260-270nm and above 300 nm in the case of titanium catalysts. The parent Montmorillonite K10 shows no absorption band in this region (fig 5.9).
FT-IR spectra of K10DP3Cu catalyst showed a weak broad peak in the region 1600cm⁻¹, characteristic of carbonyl absorption of the dipeptide fig 5.10.

5.2.8 Aza-Diels Alder reaction

5.2.8.1 Screening of the Catalyst in Aza-Diels Alder reaction

The catalysts were screened for Aza-Diels Alder reaction and the results are summarized in table 5.3, better result was obtained for K10DP3Cu and was selected as the catalyst of choice.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Metal ion</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP2</td>
<td>Cu²⁺</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>Ti⁴⁺</td>
<td>52</td>
</tr>
<tr>
<td>DP3</td>
<td>Cu²⁺</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>Ti⁴⁺</td>
<td>68</td>
</tr>
</tbody>
</table>
The prepared catalysts were tested by taking benzaldehyde (1mmol), 3, 4-dihdropyran (1mmol), and aniline (1mmol) and 200 mg of the catalyst in the Aza-Diels Alder reaction. The maximum yield was obtained for the catalyst K10DP3Cu.

The Aza-Diels Alder reaction was carried out with K10DP3Cu. Aldehyde (1mmol), amine (1mmol) and 3,4-dihdropyran or 2,3-dihydrofuran (1mmol) were reacted with 200 mg of the catalyst. Imines generated in situ from aldehydes and amines, immediately reacted with dihydropyran to afford pyrano[3,2-c]quinolines in one pot without the need of preformation of the imines. It was found that the reaction of benzaldehyde, aniline and 3, 4-dihydro-2H-pyran was efficiently catalysed by K10DP3Cu. The reaction did not occur in the absence of catalyst. Regardless of the electronic properties or steric hindrance of the substituents on the aromatic ring of aldehydes, ring-fused [3,2-c] quinolines were obtained in good to excellent yield with high enantioselectivity.

Scheme 5.6 General scheme of Aza-Diels Alder reaction

Various solvents were used in the model reaction with K10DP3Cu (200 mg) as catalyst; the results are summarized in table 5.4. Acetonitrile was the best solvent among those tested. Several amines and aldehydes were examined, and the results are listed in table 5.5. In all cases, the three component one pot reaction proceeded smoothly to give the corresponding pyrano/ furano [3,2-c] quinolines.
Table 5.4 Effect solvent on Aza-Diels Alder reaction

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Solvent</th>
<th>%Yield of the product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl₃</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>C₂H₅OH</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>CH₃OH</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>H₂O</td>
<td>79</td>
</tr>
</tbody>
</table>

Reaction condition: Reactions were carried out with benzaldehyde (1 mmol), aniline (1 mmol), 2,3-dihydropyran (1 mmol), 200 mg catalyst, at room temperature for 12 h under N₂ atmosphere.

Table 5.5 Aza-Diels Alder reaction with various substrates

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCHO</th>
<th>RNH₂</th>
<th>Olefin</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>M.p °C</th>
<th>ee(%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzaldehyde</td>
<td>Aniline</td>
<td>3,4-dihydropyran</td>
<td>79</td>
<td>120</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>3-Nitrobenzaldehyde</td>
<td>Aniline</td>
<td>3,4-dihydropyran</td>
<td>68</td>
<td>180</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>4-Chloro Benzaldehyde</td>
<td>Aniline</td>
<td>3,4-dihydropyran</td>
<td>71</td>
<td>163</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>Benzaldehyde</td>
<td>4-Bromo aniline</td>
<td>3,4-dihydropyran</td>
<td>78</td>
<td>147</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>Thiophene carboxaldehyde</td>
<td>Aniline</td>
<td>3,4-dihydropyran</td>
<td>76</td>
<td>145</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>4-Methoxybenzaldehyde</td>
<td>Aniline</td>
<td>3,4-dihydropyran</td>
<td>81</td>
<td>-</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>Benzaldehyde</td>
<td>Aniline</td>
<td>2,3-dihydrofuran</td>
<td>78</td>
<td>108</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>3-Nitrobenzaldehyde</td>
<td>4-Bromo aniline</td>
<td>2,3-dihydrofuran</td>
<td>64</td>
<td>184</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>4-Chlorobenzaldehyde</td>
<td>Aniline</td>
<td>2,3-dihydrofuran</td>
<td>66</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>3-Nitrobenzaldehyde</td>
<td>Aniline</td>
<td>2,3-dihydrofuran</td>
<td>62</td>
<td>159</td>
<td>73</td>
</tr>
</tbody>
</table>

Reactions were carried out with 1 mmol aldehyde, 1 mmol amine, 1 mmol olefin, 200 mg catalyst, in acetonitrile at room temperature 12 h under N₂ Atmosphere.

<sup>a</sup> Isolated yield of purified product

<sup>b</sup> Determined by HPLC with chiral OJ-H column
The products were characterized by determining the m.p and comparing the IR and $^1$HNMR spectra were used to establish the cis ring fusion. In the $^1$HNMR spectra, for the signals at ~5ppm, the coupling constant $(J_{4a, 5}) = 5.2$ Hz is small and typical for a gauche confirmation of the protons, consistent with all cis-configuration of the hydrogen atoms 4a, 5 and 10b. The coupling constant $(J_{4a, 10b})$ in all products (2.2-2.9 Hz) indicates the cis fusion of the pyran-and quinoline rings.

5.2.8.2 Recycling studies

After completion of the reaction the catalyst was filtered, washed with acetone, methanol and ethyl acetate repeatedly followed by drying at 100ºC for 1h and reused. The catalyst activity was found to be decreased upon each cycle. The results of recycling studies are summarized in table 5.6

<table>
<thead>
<tr>
<th>Entry</th>
<th>No. of recycling steps</th>
<th>% Yield $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 5.6 Recycling studies of the catalyst

Reaction condition: Benzaldehyde (1 mmol), aniline (1 mmol), 3, 4-dihydropyran (1 mmol), Catalyst 200 mg, Solvent: acetonitrile (5ml) Time: 12h $^a$Isolated yield

5.2.8.3 Conclusion

K10 clay supported dipeptide schiffs base complexes of copper and Ti were synthesized conveniently from natural amino acids and their catalytic activity were investigated in Asymmetric Aza Diels alder reaction. The amount of catalyst required was low, good yields and high enantioselectivity were obtained in all the cases studied.
5.3 Experimental

5.3.1 Preparation of amino acid esters

Thionyl chloride (0.5ml) was added to methanol (20ml) in a 50ml RB flask fitted with a reflux condenser and cooled in an ice-salt water bath to about -10°C (internal temperature). Amino acid (5 mmol) was added. Ice bath was removed and the mixture was heated to reflux for 2h. The mixture was concentrated in a rotary flash evaporator to about 2-5ml. The product was precipitated by the slow addition of peroxide free ether. Pure product was recrystallised from methanol/ether.

5.3.2 Preparation of Naphthaldehyde Schiff bases of amino acids

To a suspension of valine (20 mmol) in a mixture of ethanol (500 ml) and methanol (40 ml) was added 2-hydroxynaphthaldehyde (30 mmol). After being stirred for 16h, the resulting yellow solution was concentrated under vacuum to leave the mixture of N-2-hydroxy-1-naphthaldehyde. The residue was washed well with ether to remove the excess 2-hydroxy-1-naphthaldehyde. The product was obtained by filtration to yield yellow solid Schiff base of 2-hydroxy-1-naphthaldehyde of amino acids.

5.3.3 Preparation of dipeptides

5.3.3.1 N-(2-hydroxy-1-naphthyl)methylene)-(L)-valyl-(S)-phenylalanine methyl ester[Nap-L-Val-L-Phe-OMe][DP-2]

To a suspension of (L)-valine (2.34g, 20 mmol) in a mixture of ethanol (500ml) and methanol (40ml) was added 2-hydroxy-1-naphthaldehyde (5.17g, 30 mmol). After being stirred for 16h, valine had dissolved, and the resulting yellow solution was concentrated in vacuo to leave the mixture of N-((2-hydroxy-1-naphthyl)methylene)-(L)-valine and excess of 2-hydroxy-1-naphthaldehyde. The residue was washed well with ether to remove the excess 2-hydroxy-1-naphthaldehyde by filtration to yield a yellow solid of N-((2-hydroxy-1-naphthyl) methylene)-(L)-valine (5g, yield 92.2%). To a solution
of L-phenyl alanine methyl ester hydrochloride (1.24g, 6mmol) in water (10 ml) was added potassium carbonate (1.24 g, 9mmol). After the mixture was stirred at room temperature for 10 min, the aqueous layer was extracted with ether (20mlx5). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo to afford free (L)-phenylalanine methyl ester as viscous oil (0.9 g, 5mmol). To a suspension of N-((2-hydroxy-1-napthyl) methylene)-(L)-valine(1.5g, 5mmol), in dichloromethane(30mL) was added N,N’dicyclohexylcarbodiimide (DCC) (1.03g, 5mmol) at 0°C followed by freshly prepared (L)-phenylalanine methyl ester (0.9g, 5mmol). The reaction mixture was stirred at 0°C of 1h and at room temperature for 24h; the resulting white precipitate of DCU was removed by filtration through celite, and the filtrate was concentrated to give the crude product as a yellow solid which was purified by column chromatography on silica gel (dichloromethane: ethyl acetate, 4:1) to yield 1.16g (48.5%) which was recrystallised from ethanol, mp 243°C.

IR (KBr): 3460, 3200, 3026, 2976, 1740, 1660, 1625, 1540, 1510, 1490, 1430, 1310, 1270, 1140, 1010, 860, 836, 740cm⁻¹

$^1$HNMR (CDCl$_3$): 14.38 (br s, 1H), 9.05 (s, 1H), 8.02 (d, 1H, J=8.1Hz), 7.6(d, 1H, J=9.4 Hz), 7.7(d, 1H, J=7.3Hz), 7.4-7.5(m, 1H), 7.32-7.38(m, 1H), 7.13-7.28(m, 6H), 6.42(d, 1H, J=7.6Hz), 4.8-4.9(m, 1H), 3.73(d, 1H, J=4.3Hz), 3.68(s, 3H), 3.3(qd, 1H, J=13.6, J=5.6Hz), 3.0 (qd, 1H, J=13.7, J=7.7Hz), 2.39-2.51(m, 1H), 0.88(d, 3H, J=6.68), 0.82(d, 3H, J=6.8Hz)

5.3.3.2 N-(2-hydroxy-1-napthyl)methylene)-(L)valyl-(L)-tyrosine methyl ester(Nap-L-Val-L-Tyro-OMe)[DP3]

To a solution of L-tyrosine methyl ester in dichloromethane (1.2g, 6mmol) in water (10mL) a suspension of N-((2-hydroxy-1-napthyl) methylene)-(L)-valine (1.5g, 5mmol), in dichloromethane (30 mL) was added N,N’dicyclohexylcarbodiimide (DCC) (1.03g, 5mmol) at 0°C followed by freshly prepared (L)-tyrosine methyl ester (0.9g, 5mmol). The reaction mixture was stirred at 0°C of 1h and at room temperature for 24h; the resulting white precipitate of DCU was removed by filtration through celite, and the filtrate was
concentrated to give the crude product as a yellow solid which was purified by column chromatography on silica gel (dichloromethane-ethyl acetate, 4:1) to yield. 1.38g (55.6%) which was recrystallised from ethanol mp 225-228°C.

IR (KBr): 3460, 2945, 2858, 1637, 1499, 1463, 1380, 1265, 1220, 1105, 860, 710, 680 cm⁻¹

¹HNMR (CDCl₃): 14.1 (br s, 1H), 9.0 (s, 1H), 7.86 (d, 1H, J=8.0Hz), 7.66(d, 1H, J= 9.2 Hz), 7.72 (d, 1H, J=7.2Hz), 7.5(m, 1H), 7.32-7.38 (m, 4H), 7.1-7.2 (d, 1H, J=7.2 Hz), 6.8 (d, 1H, J=7.2Hz), 5.1(m, 1H), 5.3(m,1H), 4.81(m, 1H), 4.06(d, 1H, J= ), 3.6(s, 3H), 3.29-3.08 (m, 2H), 2.1(m,1H), 1.01(s, 6H)

5.3.4.1 DP₂Cu Complex

The dipeptide DP₂ (0.87g, 2mmol) was dissolved in dry dichloromethane (20ml). To this CuCl₂ (0.34g, 2mmol) was added. The mixture was stirred for 2h under N₂ atmosphere. After reaction, the product was filtered and washed with methanol (20ml x 2 times) and dry ether (20ml x 2 times). Drying under vacuum afforded the DP₂Cu (0.6g, 56%).

5.3.4.2 DP₂TiP complex

The dipeptide DP₂ (0.87g, 2mmol) was dissolved in dry dichloromethane (20ml). To this Ti(O-i-Pr)₄ (0.5 ml, 2mmol) was added. The mixture was stirred for 2h under N₂ atmosphere. After reaction, the product was filtered and washed with methanol (20ml x 2times) and dry ether (20ml x 2times). Drying under vacuum afforded the DP₂TiP (0.7g, 62%).

5.3.4.3 DP₃ Cu complex

The dipeptide DP₃ (0.87g, 2mmol) was dissolved in dry dichloromethane (20ml). To this CuCl₂ (0.34g, 2mmol) was added. The mixture was stirred for 2h under N₂ atmosphere. After reaction, the product was filtered and washed with methanol (20ml x 2times) and dry ether (20ml x 2times). Drying under vacuum afforded the DP₃Cu (0.72 g, 67%).
5.3.4.4 DP₃TiP complex

The dipeptide DP₂ (0.87g, 2mmol) was dissolved in dry dichloromethane (20ml). To this CuCl₂ (0.5ml, 2mmol) CuCl₂ was added. The mixture was stirred for 2h under N₂ atmosphere. After reaction, the product was filtered and washed with methanol (20ml X 2times) and dry ether (20ml X 2times). Drying under vacuum afforded the DP₃TiP (0.87g, 74%).

5.3.5 Preparation of clay supported dipeptide complex catalysts

The clay supported dipeptide metal complex was prepared by exchange of ions in the inter layer of the clay. The sodium ion exchanged K10 was used for this purpose. 3g of activated montmorillonite K10 clay was swelled in water and stirred with 2M solution of NaNO₃ overnight. The sodium exchanged clay so obtained after purification was made to react with 20wt% of the complex in dichloromethane under N₂ atmosphere. The catalyst so obtained was used of Aza-Diels Alder reaction.

5.3.6 General procedure for Aza-Diels Alder reaction

To a suspension of aldehydes (1mmol), amine (1mmol) in acetonitrile (5 ml), at room temperature, 200 mg of the catalyst (K10DP₃Cu) was added. The mixture was stirred for 10 min at room temperature. 3,4-dihydo-2H-pyran or 2,3-dihydrofurran (1mmol) was added. The mixture was further stirred for 12 h. After the reaction it was filtered through a short plug of silica gel. After evaporation of the filtrate, the residue was chromatographed using hexane: ethyl acetate (9:1) on silica gel column to afford the pure products.

In the reaction of benzaldehyde, aniline and 3, 4-dihydro-2H-pyran the elution using hexane: ethyl acetate (9:1 v/v) afforded the major product (1) with an yield of 84%. A minor product (12%) was also isolated. It is marked as 2. The difference between 1 and 2 is the difference in stereochemistry at 5 in 1, it is R and for 2 it is S.
Characterisation of products

Entry 1 table 5.5

\[
\begin{align*}
(4aR,5R,10bR)-3,4,4a,5,6,10b\text{-hexahydro-5-phenyl-2H-pyrano}[3,2-c]\text{quinoline} \\
\text{\textsuperscript{1}H NMR (400 MHz; CDCl}_3\text{): } & \delta 1.25-1.50 \text{ (m, 4H)}, 2.15 \text{ (m, 1H)}, 3.58-3.85 \text{ (m, 3H)}, \\
& 4.68 \text{ (d, 1H, } J=2.6\text{Hz)}, 5.31 \text{ (d, 1H, } J=5.6\text{Hz)}, 6.68 \text{ (dd, 1H, } J=7.8, 0.9 \text{ Hz)}, 7.03 \text{ (t, 1H, } J=7.6, 0.6\text{Hz}), 7.43-7.25 \text{ (m, 6H)}. \\
\end{align*}
\]

Entry 1 Table 5.5

\[
\begin{align*}
(4aR,5S,10bR)-3,4,4a,5,6,10b\text{-hexahydro-5-phenyl-2H-pyrano}[3,2-c]\text{quinoline} \\
\text{\textsuperscript{1}H NMR (400 MHz; CDCl}_3\text{): } & \delta 1.250 \text{ (m, 1H)}, 1.48 \text{ (m, 2H)}, 1.66 \text{ (m, 1H)}, 1.83 \text{ (m, 1H)}, \\
& 2.11 \text{ (m, 1H)}, 3.71 \text{ (td, 1H, } J=11.6, 2.5\text{Hz)}, 4.08 \text{ (m, 2H)}, 4.39 \text{ (d, 1H, } J=2.7\text{Hz)}, 4.72 \text{ (d, 1H, } J=10.8\text{Hz)}, 6.51 \text{ (dd, 1H, } J=7.1, 1\text{Hz)}, 6.7 \text{ (td, 1H, } J=7.0, 1.1\text{Hz)}, 7.25 \text{ (dd, 1H, } J=7.1, 0.5\text{Hz)}, 7.42-7.36 \text{ (m, 5H)}. \\
\end{align*}
\]
Entry 2 Table 5.5

(4aR,5R,10bR)-3,4,4a,5,6,10b-hexahydro-5-(3-nitrophenyl)-2H-pyrano[3,2-c]quinoline

$^1$HNMR (400 MHz; CDCl$_3$): δ 1.1 (m, 2H), 2.2 (s, 1H), 3.58-3.62 (m, 5H), 3.9 (s, 1H), 4.8 (d, 1H, J=2Hz), 5.3 (d, 1H, J=5.6Hz), 6.65 (d, 1H, J=6.7Hz), 6.83 (td, 1H, J=7.2Hz), 7.11 (tt, 1H, J=7.6Hz), 7.43-7.58 (m, 5H), 7.7 (d, 1H, J=7.6Hz), 8.16-8.19 (dd, 1H, J=9.6Hz, J=1.6Hz), 8.33 (s, 1H).

Entry 3 Table 5.5

(4aR,5R,10bR)-5-(4-chlorophenyl)-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline

$^1$HNMR (400 MHz; CDCl$_3$): δ 1.25-1.55 (m, 4H), 2.13-2.15 (m, 1H), 3.42-3.60 (m, 2H), 3.80 (s, 1H) 4.6 (d, 1H, J=5.6Hz) 5.30-5.32 (d, 1H, J=5.6Hz) 6.59 (dd, 1H, J=1.2, 0.8Hz), 6.78-6.82 (td, 1H, J=7.6, J=0.8 Hz), 7.07-7.1 (dt, 1H, J=2, 1.2 Hz), 7.44 (d, 1H, J=8 Hz),
Entry 4 Table 5.5

(4aR,5R,10bR)-9-bromo-3,4,4a,5,6,10b-hexahydro-5-phenyl-2H-pyrano[3,2-c]quinoline

$^1$HNMR (400 MHz; CDCl$_3$): $\delta$ 1.31−1.52 (m, 4H), 2.14−2.16 (m, 1H), 3.41-3.44 (m, 1H), 3.5-3.6 (m, 1H), 3.8 (s, 1H), 4.65 (d, 1H, $J= 2.8$ Hz) 5.26−5.28 (d, 1H, $J=5.2$Hz) 6.4-6.6 (d, 1H, $J= 8.4$Hz), 7.15-7.17 (dd, 1H, $J= 8$, $J= 4$ Hz), 7.31-7.38 (m, 5H), 7.52 (d, 1H, $J= 2$ Hz),

Entry 5 Table 5.5

$^1$HNMR (400 MHz; CDCl$_3$): $\delta$ 1.48−1.61 (m, 5H), 2.2 (m, 1H), 3.40 (m, 1H), 3.6 (m, 1H), 4 (s, 1H) 4.97 (d, 1H, $J= 4$ Hz) 5.9 (d, 1H, $J= 4$Hz) 6.59 (d, 1H, $J= 8$ Hz), 6.8 (td, 1H, $J= 8$, $J= 4$ Hz), 7.06 (t, 1H), 7.09-7.11 (m, 3H), 7.23-7.25 (dd, 1H, $J= 8$, $J= 4$ Hz), 7.42 (d, 1H, $J= 7.4$ Hz),
References


