Chapter 5

Proline Derivatives for Studies in Asymmetric Organocatalysis Reaction
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Section A: Synthesis of Polymeric Organocatalyst: Immobilized Proline Analogue

Introduction to Asymmetric Organocatalysis In general:
Orgacatalytic reactions have in the past few years emerged as a powerful tool for the preparation of the optically active compounds. Several popular organocatalysts are actually well known as ligands in organometallic chemistry and can function as asymmetric catalyst themselves. Varieties of organic molecules have been employed as asymmetric catalyst, particularly the chinchona alkaloids, amino acids and derivatives, small peptide-based molecules etc. Organocatalysis has several advantages over the traditional transition-metal catalysis. In particular, the catalysts are typically more robust, less expensive, and more readily available. Many of the catalyst available in the organocatalysis tool box are acquired from the chiral pool, so highly diverse structural features are available. However, organocatalysis also suffers from several drawbacks. These are mainly related to high catalyst loading applied, the long reaction time necessary and the need to have a particular starting material in excess to drive the reactions to completion.

Organocatalysts exert their influence by either passive or active binding, where to former refers to non-covalent catalysis. The term non-covalent catalysis implies activation of the substrates by hydrogen bonding, hydrophobic, van der Waals, or electrostatic interactions. Active or covalent bonding refers to interactions between the catalyst and substrate at the reaction centers. Prominent examples of non-covalent organocatalysis are hydrogen bonding catalysis and phase-transfer catalysis. Examples of covalent organocatalysis includes nucleophilic catalysis, amine catalysis via enamine, and amine catalysis via iminium ions.

Introduction to Immobilized Proline Derivatives:
Catalytic asymmetric synthesis is now the most popular and an important protocol, utilized for the synthesis of optically active compounds. Ever since the pioneered work of proline-based asymmetric catalysis by List, Lerner and Barbas
III, it has become an important challenge worldwide to discover new and more effective catalyst than proline itself. L-proline can be regarded as the simplest "enzyme" and in addition to the aldol reaction, it has been successfully applied to many other reactions such as Robinson annulation, Mannich reaction, Michael reaction, Diel-Alder reaction, Baylis-Hillman reaction etc. At the same time, efforts were devoted to the immobilization and recycling of L-proline. In recent years, supported chiral organic catalysts have been the subject of the many reviews. In the year 2008, Gruttadauria et al. gave comprehensive review entitled “Supported Proline and Proline-derivatives as Recyclable Organocatalysts”, which summarized the immobilization procedures of the organocatalyst such as L-proline and its derivatives and highlighted their applications, recoverability and reusability (year 2000-2008). Generally important aspects in the immobilization of the reagents as a polymeric form are the simplification of the separation procedure, and in many cases the ease of handling and reusability of the reagents. However, immobilization of proline may enhance its activity and the stereoselectivity. Moreover, immobilization allows the use of the supported proline derivatives in the different solvents giving new solubility profile. Finally, immobilizations give the possibility to explore modifications of the properties of the supported catalyst by employing specific characteristic of the support.

Among, the catalyst employed for asymmetric aldol reactions, L-proline and its derivatives like hydroxy proline, prolinamide are widely used and some times proline-like organocatalyst containing protonated nitrogen heterocycles substituent in the side chain in place of the carboxylic acid moiety. There has been no report in literature about organocatalysis utilizing prolinate ester as organocatalyst and hence with aim of designing new catalyst for asymmetric reaction, we employed prolinate as candidate for our catalytic studies.

Review of Literature for Organocatalyst Immobilization:

A great deal of success has been achieved in a wide variety of asymmetric transformations using a series of proline and related organocatalyst. In designing a
catalyst of this type, the essential point is how to explore the active site of the proline catalyst on the polymer supports. Three different general approaches can be summarized for the organocatalyst immobilization.¹⁷

1. Covantly-supported catalyst: in this case L-proline, or a proline derivative has been covalently anchored to as soluble (e.g. PEG, dendrimer) or insoluble (e.g. polystyrene, Magnite) support.

2. Non-covalently supported catalyst: in this case the organocatalyst has been adsorbed (e.g. onto IL-modified SiO₂), dissolved (e.g. polyelectrolytes).

3. Biphasic catalyst: in this case L-proline has been dissolved into ionic liquid and the product extracted with immiscible solvent.

Some of the typical examples of the immobilized proline derivatives (1-9) are depicted below.

**PEG supported proline**¹⁹

![PEG supported proline](image)

**Polystyrene supported proline**²⁰

![Polystyrene supported proline](image)
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**Silica supported Proline**\(^{21}\)

\[
\text{O} \quad \text{O} \\
\text{Si} \quad \text{NH} \\
\text{O} \\
\text{O} \\
\]

(8) MCM 41-pro

**Dendrimer supported Proline**\(^{22}\)

\[
\text{NH} \\
\text{O} \\
\text{O} \\
\text{DAB(AM)}_2 \\
\text{COOH} \\
\text{H} \\
\text{H} \\
\text{Cl}^- \\
\]

(9) Proline moiety on dendrimer

**Objective:**

Our main objective was to design an immobilized small organic molecule acting as catalyst in various organocatalytic transformations. Typical drawbacks of the current methodologies of the immobilization are high cost factor and long reaction time for the catalyses reaction. Hence our aim was to design an immobilized organocatalyst in simple and inexpensive way.

**Present Work:**

Catalysts incorporating both a secondary amine and additional functionality are frequently encountered in the literature. This prompted us to investigate the possibility
of altering structural features of the existing catalyst in order to develop a better catalyst for the enantioselective aldol reaction. The catalyst structure should incorporate functionality that enables control of the iminium ion geometry, enough steric bulk to provide facial selectivity. Hence catalyst fulfilling the above criteria was envisaged (Figure 1)

![Catalyst Structure](image)

**Figure 1.** Suggested catalyst structure, important structural features are highlighted.

We sought to develop a simple and general method for the preparation of organic polymer-supported material based on radical copolymerization. Specifically we choose to prepare copolymer of the allyl prolinate and allyl diglycol carbonate (ADC) for the use in asymmetric aldol reaction.

**Results and Discussion:**

Our approach towards immobilization of proline derivative is depicted in Scheme 1.

![Reaction Scheme](image)

**Scheme 1.** *Reagents and condition:* a) allyl alcohol, SOCl2, reflux; b) Boc2O, Et3N; c) allyl diglycol carbonate (80% w/w); IPP (4% w/w); d) TFA, then aq NH3
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The synthesis commenced with L-proline 10, which was subjected to esterification using SOCl₂/allyl alcohol to give the corresponding salt of allyl prolinate 11. Its IR spectrum showed a band at 1740 cm⁻¹ indicating the presence of the carbonyl functionality. The ¹H NMR spectrum of 11 showed a multiplet at δ 1.93-2.41 integrating for four protons of CH₂CH₂ fragment of the pyrrolidine ring. The NCH₂ appeared at δ 3.26-3.41 as a multiplet, whereas NCH appeared as a multiplet at δ 4.31-4.64. The olefinic protons appeared as multiplets at δ 5.07-5.34 (2 protons), and δ 5.90 (1 proton). The ¹³C NMR spectrum of 11 (Figure 9) showed peaks at δ 23.3, 28.3, 46.2 corresponding to CH₂CH₂CH₂N fragment, whereas the NCH carbon peak appeared at δ 59.3. The peak at δ 67.6 was attributed to OCH₂. The olefinic carbons appeared at δ 119.5 (=CH₂) and 130.9 (CH=) whereas carbonyl carbon was seen at δ 172.0.

The hydrochloride salt of allyl prolinate 11 was treated with Boc₂O/Et₃N to get the corresponding N-Boc protected allyl prolinate 12 having [α]D ³₀ -48.51 (c 3.80, CHCl₃). Its IR spectrum showed bands at 1747 and 1697 cm⁻¹, indicating the presence of carbonyl functionalities. In the ¹H NMR spectrum of 12 (Figure 10), the singlet at δ 1.38 [1.43] integrating for 9 protons was attributed to three methyls of the Boc group. The two multiplets at δ 1.83-2.21 integrating for four protons were attributed to CH₂CH₂ fragment of the pyrrolidine ring. The NCH₂ appeared as a multiplet at δ 3.38-3.52, whereas the NCH appeared as a multiplet at δ 4.20-4.33. The OCH₂ protons were seen at δ 4.59 as a multiplet. The olefinic protons appeared as multiplets at δ 5.21-5.36 (2 protons) and 5.87-5.93 (1 proton). The ¹³C NMR spectrum (Figure 11) showed peaks at δ 23.6 [24.2], 29.9 [30.8], 46.3 [46.5] and 59.1 [58.8] were attributed to CH₂CH₂CH₂N fragment and NCH of the pyrrolidine ring respectively. The OCH₂ peak was seen at δ 65.4, whereas the olefinic carbons were seen at δ 118.6 [118.1] (=CH₂) and 131.8 (CH=). The ester carbonyl carbon was seen at δ 172.8 [172.6]. Further the assigned structure 12 was confirmed by HRMS, whose [M+Na]⁺ peak seen at m/z 278.1363 for C₁₃H₂₁NO₄Na. Further, the allyl-N-Boc prolinate monomer 12 was mixed with the allyl diglycol carbonate (ADC) monomer 15 (2:8 w/w). This mixture was stirred under nitrogen atmosphere to remove any dissolved air or oxygen.
Isopropyl peroxydicarbonate (IPP) initiator (4% w/w of monomer mixture) and dioctyl phthalate plasticizer (1% w/w) were added, and the mixture was carefully injected in a previously assembled mold using a syringe. The mold was sealed and kept in the pressurizing assembly, and was polymerized using 12 h constant rate of polymerization cycle devised for ADC as per its polymerization kinetics which gave polymer 13 as a glassy polymeric film (Scheme 2). Its IR spectrum (Figure 12) showed bands at 1745, 1697 cm⁻¹ indicating the presence of the carbonyl functionality.

![Scheme 2. Polymerization of allyl-N-Boc prolinate with ADC](image)

The polymeric film of 13 was cut into small pieces and subjected to Boc-deprotection using TFA followed by neutralization with aq NH₃ to give polymeric material containing secondary amine 14 (Scheme 1). Its IR spectrum (Figure 12) showed bands at 3377, 1745 cm⁻¹ indicating the presence of the amine and carbonyl functionalities. Thus, we successfully synthesized a allyl diglycol carbonate pyrrolidine-derived copolymer in very simple way and the cost effective methodology. This polymeric material 14 was evaluated for its organocatalysis reaction, which is discussed in the section B of this chapter.

**Conclusion:**

We have successfully designed a polymeric material by combination of proline core with that of the side arm of allyl carbonate backbone to provide a new class of the ester-based catalyst that can be used for organocatalysis reaction.
Section B: Aldol Reaction Catalyzed by Proline Analogues

Introduction to Direct Catalytic Asymmetric Aldol reaction:

The asymmetric aldol reaction is one of the most useful chiral C-C bond forming reactions, because it can produce versatile biologically active intermediates. The reaction could be catalyzed by either basic or acidic compounds. Further, the aldol reaction relies on the selective enolization of the carbonyl compound and then subsequently reacts with an acceptor, resulting the formation of C-C bond and hence this transformation is chosen as chemical test to prove the efficiency of the new methodology especially asymmetric one. Recently in 2007, the comprehensive review entitled “Enantioselective direct aldol reaction: the blossoming of modern organocatalysis” is given by Ramon and coworkers comprising the brief account on aldol reaction using pyrrolidine motif as the source of the catalyst and its catalytic applications towards the synthesis of biologically active compounds.

Shibasaki and Trost realized the first two examples of the direct asymmetric aldol reactions utilizing bifunctional, chiral transition metal catalyst that activate both the aldol doner and acceptor. The direct asymmetric organocatalytic intermolecular aldol reaction stems from earlier studies on the equivalent intramolecular Hajos-Parrish-Eder-Sauer-Wiechert process (Scheme 3) and on the ability of the class I aldolase and catalytic aldolase antibodies to catalyze the intermolecular reactions.

Scheme 3. The intramolecular Hajos-Parrish-Eder-Sauer-Wiechert reaction

The mechanism of this intramolecular aldol reaction has been debated for the long time. Earlier studies stressed the importance of a reaction mechanism incorporating two L-proline molecules. The first L-proline was proposed to be responsible for the enamine formation, whereas the second was believed to mediate the proton transfer. However, lately the mechanistic picture has shifted dramatically towards the
acceptance of the mechanism\textsuperscript{30} in which the single L-proline entity mediates the C-C bond formation.

Asymmetric aldol reaction can be classified into following five types:

1. Chiral auxiliary assisted aldol reactions based on the use of stoichiometric amount of the chiral appendages.
2. Chiral Lewis acid and Lewis base catalyzed reaction.
3. Heterobimetallic bifunctional Lewis acid/Bronsted base catalyzed reaction.
4. Antibody or enzyme catalyzed reaction.
5. Organocatalysis with L-proline or its structural analogs.

**Results and Discussion:**

**Aldol reaction using protonated allyl prolinate:**

Early in 2003, the field of the direct asymmetric organocatalyzed aldol reaction was limited to the use of L-proline and closely related analogues.\textsuperscript{9} The direct asymmetric organocatalyzed aldol reaction typically required 20 mol\% of L-proline and less reactive substrates required up to 48 h to get acceptable yields. The asymmetric version of the pyrrolidine catalyzed aldol reaction in water can be achieved by designing pyrrolidine-based catalyst capable of inducing asymmetry in the product. We thought that the introduction of the asymmetric center and suitable hydrophobic unit may provide pyrrolidine-based asymmetric organocatalyst useful for aldol reaction in water. Further, inspired by the work of Chimni S. S. and Mahajan D. employing protonated pyrrolidine-based\textsuperscript{31a} small organic molecule having an amide linkage for asymmetric reaction in water and our interest in field of designing new catalyst has prompted us to evaluate the efficacy of our synthesized allyl prolinate salt 11 towards aldol reaction.

![Structure of Allyl prolinate salt 11](image)

**Figure 2. Structure of Allyl prolinate salt 11**
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To investigate the effect of substituting allyl group for the proton of carboxylic acid in L-proline, the prolinate salt 11 (Figure 2) was assessed in the direct aldol reaction. The reaction between acetone and 2-nitrobenzaldehyde was studied. As initial test run, the 2-nitrobenzaldehyde (1 equiv) and acetone (10 equiv) in water (2 mL) using (S)-2-(allyloxy carbonyl) pyrrolidinium chloride 11 (30 mol%) as a catalyst at room temperature were stirred for 48 h. Disappointingly, the reaction did not give the expected product.

According to Zheng J-F. et al., equal molar amount of Et₃N to the catalyst (N-terminal prolyl-dipeptide derivative) improved the reaction yield. Thus, the aldol reaction of 2-nitrobenzaldehyde 18 with acetone 19 was attempted by addition of 30 mol% of Et₃N with respect to prolinate catalyst 11 at room temperature. On continuous stirring for 1 h, afforded (4)-hydroxy-4-(2'-nitrophenyl)-butan-2-one 20 in 90% yield and 4% ee. Although we obtained good yield, unfortunately, we didn't obtain good enantioselectivity for this reaction.

Table 1. Aldol reaction using pollinate salt 11 as catalyst

<table>
<thead>
<tr>
<th>entry</th>
<th>Catalyst (mol%)</th>
<th>Et₃N (mol%)</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>30</td>
<td>0</td>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>30</td>
<td>30</td>
<td>1</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>3.</td>
<td>20</td>
<td>10</td>
<td>1</td>
<td>89</td>
<td>5</td>
</tr>
<tr>
<td>4.</td>
<td>20</td>
<td>05</td>
<td>1</td>
<td>73</td>
<td>5</td>
</tr>
<tr>
<td>5.</td>
<td>20</td>
<td>10</td>
<td>7 h, 0°C</td>
<td>91</td>
<td>11</td>
</tr>
</tbody>
</table>

<sup>a</sup>ee determined by chiral HPLC, using Chiralpak AD column

Next our aim was to search for the standard condition to improve asymmetric induction of reaction. Having established the greater reactivity of the catalyst 11,
further we investigated the effect of the amount of additives (Et₃N) on the stereochemistry and reactivity of the expected product. We tried the same reaction by using different amount of additive i.e. 20%, 10%, 5%, 2% (mol% of Et₃N), but we did not succeed in increasing the enantioselectivity of the product (4R)-hydroxy-4-(2'-nitrophenyl)-butan-2-one 20. Our results are summarized in Table 1. The use of 20 mol% of catalyst 11 and 10 mol% of NEt₃ was found to be the better reaction condition with 89% yield and 5 % ee. Further the stereochemistry of the product was assigned to be ‘R’ by comparing its specific optical rotation values with the literature value.31,33 Hence we obtained the standard condition using 20 mol% of catalyst and 10 mol% of Et₃N. Further we tested the reaction of 2-nitrobenzaldehyde with acetone at 0 °C, which required 7 h to give the required product in 91% yield and 11% ee (Table 1). The product (4R)-hydroxy-4-(2'-nitrophenyl)-butan-2-one 20 in its IR spectrum showed bands at 3377, 1745 cm⁻¹ indicating the presence of hydroxyl and carbonyl functionalities. The ¹H NMR spectrum of 20 (Figure 13) showed singlet at δ 2.24 integrating for three protons of the methyl group. The peak at δ 2.68 (dd, J = 9.6, 17.7 Hz, 1H) and peak at δ 3.16 (m, 1H) were attributed to methylene. The broad singlet at δ 3.78 (1 proton) indicated the presence of hydroxyl group. The doublet at δ 5.68 (J = 9.3 Hz, 1H) was attributed to CHOH. The aromatic protons appeared as two triplets at δ 7.45 (J = 7.5 Hz, 1H) and δ 7.68 (J = 7.5 Hz, 1H), and two doublets at δ 7.45 (J = 7.8 Hz, 1H), and δ 7.96 (J = 8.1 Hz, 1H). Further the assigned structure 20 was confirmed by recording ¹³C NMR and DEPT spectrum.

Hence, we demonstrated the application of new class of prolinate as organocatalyst towards aldol reaction with good yield but less asymmetric induction. Further, it was speculated that the increased reactivity observed for catalyst 11 was a result of the higher acidity of generated HCl, which could provide greater charge stabilization in the transition state and thereby increase the reaction rate.
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Aldol reaction using polymeric organocatalyst:

The use of synthetic polymers as enzyme models of asymmetric syntheses is an interesting field in chemistry. Though most of such polymers have not possessed as high stereoselectivity as enzyme, it is also important to use synthetic polymers for the studies of stereochemistry, polymer effect and new catalysts. Advantages of using an organocatalyst would be higher, if an efficient recovery and reuse of the catalyst could be accomplished, hence it is desirable to have the catalyst immobilized, so that the product purification can be facilitated and the catalyst recycled. Hence with above objectives in mind we tested our synthetic polymeric material for asymmetric aldol reaction. Our other objectives includes investigation of the direct asymmetric organocatalytic aldol reaction mediated by structurally modified L-proline derivative 14 (Figure 3) and the consequent implications on reactivity and selectivity.

![Figure 3. Structure of supported co-polymer 14](image)

Initially, the catalytic effect of polymer 14 was tested in the model reaction of 2-nitrobenzaldehyde (1 equiv) with acetone (10 equiv) in presence of 5 mol% of catalyst which showed only little conversion to corresponding product 20 (Table 2). Further, we attempted the same reaction using different catalyst loading as depicted in Table 2. The good yield was obtained by employing 20 mol% of catalyst 14 for aldol reaction at room temperature. With this standard condition, the catalyst found to be effective for one recycle. Its yield as well as asymmetric induction diminishes with the number of recycling. Since catalyst loading has no influence on stereoselectivity, 20 mol% loading was selected for further studies.
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Table 2. Optimization of reaction condition for aldol reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol%)a</th>
<th>yield (%)b</th>
<th>ee (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>5</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2.</td>
<td>10</td>
<td>62</td>
<td>30</td>
</tr>
<tr>
<td>3.</td>
<td>20</td>
<td>92</td>
<td>30</td>
</tr>
<tr>
<td>4.</td>
<td>Entry 3, cycle1</td>
<td>76</td>
<td>19</td>
</tr>
<tr>
<td>5.</td>
<td>cycle 2</td>
<td>50</td>
<td>10</td>
</tr>
</tbody>
</table>

a Theoretical N content based on monomer mixture, b Isolated yield, c The ee values were determined by HPLC analyses

As the polymer swelling would likely be a key factor for catalysis reaction, attention was paid to resolve the optimal solvent system for the reaction. We next explored the effect of solvent on the reaction (Table 3). Interestingly, the reaction worked nicely in water, yielding aldol product in high yield 92% after 1 h but imparted less asymmetric induction (Table 3, entry 2). On the other hand the enantiomeric excess was enhanced, when good polymer-swelling solvents such as THF, DMF, and DMSO (Table 3, entry 3, 4, 5) were used in the reaction. However, the overall yield decreased noticeably in this reaction. Our above observation of reaction in water as solvent (catalyses faster), and good enantioselectivity in DMF as solvent, prompted us to use the combined solvent system (DMF: H₂O). The addition of water to this solvent (DMF: H₂O) improved the overall yield, but at the expense of lower asymmetric induction (Table 3, entry 6). The reaction in CHCl₃ solvent was found to be ideal which provided aldol product in 63% ee and 67% yield (HPLC chromatograms are shown in Figure 14-17). The results are summarized in Table 3.
Table 3. Effect of solvent on the aldol reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>solvents (2 mL)</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>acetone</td>
<td>24</td>
<td>92</td>
<td>33</td>
</tr>
<tr>
<td>2.</td>
<td>water</td>
<td>1</td>
<td>92</td>
<td>17</td>
</tr>
<tr>
<td>3.</td>
<td>THF</td>
<td>24</td>
<td>74</td>
<td>52</td>
</tr>
<tr>
<td>4.</td>
<td>DMF</td>
<td>24</td>
<td>37</td>
<td>70</td>
</tr>
<tr>
<td>5.</td>
<td>DMSO</td>
<td>24</td>
<td>30</td>
<td>74</td>
</tr>
<tr>
<td>6.</td>
<td>DMF:H&lt;sub&gt;2&lt;/sub&gt;O (2:0.2)</td>
<td>24</td>
<td>71</td>
<td>33</td>
</tr>
<tr>
<td>7.</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>24</td>
<td>67</td>
<td>63</td>
</tr>
</tbody>
</table>

<sup>*Isolated yield, <sup>ЬThe ee values were determined by HPLC, using Chiralpak AD column.

Having established the good reactivity and selectivity of the catalyst 14 i.e. the CHCl<sub>3</sub> as solvent of choice (Table 3, entry 7), the performance of the recovered catalyst was also evaluated after a simple filtration from the reaction mixture without any further treatment. Our results of reuse of catalyst are summarized in Table 4. The catalyst 14 found to be effective for one recycle and then the yield as well as enantiomeric excess values decreases with the increase in number of cycle.

Table 4. Reuse of catalyst 14

<table>
<thead>
<tr>
<th>entry</th>
<th>Reuse Catalyst</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cycle 1</td>
<td>36</td>
<td>65</td>
<td>48</td>
</tr>
<tr>
<td>2.</td>
<td>Cycle 2</td>
<td>36</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>3.</td>
<td>Cycle 3</td>
<td>36</td>
<td>52</td>
<td>15</td>
</tr>
<tr>
<td>4.</td>
<td>Cycle 4</td>
<td>48</td>
<td>30</td>
<td>13</td>
</tr>
</tbody>
</table>

<sup>aThe ee values were determined by polarimetry.
Having established the standard conditions for aldol reaction using catalyst 14, we next investigated the substrate scope. A range of aldehyde were reacted with acetone using optimized reaction time and furnished corresponding β-hydroxy ketone. Our results are depicted in Figure 4.

**Figure 4.** Substrate scope of the direct asymmetric aldol reaction catalyzed by 20 mol% of catalyst 14

**Conclusion:**

1. The protonated pyrrolidine ester enhances the direct asymmetric organocatalytic aldol reaction in the presence of Et₃N. Thus our catalyst displays higher reactivity, although low asymmetric induction in the reaction has been observed.

2. We designed a new class of ester-based allyl diglycol carbonate pyrrolidine-derived copolymer as organocatalyst.

3. The synthesized polymeric material is tested for its catalytic activity, which promotes the aldol reaction of 2-nitrobenzaldehyde and acetone with moderate levels of enantiomeric excess and good yield.
Section C: N-Methyl pyrrolidine Mediated Asymmetric Baylis-Hillman reaction

Introduction to Asymmetric Baylis-Hillman reaction:

The Baylis-Hillman reaction is a synthetically useful method for the preparation of $\beta$-hydroxy-$\alpha$-methylene carbonyl compounds in one-step from the electrophilic alkene and carbonyl compounds by using tertiary amine or tertiary phosphine as a organocatalyst\(^{34}\) (Scheme 4). As chiral $\beta$-hydroxy-$\alpha$-methylene carbonyl compounds are useful intermediates in natural products synthesis, several enantioselective version of this reaction involving chiral catalyst have been developed. Some of the examples of these catalysts\(^{35}\) are depicted in Figure 5.

Scheme 4. Examples of Baylis-Hillman reaction

Lots of efforts had been devoted to design a new catalyst which will be effective and efficient towards Baylis-Hillman reaction (Figure 5). However, highly efficient catalytic systems which give high enantioselectivity for the broad range of the substrates with low catalyst loading are still limited. Therefore the development of the new and inexpensive organocatalyst system is still a frontier research topic in asymmetric synthesis.
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Figure 5. Examples of the chiral catalyst employed for Baylis-Hillman reaction

Present Work:

The generally accepted concept used in designing effective catalyst for the Baylis-Hillman reaction is that they should possess both nucleophilic moiety and an acid part or those two molecules, one acting as a nucleophile and the other as an acid. We envisaged that the introduction of the suitable hydrophobic unit with the chiral centers may provide pyrrolidine-based asymmetric organocatalyst. We thought that, the hydrophobic interaction of the long chain alkyl group and ketone could enforce an asymmetric environment and hence we choose a natural product (R)-bgugaine as a candidate to check for its catalytic activity towards Baylis-Hillman reaction. The structural features of (R)-bgugaine required for Baylis-Hillman reaction are highlighted in Figure 6.
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Figure 6. Important structural features of N-methyl-2-alkyl pyrrolidine are highlighted

We postulated that the long alkyl chain will control the stereochemistry of the product by blocking one side, whereas the tertiary amine group will catalyze the Baylis-Hillman reaction to give expected product. Further the reaction could be carried out in organic solvent like CHCl₃, which will provide the homogeneous reaction condition and hence may enhance the reactivity.

Results and Discussion:
As initial test run, we conducted only two reactions using the synthesized (R)-bgugaine and (S)-N-methyl prolinol in CHCl₃ for the Baylis-Hillman reaction of 2-nitrobenzaldehyde and methyl vinyl ketone as depicted in Scheme 5. The 2-nitrobenzaldehyde 26 and methyl vinyl ketone 24 was stirred in CHCl₃ in the presence of 20 mol% of catalyst (48 h). The two sets of experiment were conducted, one using (S)-N-methyl prolinol whereas other in (R)-bgugaine.

Scheme 5. Baylis-Hillman reaction using N-methyl pyrrolidine catalysts
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The $^1$H NMR spectrum of 27 (Figure 18) showed a singlet at $\delta$ 2.38 integrating for three protons of the methyl group, whereas a broad singlet at $\delta$ 3.54 (1H) was attributed to the hydroxyl group. The benzylic proton appeared as singlet at $\delta$ 5.81 (1H), whereas the vinylic protons appeared as two singlets at $\delta$ 6.18 (1H) and 6.23 (1H). The triplets at $\delta$ 7.47 ($J = 7.2$ Hz, 1H) and at $\delta$ 7.66 ($J = 7.5$ Hz, 1H) and the doublets at $\delta$ 7.79 ($J = 7.5$ Hz, 1H) and $\delta$ 7.97 ($J = 8.1$ Hz, 1H) were attributed to aromatic protons (4H). The $^{13}$C NMR spectrum of 27 showed the carbonyl carbon peak at $\delta$ 199.8 and the vinylic carbon at $\delta$ 126.4, whereas the benzylic carbon appeared at $\delta$ 67.4. Further the assigned structure 27 was confirmed by recording multiplicities of the carbon signals using DEPT experiment. The HPLC chromatogram of 27b is shown in figure 19.

Further, we got interesting results regarding the stereochemistry of the product 3-[hydroxyl-(2-nitrophenyl)-methyl]-but-3-en-2-one 27. The product 27a obtained using (S)-N-methyl prolinol is having $[\alpha]_D^{30}$ -7.44 (1.02, CHCl$_3$), whereas the product 27b obtained using (R)-bgugaine showed $[\alpha]_D^{30}$ +15.96 (0.47, CHCl$_3$). Hence the product 27a is having $R$ configuration and 27b is having $S$ configuration (configuration was assigned by comparing specific optical rotation values with literature value$^{35}$). The reason for observed stereochemistry of 27b may be perhaps attributed to the presence of the long alkyl chain of (R)-bgugaine.

Conclusion:

The synthesized (R)-bgugaine, a natural product was tested for its catalytic activity towards Baylis-Hillman reaction.
**Experimental part of Section A**

5.01 Preparation of (2S)-allyl-N-Boc prolinate (ABP) 12.

Proline 10 (4.00 g, 0.035 mol) was mixed with allyl alcohol (8 mL) and stirred at 0 °C for 15 min. Thionyl chloride (4.547 g, 0.038 mol) was added drop wise to the reaction mixture over a period of 20 min. After complete addition of thionyl chloride, the reaction mixture was refluxed for 12 h. The excess of allyl alcohol was removed under reduced pressure to give the corresponding salt of allyl prolinate 11 (5.120 g, 77%). Allyl prolinate salt (5.00 g, 0.026 mol) was suspended in dry THF (20 mL) and reacted with Boc$_2$O (6.278 g, 0.026 mol) in presence of triethyl amine (9.261 g, 0.092 mol) at room temperature for 20 h. THF was removed under reduced pressure and CH$_2$Cl$_2$(50 ml) was added. The mixture was washed with dilute HCl (3 x 30 mL), followed by aq. NaHCO$_3$ (2 x 30 mL) and finally with H$_2$O (2 x 30 mL). The organic layer was dried over anhyd Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Purification of oily crude product by column chromatography on silica gel (hexanes: EtOAc = 8:2) afforded allyl-N-Boc prolinate 12 (5.990 g, 89.8%) as a colorless thick liquid.

$\left [\alpha \right ]_{D}^{30} = -48.51 \text{(c 3.80, CHCl}_3\text{)}$.

IR (neat): 1747, 1697 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): δ 1.38 [1.43] (s, 9H, 3CH$_3$); 1.83-2.21 (m, 4H, CH$_2$-CH$_2$); 3.38-3.52 (m, 2H, NCH$_2$); 4.20-4.33 (m, 1H, NCH); 4.59 (m, 2H, OCH$_2$); 5.18-5.33 (m, 2H, C=CH$_2$); 5.85-5.94 (m, 1H, CH=C).

$^{13}$C NMR (75 MHz, CDCl$_3$): 23.6 [24.2] (CH$_2$); 28.2 [28.4] (CH$_3$); 29.9 [30.8] (CH$_2$); 46.3 [46.5] (NCH$_2$); 59.1 [58.8] (NCH); 65.4 (OCH$_2$); 79.9 [79.7] (C(CH$_3$)); 118.6 [118.1] (=CH$_2$); 131.8 (CH=C); 153.1 [154.3] (CON); 172.8 [172.6] (COO).

HRMS: $m/z$ [M+Na]$^+$ calcd for C$_{13}$H$_{21}$NO$_4$Na: 278.1368; found: 278.1363.
5.02 Preparation of allyl prolinate polymer [Poly(ABP-co-ADC)] 13:

Preparation of polymer films:

\[
\text{BocIPP initiator} \quad \text{42-90 °C, 12 h}
\]

Mold Assembly: Polymerization was carried out using a mold designed for casting thin films of size 500-600 micron thickness. Optical glass plates of size 100 mm x 100 mm x 4 mm obtained from (Schott, Germany) were used to assemble the molds. A square shaped gasket of Teflon of outer length 100 mm, with an inner window of length 80 mm, and thickness of 500±10 µm was specially prepared for this purpose. A thin layer of a commercially available adhesive was applied from both sides of gasket and was sandwiched between two clean optical glass plates. The molds were then pressurized to make it leak proof²³b.

Figure 7. Mold pressurizing assembly.
Cast polymerization: Allyl-N-Boc prolinate monomer 12 (1 g) was mixed with allyl diglycol carbonate (ADC) monomer 15 (4 g) in a 25 mL round bottom flask. The monomer mixture was subjected to a high vacuum of 0.1 mbar and flushed with dry nitrogen for 30 min in order to remove dissolved oxygen. Isopropyl peroxydicarbonate (IPP) initiator 0.2 g (4% w/w of monomer mixture) and 0.050g of Dioctyl phthalate (1% w/w of monomer mixture) was added as a plasticizer. The mixture was injected in the mold after filtering through a 200 µm teflon filter. Special care was taken to avoid formation of air bubbles in the mold during filling of the monomer. The mold was sealed using Teflon plug and was sandwiched between two flat aluminum plates. The combined system was then placed in a mold pressurizing assembly as shown in figure 7. It consists of a stainless steel support and a piston which can be drilled down to apply the pressure on the molds. The molds were periodically pressurized during polymerization using the mold polymerization assembly. The whole assembly was then placed in a polymerization bath and heated according to the predefined 12 hour constant rate polymerization profile (Figure 8). The constant rate polymerization ensures a constant rate of initiator decomposition and heat evolution during polymerization. Thus, a polymer film with uniform bulk properties is obtained\textsuperscript{23a}. The bath temperature was controlled by externally using programmable water circulatory bath (Julabo, F 25 HP, Germany) with a temperature control accuracy of ± 0.01°C. After completion of polymerization, the molds were allowed to cool for further 12 h and opened to remove polymer films.

IR (KBr): 1745, 1697 cm\textsuperscript{-1}.
Figure 8. Constant rate polymerization cycle used for synthesis of the copolymer Poly(ABP-co-ADC)

5.03 Preparation of polymer 14.

Polymer 13 (1.122 g) was stirred (cut pieces of polymer of dimension 0.2×0.2 mm) with dichloromethane (10 mL) in presence of TFA (10 mL) for 12 h at room temperature. The insoluble solid polymer was filtered and washed with dichloromethane (3×30 mL). The polymer was than treated with aq. NH₃ (30 mL) at room temperature for 12 h to give polymer 14. It was filtered and washed successively with dry CHCl₃ (2×50 mL); dry EtOAc (2×50 mL), water (3×50 mL), MeOH (3×25 mL) and Et₂O (2×30 mL). The product obtained was dried to give polymer 14 as light yellow crystalline beads.

IR (KBr): 3377, 1745 cm⁻¹.
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Experimental part of Section B

5.04 General procedure for aldol reaction using protonated pyrrolidine salt 11 as catalyst:

To a stirred solution of anhyd acetone (10 equiv) and the 2-nitrobenzaldehyde (1 equiv), salt 11 (20 mol%) was added. Water (2 mL) was added to it, followed the addition of Et₃N (10 mol%), and the reaction mixture was then stirred at room temperature for 1 h. The reaction mixture was extracted with CHCl₃ (4 × 15 mL). The combined organic layer was washed with 2N HCl (2 × 25 mL), water (3 × 20 mL), dried over anhyd Na₂SO₄, concentrated and the residue was purified using flash column chromatography on silica gel (hexanes: EtOAc = 8:2) to give the pure light yellow oily product 20.

5.05 General procedure for aldol reaction using polymer catalyst 14:

To a stirred solution of anhydrous acetone (10 equiv) and the 2-nitrobenzaldehyde (1 equiv), polymer 14 (20 mol%, calculated based on theoretical N content of the monomer mixture) was added. Appropriate solvent (2 mL) was added to it and the reaction mixture was then stirred at room temperature for 24 h. The reaction mixture was filtered through sintered glass funnel and the polymeric material obtained was further washed with CHCl₃ (4 × 15 mL). The catalyst was recovered for reuse. The combined filtrates was then evaporated, and the residue was purified using flash column chromatography on silica gel (hexanes: EtOAc = 8:2) to give the pure light yellow oily product 20.

(4R)-Hydroxy-4-(2'-nitrophenyl)-butan-2-one³³ (20):

\[
\begin{align*}
\text{IR (neat):} & \quad 3600-3300, \, 1702 \text{ cm}^{-1}. \\
\text{¹H NMR (300MHz, CDCl₃):} & \quad \delta 2.24 (s, 3H); 2.68 (dd, J = 9.6 Hz, 17.7 Hz, 1H, CH₂); 3.16 (m, 1H, CH₂); 3.78 (br s, 1H, OH); 5.71 (d, J = 9.3 Hz, 1H); 7.45 (t, J = 7.5 Hz,}
\end{align*}
\]

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1H, Ar-H); 7.68 (t, \( J = 7.5 \) Hz, 1H, Ar-H); 7.90 (d, \( J = 7.8 \) Hz, 1H, Ar-H); 7.96 (d, \( J = 8.1 \) Hz, 1H, Ar-H).

\(^{13}\)C NMR (75MHz, CDCl\(_3\)): \( \delta \) 30.4 (CH\(_3\)); 51.1 (CH\(_2\)); 65.6 (CHOH); 124.4 (Ar-H); 128.2 (Ar-H); 133.7 (Ar-H); 138.4 (Ar-C); 147 (Ar-C); 208.6 (CO).

HPLC: The optical purity was determined by HPLC on chiralpak AD column [hexane/2-propanol 98:2]; flow rate 1.0 mL/min; Rt = 36.3 min (R), 39.1 min (S). The configuration was assigned as R by comparison of the sign of optical rotation value with literature.\(^{33}\)

(4R)-Hydroxy-4-(4'-nitrophenyl)-butan-2-one\(^{31}\):

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{O}_2\text{N} & \quad \text{CH}_3
\end{align*}
\]

\([\alpha]_D^{30} = +5.00 \text{ (c 1.78, CHCl}_3\), [lit\(^{31b}\) \([\alpha]_D^{30} +62.5 \text{ (0.2, CHCl}_3\), 93% ee)]

IR (neat): 3448, 1711, 1517, 1348 cm\(^{-1}\).

(4R)-Hydroxy-4-(2'-chlorophenyl)-butan-2-one\(^{31}\):

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{Cl} & \quad \text{CH}_3
\end{align*}
\]

\([\alpha]_D^{30} = +38.33 \text{ (c 1.20, CHCl}_3\), [lit\(^{31b}\) \([\alpha]_D^{30} +50.0 \text{ (1.07, CHCl}_3\), 41% ee)]

IR (neat): 3459, 1705 cm\(^{-1}\).

(4R)-Hydroxy-4-(4'-chlorophenyl)-butan-2-one\(^{31}\):

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{Cl} & \quad \text{CH}_3
\end{align*}
\]

\([\alpha]_D^{30} = +7.95 \text{ (c 0.75, CHCl}_3\), [lit\(^{31b}\) \([\alpha]_D^{30} +109.3 \text{ (0.22, CHCl}_3\), 95% ee)]

IR (neat): 3469, 1705 cm\(^{-1}\).
Chapter 5: Proline Derivatives for Studies in Asymmetric Organocatalysis Reaction

Optical rotations and enantiomeric excess for aldol product (4R)-hydroxy-4-(2'-nitrophenyl)-butan-2-one (20):

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>[\alpha]_D\textsuperscript{28} for Aldol product</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Acetone</td>
<td>-27.76 (c 1.783, CHCl\textsubscript{3})</td>
<td>33</td>
</tr>
<tr>
<td>2.</td>
<td>Water</td>
<td>-10.08 (c 0.794, CHCl\textsubscript{3})</td>
<td>17</td>
</tr>
<tr>
<td>3.</td>
<td>THF</td>
<td>-50.44 (c 0.456, CHCl\textsubscript{3})</td>
<td>52</td>
</tr>
<tr>
<td>4.</td>
<td>DMF</td>
<td>-71.43 (c 0.308, CHCl\textsubscript{3})</td>
<td>70</td>
</tr>
<tr>
<td>5.</td>
<td>DMSO</td>
<td>-76.66 (c 0.135, CHCl\textsubscript{3})</td>
<td>74</td>
</tr>
<tr>
<td>6.</td>
<td>DMF:H\textsubscript{2}O (2: 0.2)</td>
<td>-34.0 (c 0.765, CHCl\textsubscript{3})</td>
<td>33</td>
</tr>
<tr>
<td>7.</td>
<td>CHCl\textsubscript{3}</td>
<td>-64.07 (c 0.718, CHCl\textsubscript{3})</td>
<td>63</td>
</tr>
</tbody>
</table>

Optical rotations and enantiomeric excess for aldol product

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldol product</th>
<th>[\alpha]_D\textsuperscript{28} for Aldol product</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>(4R)-hydroxy-4-(4'-nitrophenyl)-butan-2-one</td>
<td>+5.00 (c 1.78, CHCl\textsubscript{3})</td>
<td>30</td>
</tr>
<tr>
<td>2.</td>
<td>(4R)-hydroxy-4-(2'-chlorophenyl)-butan-2-one</td>
<td>+38.33 (c 1.20, CHCl\textsubscript{3})</td>
<td>34</td>
</tr>
<tr>
<td>3.</td>
<td>(4R)-hydroxy-4-(4'-chlorophenyl)-butan-2-one</td>
<td>+7.95 (c 0.75, CHCl\textsubscript{3})</td>
<td>12</td>
</tr>
</tbody>
</table>

Experimental part of Section C:

5.06 General procedure for Baylis-Hillman reaction:

To a 50 mL round bottom flask, equipped with a stir bar was added (R)-bgugaine (20 mol%) dissolved in CHCl\textsubscript{3} (10 mL), 2-nitrobenzaldehyde (1 equiv) and methyl vinyl ketone (2 equiv). The resulting mixture was stirred until complete loss of starting material was observed on tlc (8:2, hexanes:EtOAc). The reaction was diluted with CHCl\textsubscript{3} and purified by column chromatography on silica gel (hexanes: EtOAc = 8:2)
to afford a pale yellow product 27b (48%). Measurement of the optical rotation and comparison to the literature\textsuperscript{36} showed the sample have the (S)-configuration whereas the product 27a obtained using (S)-N-methyl prolinol showed (R)-configuration.

### 3-[(R)-hydroxy(2-nitrophenyl)methyl]but-3-en-2-one\textsuperscript{36} (27a):

\[
\text{[a]}_D^{30} = -7.44 (1.02, \text{CHCl}_3), \text{[lit]}^{36} \text{[a]}_D^{30} = -144.0 (1.0, \text{CHCl}_3, 78\%\ \text{ee})
\]

**IR (neat):** 3414, 1675, 1525, 1351 cm\textsuperscript{-1}.

**\textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}):** \(\delta 2.38 (\text{s, 3H, CH}_3), 3.54 (\text{br s, 1H, OH}), 5.81 (\text{s, 1H, CH}), 6.18 (\text{s, 1H, CH}_2), 6.23 (\text{s, 1H, CH}_2), 7.47 (t, J = 7.8 Hz, 1H, Ar-H), 7.66 (t, J = 7.5 Hz, 1H, Ar-H), 7.79 (d, J = 7.5 Hz, 1H, Ar-H), 7.97 (t, J = 8.1 Hz, 1H, Ar-H).

**\textsuperscript{13}C NMR (75MHz, CDCl\textsubscript{3}):** \(\delta 26.0 (\text{CH}_3), 67.4 (\text{CH}), 124.6, 128.5, 128.8, 133.4 (\text{Ar-H}), 126.4 (=\text{CH}_2), 136.4 (\text{Ar-C}), 148.0 (\text{Ar-C}), 149.0 (\text{C-3}), 199.8 (\text{C-O}).

**HPLC:** The optical purity was determined by HPLC on chiralpak AD column [hexane/2-propanol 95:5]; flow rate 0.75 mL/min; Rt = 38.2 min (R, major ent.), 34.5 min (S, minor ent.). The configuration was assigned as R by comparison of the sign of optical rotation value with literature.\textsuperscript{36}

### 3-[(S)-hydroxy(2-nitrophenyl)methyl]but-3-en-2-one (27b):

\[
\text{[a]}_D^{30} = +15.96 (0.47, \text{CHCl}_3). \text{IR (neat):} 3414, 1675, 1525, 1351 \text{ cm}^{-1}.
\]

**HPLC:** The optical purity was determined by HPLC on chiralpak AD column [hexane/2-propanol 95:5]; flow rate 0.75 mL/min; Rt = 34.1 min (S, major ent.), 37.3 min (R, minor ent.). The configuration was assigned as S by comparison of the sign of optical rotation value with literature.\textsuperscript{36}
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Spectra:

Figure 9. $^{13}$C NMR spectrum of 11

Figure 10. $^1$H NMR spectrum of 12
Figure 11. $^{13}$C NMR spectrum of 12

Figure 12. IR spectrum of 13 and 14
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Figure 13. $^1$H NMR spectrum of 20

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>RT</th>
<th>Area [μV.Sec]</th>
<th>%Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R-isomer</td>
<td>36.292</td>
<td>29666094.277</td>
<td>85.07</td>
</tr>
<tr>
<td>2</td>
<td>S-isomer</td>
<td>39.142</td>
<td>5207657.231</td>
<td>14.93</td>
</tr>
</tbody>
</table>

Total Area of Peak = 34873751.508 [μV.Sec]

Figure 14. HPLC chromatogram of 20 (reaction in DMF solvent)
### Chapter 5: Proline Derivatives for Studies in Asymmetric Organocatalysis Reaction

#### Figure 15. HPLC chromatogram of 20 (reaction in DMSO solvent)

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>RT</th>
<th>Area [$\mu$V.Sec]</th>
<th>%Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R-isomer</td>
<td>35.908</td>
<td>38804116.004</td>
<td>87.01</td>
</tr>
<tr>
<td>2</td>
<td>S-isomer</td>
<td>38.708</td>
<td>5794637.793</td>
<td>12.99</td>
</tr>
</tbody>
</table>

Total Area of Peak = 44598753.797 [$\mu$V.Sec]

#### Figure 16. HPLC chromatogram of 20 (reaction in DMF:H$_2$O solvent)

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>RT</th>
<th>Area [$\mu$V.Sec]</th>
<th>%Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R-isomer</td>
<td>36.275</td>
<td>23403133.347</td>
<td>66.14</td>
</tr>
<tr>
<td>2</td>
<td>S-isomer</td>
<td>39.075</td>
<td>11981623.685</td>
<td>33.86</td>
</tr>
</tbody>
</table>

Total Area of Peak = 35384757.032 [$\mu$V.Sec]

#### Figure 17. HPLC chromatogram of 20 (reaction in CHCl$_3$ solvent)

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>RT</th>
<th>Area [$\mu$V.Sec]</th>
<th>%Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R-isomer</td>
<td>36.742</td>
<td>25458958.575</td>
<td>81.37</td>
</tr>
<tr>
<td>2</td>
<td>S-isomer</td>
<td>39.517</td>
<td>5830183.973</td>
<td>18.63</td>
</tr>
</tbody>
</table>

Total Area of Peak = 31289142.549 [$\mu$V.Sec]

---

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Figure 18. ^1_H NMR spectrum of 27

File name: Baylis(Bgugaine 5)004.CH1

Info:
5% 2-Propanol: N-Hexane is mobile phase, Baylis Hillmann reaction of 2-Nitrobenzaldehyde with MVK in CHCl₃ using Bgugaine, Flow rate 0.75 ml/min.

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>RT</th>
<th>Area[µ.V.Sec]</th>
<th>%Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>34.075</td>
<td>3214581.334</td>
<td>52.86</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>37.333</td>
<td>2866282.178</td>
<td>47.14</td>
</tr>
</tbody>
</table>

Total Area of Peak = 6080863.512 [µ.V.Sec]

Figure 19. HPLC chromatogram of 27b

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References:


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