5.1 Introduction

The construction of suitably functionalized cyclohexane frameworks plays a central role in many natural product synthesis. Although the Diels-Alder reaction is among the most powerful tools for generating such carboycles, it is often difficult to form systems that are highly congested or possess substituted arrays that are incompatible with the reaction. A number of alternative methods for synthesizing cyclohexanes have arisen from catalytic approaches, such as the base-catalyzed Michael-aldol, Michael-Mannich and Michael-Michael reactions, transition-metal-catalyzed ring-closing metathesis (RCM) followed by hydrogenation, and cycloisomerization reactions. In contradistinction to the widespread use of these intramolecular processes, intermolecular counterparts for catalytic cyclohexane synthesis are less well developed.

Nucleophilic amine catalysis or organocatalysis has emerged recently as an efficient means of generating carbo- and heterocycles. In particular, Barbas three-component [4+2] cycloaddition to form functionalized cyclohexanes from 4-substituted-3-buten-2-ones, aldehydes and Meldrum’s acid or 1,3-indandione under proline-catalysis has been applied in the syntheses of several cis-spirane products. Nevertheless, proline-catalysis has not been utilized previously for the formation of functionalized cyclohexanes by utilizing (E)-2-cyano-3-aryl-acrylic acid alkyl esters as dienophiles in Diels-Alder chemistry. Building upon our proline-catalyzed regioselective synthesis of (E)-2-cyano-3-aryl-acrylic acid alkyl esters, we reasoned that it might be possible to use as dienophiles in [4+2] cycloaddition reaction.
Herein, we disclose the facile synthesis of cyclohexanes 68/69 and 72 via proline-catalyzed cascade annulations from simple substrates (Scheme 11).

Scheme 11: Development of Organocatalytic Cascade Reactions Based on Barbas Dienamine Platform.

As a part of our program to engineer novel organocatalytic cascade or multi-component reactions,\textsuperscript{11,12,16} herein we reported the highly regio- and diastereoselective direct organocatalytic cascade olefination/Diels-Alder/epimerization, olefination/Diels-Alder/epimerization/three-component reductive alkylation and olefination/Diels-Alder/epimerization/three-component reductive alkylation/\textit{trans}-esterification reactions that provide highly substituted prochiral 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters 68/69 and 1-cyano-4-(cyano-alkoxycarbonyl-methyl)-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters 72 from commercially available 4-substituted-3-buten-2-ones 1a-i, aldehydes 2a-l and CH-acids, cyano-acetic acid alkyl esters 3n, 3q-t using \textit{in situ} generated (\textit{E})-2-cyano-3-aryl-acrylic acid alkyl esters 73 as dienophiles and Barbas dienamines 74 (2-amino-1,3-butadienes)\textsuperscript{6-8} as diene source (Scheme 11). The highly
Double Cascade Reactions Based on the Barbas Dienamine Platform

functionalized cyclohexanes $68/69$ and $72$ are attractive intermediates in the synthesis of natural products, and in materials chemistry and are excellent starting materials for the synthesis of cardiovascular agents and hypnotic active products.\(^{40}\)

In our reaction we envisioned that amino acid, proline $4c$ would catalyze the cascade regio-selective olefination reaction of aldehyde $2$ with CH-acids (alkyl cyanoacetates) $3$ to provide $(E)$-2-cyano-3-aryl-acrylic acid alkyl esters $73$ via iminium-catalysis, which would then undergo a concerted [4+2] cycloaddition with a 2-amino-1,3-butadienes $74$ (Barbas dienamine) generated \textit{in situ} from enone $1$ and proline $4c$ to form substituted 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters $68$ and $69$ in a diastereoselective manner. Novel epimerization at $\alpha$-position to carbonyl of the minor diastereomer \textit{trans}-isomer $68$ to the more stable \textit{cis}-isomer $69$ could occur under the same reaction conditions as shown in Scheme 11. Further treatment of \textit{cis}-isomer $69$ with CH-acids $3$ and Hantzsch ester $15$ would generate the highly functionalized cyclohexanes $72$ in one-pot as shown in Scheme 11. The cascade olefination/Diels-Alder/epimerization, olefination/Diels-Alder/epimerization/three-component reductive alkylation and olefination/Diels-Alder/epimerization/three-component reductive alkylation/trans-esterification reaction sequences would then generate a quaternary center with the formation of three new carbon–carbon $\sigma$ bonds, and four new carbon–carbon $\sigma$ bonds/two carbon-hydrogen bonds respectively \textit{via} organocatalysis.

\subsection*{5.2 Results and Discussion}

We initiated our investigation by seeking a viable proline $4c$ catalyst for the cascade [4+2] annulation of the enone $1b$, benzaldehyde $2b$ and methyl cyanoacetate $3q$ to provide the cyclohexanone $69bbq$\(^*\) (Table 15). We were pleased to find that the three-component reaction of \textit{trans}-4-phenyl-3-buten-2-one $1b$, benzaldehyde $2b$ and methyl cyanoacetate $3q$ with a catalytic amount of $L$-proline $4c$ in methanol at

\* In all compounds denoted $69xyz$, $x$ is incorporated from reactant enones $1$, $y$ is incorporated from the reactant aldehydes $2$ and $z$ is incorporated from the reactant CH-acids $3$. 

80
ambient temperature for 30 h furnished Diels-Alder products $68bbq$ and $69bbq$ in 76% yield with prochiral cis-isomer $69bbq$ as the major isomer with only 9% de (Table 15, entry 1).

**Table 15**: Effect of Solvent on the Direct Amino acid-Catalyzed Cascade O/DA/E Reaction of $1b$, $2b$ and $3q$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (0.5 M)</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Products</th>
<th>Yield%</th>
<th>de%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>25° C</td>
<td>30</td>
<td>$68bbq$, $69bbq$</td>
<td>76</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>25° C</td>
<td>96</td>
<td>$68bbq$, $69bbq$</td>
<td>78</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>25° C</td>
<td>96</td>
<td>$68bbq$, $69bbq$</td>
<td>75</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>70° C</td>
<td>72</td>
<td>$69bbq$</td>
<td>80</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>DMSO</td>
<td>25° C</td>
<td>6</td>
<td>$68bbq$, $69bbq$</td>
<td>80</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>25° C</td>
<td>72</td>
<td>$69bbq$</td>
<td>85</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>DMSO</td>
<td>50° C → 25° C</td>
<td>24 → 48</td>
<td>$69bbq$</td>
<td>80</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>DMF</td>
<td>25° C</td>
<td>24</td>
<td>$68bbq$, $69bbq$</td>
<td>77</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>DMF</td>
<td>25° C</td>
<td>72</td>
<td>$68bbq$, $69bbq$</td>
<td>75</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>NMP</td>
<td>25° C</td>
<td>24</td>
<td>$68bbq$, $69bbq$</td>
<td>76</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>NMP</td>
<td>25° C</td>
<td>72</td>
<td>$68bbq$, $69bbq$</td>
<td>75</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>25° C</td>
<td>168</td>
<td>$68bbq$, $69bbq$</td>
<td>≤ 5%</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>CH$_3$CN</td>
<td>25° C</td>
<td>36</td>
<td>$68bbq$, $69bbq$</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>CHCl$_3$</td>
<td>25° C</td>
<td>72</td>
<td>$68bbq$, $69bbq$</td>
<td>73</td>
<td>33</td>
</tr>
<tr>
<td>15</td>
<td>C$_6$H$_5$CH$_3$</td>
<td>25° C</td>
<td>120</td>
<td>$68bbq$, $69bbq$</td>
<td>65</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>CH$_2$Cl$_2$</td>
<td>25° C</td>
<td>120</td>
<td>$68bbq$, $69bbq$</td>
<td>68</td>
<td>20</td>
</tr>
<tr>
<td>17</td>
<td>[bmim]Br</td>
<td>25° C</td>
<td>72</td>
<td>$68bbq$, $69bbq$</td>
<td>80</td>
<td>44</td>
</tr>
<tr>
<td>18</td>
<td>[bmim]BF$_4$</td>
<td>25° C</td>
<td>72</td>
<td>$68bbq$, $69bbq$</td>
<td>71</td>
<td>0</td>
</tr>
</tbody>
</table>

$a$ Experimental conditions: Amino acid $4c$ (0.1 mmol), benzylidene acetone $1b$ (1 mmol), benzaldehyde $2b$ (0.5 mmol) and CH-acid $3q$ (0.5 mmol) in solvent (1 mL) were stirred at ambient temperature for 6 to 120 h.

$b$ Yield refers to the purified product obtained by column chromatography.

$c$ Diastereomeric excesses determined by using $^1$H and $^{13}$C NMR analysis on isolated products.

d All reactants ($1b$, $2b$ and $3q$) were used in same equivalents.
Figure-20: $^1$H NMR and $^{13}$C NMR Spectra of Product 69bbq.
The same reaction albeit with an extended reaction time furnished cis-isomer 69bbq with 33% de in 78% yield (Table 15, entry 2). The minor diastereomer, trans-isomer 68bbq was effectively epimerized to the thermodynamically stable cis-isomer 69bbq under prolonged reaction times via proline catalysis. The stereochemistry of products 68bbq and 69bbq was established by NMR analysis [see Fig. 20].

In the three-component cascade olefination/Diels-Alder/epimerization (O/DA/E) reaction of enone 1b, benzaldehyde 2b and methyl cyanoacetate 3q catalyzed directly by L-proline 4c, we found that the solvent (dielectric constant) and temperature had a significant effect on reaction rates, yields and de’s (Table 15). Our studies revealed that the cascade O/DA/E reaction catalyzed by L-proline produces products 68bbq and 69bbq in moderate yields and poor selectivity in aprotic non-polar solvents (Table 15, entries 12-16) and with excellent yields and selectivity in protic/polar solvents (Table 15, entries 4-7). But interestingly, cascade O/DA/E reaction in polar solvents like DMF and NMP looks different compared to DMSO as shown in Table 15, entries 8-11. The same cascade reaction in the ionic liquids [bmim]Br and [bmim]BF₄ catalyzed by L-proline provided the cascade product cis-isomer 69bbq with 44% de and 0% de in good yield, respectively (Table 15, entry 17 and 18). Interestingly, under proline catalysis, the cascade O/DA/E reaction worked well in EtOH and DMSO solvents and the optimal conditions involved mixing equimolar amounts of enone 1b, aldehyde 2b and CH-acid 3q in ethanol with heating to 70 °C for 72 h to furnish cis-isomer 69bbq as a single diastereomer in 80% yield (Table 15, entry 4) or mixing equimolar amounts of 1b, 2b and 3q in DMSO with heating to 50 °C for 24 h and 25 °C for 48 h to furnish cis-isomer 69bbq as a single diastereomer in 80% yield (Table 15, entry 7).

After this preliminary understanding, we proceeded to investigate the scope and limitations of the cascade O/DA/E reaction of 1b and 2b with a range of active CH-acids 3n and 3q-t under proline-catalysis in DMSO (Table 16). As shown in

* In all compounds denoted 68xyz and 69xyz, x is incorporated from reactant enones 1, y is incorporated from the reactant aldehydes 2 and z is incorporated from the reactant CH-acids 3.
Table 16, the acyclic CH-acids 3n and 3q-t furnished the expected cascade products 69bbn and 69bbq-bbt in good yields with 99% de respectively except for ethyl cyano acetate 3n, where the cascade product 69bbn was formed in 92% yield with only 77% de.

**Table 16**: Effect of CH-acids 3 on the Direct Amino acid-Catalyzed Cascade O/DA/E Reaction of 1b, 2b and 3p-t

<table>
<thead>
<tr>
<th>Entry</th>
<th>Products</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>de&lt;sup&gt;c&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69bbq</td>
<td>85</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>69bbn</td>
<td>92</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>69bbr</td>
<td>76</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>69bbs</td>
<td>80</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>69bbt</td>
<td>85</td>
<td>99</td>
</tr>
</tbody>
</table>

<sup>a</sup> Amino acid 4c (0.1 mmol), benzylidene acetone 1b (1 mmol), benzaldehyde 2b (0.5 mmol) and CH-acids 3n, 3q-t (0.5 mmol) in DMSO (1 mL) were stirred at 25°C for 72 h.

<sup>b</sup> Yield refers to the purified product obtained by column chromatography.

<sup>c</sup> Diastereomeric excesses determined by using <sup>1</sup>H and <sup>13</sup>C NMR analysis on isolated products.
Figure-21: $^1$H NMR and $^{13}$C NMR Spectra of Product 69bbs.
We generated a useful library of cascade O/DA/E products 69 under proline-catalysis. The results in Table 17 demonstrate the broad scope of this green methodology covering a structurally diverse group of less reactive ketones 1a-i, aldehydes 2a-l and CH-acids 3n, 3q-t with many of the yields and de’s obtained being very good, or indeed better, than previously published reactions starting from
the divinyl ketones and CH-acids via double Michael reactions. Each of the targeted prochiral cis-isomer 69 was obtained as a single diastereomer in excellent yield. Prochiral cis-isomers 69caq-jjq were generated in very good yields with aromatics bearing either electron withdrawing or electron donating groups in the para position as shown in Table 17. Interestingly, the prochiral hetero aromatic cis-isomer 69jjq was synthesized in 90% yield with only 0% de under the same reaction conditions (Table 17).

**Table 18**: Direct Proline-Catalyzed Epimerization of trans-isomers of O/DA Products 68

*In all compounds denoted 69xyz, x is incorporated from reactant enones 1, y is incorporated from the reactant aldehydes 2 and z is incorporated from the reactant CH-acids 3.*
Figure-22: $^1$H NMR and $^{13}$C NMR Spectra of Product 68jjq/69jjq.
Proline-catalyzed cascade O/DA/E reaction of \textit{trans}\textsuperscript{-}4-(4-nitro-phenyl)-3-buten-2-one \textbf{1c}, 4-nitrobenzaldehyde \textbf{2a} and methyl cyanoacetate \textbf{3q} furnished the cascade esters cis-\textbf{69caq}/\textit{trans}\textsuperscript{-}68caq\textsuperscript{*} in 80\% yield with 50\% de of \textbf{69caq} (Table 17, entry 1). Interestingly, cascade reaction of \textbf{1d}, \textbf{2d} and \textbf{3q} furnished the esters \textbf{68ddq}/\textbf{69ddq} in 86\% yield with 0\% de. Cascade O/DA/E reactions produced cyclohexanone products \textbf{69eeq}, \textbf{69ffq}, \textbf{69ggq}, \textbf{69hhq}, \textbf{69biq} and \textbf{69bkq} in very good yields with 99\% de as shown in Table 17. Proline-catalyzed O/DA/E reaction of \textbf{1b}, \textbf{2a} and \textbf{3n} furnished the non-symmetrical \textit{cis}-isomer \textbf{69ban} in 75\% yield with 82\% de and 14\% ee as shown in Table 17. Non-symmetrical \textit{cis}-isomers \textbf{69biq}, \textbf{69bkq} and \textbf{69blq} are also generated using cascade O/DA/E reaction in very good yields with good de’s as shown in Table 17. The cascade \textit{trans}-isomers \textbf{68caq}, \textbf{68ddq}, \textbf{68iiq} and \textbf{68jjq} were epimerized to \textit{cis}-isomers \textbf{69caq}, \textbf{69ddq}, \textbf{69iiq} and \textbf{69jjq} under proline-catalysis in very good yields with complete conversion at 25\°C for 48 h (Table 18).

With pharmaceutical and material applications in mind, we extended the three-component cascade O/DA/E reactions into a novel double cascade proline-catalyzed five-component olefination/Diels-Alder/epimerization/three-component reductive alkylation (O/DA/E/TCRA) reaction of enones \textbf{1}, aldehydes \textbf{2}, CH-acids \textbf{3}, and Hantzsch ester \textbf{15} with various CH-acids \textbf{3n} and \textbf{3q-t} in one-pot (Table 19). Library of double cascade products \textbf{72} as shown in Table 19 are furnished in good yields with 99\% de under proline-catalysis at 25\°C for 96 h. Interestingly, proline-catalyzed double cascade reaction of \textbf{1b}, \textbf{2b}, \textbf{3q} (2 equiv.) and \textbf{15} in EtOH at 70\°C for 96 h furnished the product \textbf{72bbqn}\textsuperscript{v} in 60\% yield with 99\% de via olefination/Diels- Alder/epimerization/three-component reductive alkylation/\textit{trans}-esterification (O/DA/E/TCRA/TE) reaction sequence. Structure and regiochemistry of

\textsuperscript{*} In all compounds denoted \textbf{68xyz} and \textbf{69xyz}, \textit{x} is incorporated from reactant enones \textbf{1}, \textit{y} is incorporated from the reactant aldehydes \textbf{2} and \textit{z} is incorporated from the reactant CH-acids \textbf{3}.

\textsuperscript{v} In all compounds denoted \textbf{72wxyz}, \textit{w} is incorporated from reactant enones \textbf{1}, \textit{x} is incorporated from the reactant aldehydes \textbf{2}; \textit{y} and \textit{z} are incorporated from the reactant CH-acids \textbf{3}.
the double cascade products 72 were confirmed by NMR analysis [for example see Fig. 23] and also by X-ray structure analysis of 72bbtt as shown in Scheme 12.\textsuperscript{43}

Table 19: Chemically Diverse Libraries of Cascade O/DA/E/TCRA Products 72\textsuperscript{a,b}

\begin{tabular}{l l l l}
\hline

| Product  | Yield (\%) | de (\%) |
\hline

72bbqq & 73 & 99
72bbnn & 75 & 82
72bbr & 70 & 99
72bbss & 75 & 99
72bbtt & 73 & 99
72bbqn\textsuperscript{c} & 60 & 99
72bbqq & 70 & 99
72bbqn & 75 & 99

\hline

\end{tabular}

\textsuperscript{a} Experimental conditions: proline 4c (0.1 mmol), benzylidene acetone 1b (0.5 mmol), benzaldehyde 2b (0.5 mmol), and CH-acid 3 (0.5 mmol) in solvent (1 mL) were stirred at ambient temperature for 72 h, and then CH-acid 3 (0.5 mmol) and Hantzsch ester 15 (0.5 mmol) was added (see the Experimental Section).

\textsuperscript{b} Yield refers to the column purified product and diastereomeric excesses determined by using \textsuperscript{1}H and \textsuperscript{13}C NMR analysis on isolated products.

\textsuperscript{c} Product 72bbqn were obtained from cascade O/DA/E/O/H/TE reaction of 1b, 2b, 3q (2 equiv), 4c, and 15 in EtOH (1.0 mL) at 70°C for 96 h.
Figure-23: $^1$H NMR and $^{13}$C NMR Spectra of Product 72bbtt.
Prochiral cis-isomers 69 are excellent starting materials for the synthesis of cardiovascular agents and hypnotic active products; and the highly functionalized cyclohexanes 72 could serve as suitable synthons for the synthesis of various useful materials with different properties.

**Scheme 12**: Crystal Structure of 4-(Benzyloxycarbonyl-cyano-methyl)-1-cyano-2,6-diphenyl-cyclohexanecarboxylic acid benzyl ester (72bbtt).

![Crystal Structure](image)

### 5.3 Mechanistic Insights

The possible reaction mechanism for L-proline-catalyzed regio- and diastereoselective synthesis of the cascade products 69 and 72 through the reaction of enone 1, aldehyde 2, CH-acid 3 and Hantzsch ester 15 is illustrated in Schemes 13 and 14. This catalytic sequential one-pot, double cascade is a five component reaction comprising of enone 1, aldehyde 2, CH-acid 3, Hantzsch ester 15, CH-acid 3 and a simple chiral amino acid 4c; which is capable of catalyzing each step of this double cascade reaction. In the first step (Scheme 13), the catalyst (S)-4c activates component 2 by most likely iminium ion formation, which then selectively adds to the CH-acid 3 via a Mannich and amine elimination reaction to generate regio-selectively active olefin 73 as dienophile. The following second step is proline mediated generation of Barbas dienamine 74 (2-amino-1,3-butadiene) as diene source from enone 1 and proline 4c. In the subsequent third step, Diels-Alder reaction of 73 with in situ generated Barbas dienamine 74 via most likely concerted [4+2]-cycloaddition leads to the formation of cascade O/DA
products 68/69 in good yield with prochiral cis-isomer 69 as the major isomer with moderate de. In the fourth step, (S)-4c catalyzed the epimerization at β-position to the carbonyl of trans-isomer 68 via enamine catalysis and subsequent hydrolysis returned the catalyst (S)-4c for further cycles and released the desired major cis-isomer 69. In the fifth step, (S)-4c catalyzed the olefination of the major isomer 69 with CH-acid 3 to furnish the functionalized olefin 75 via most likely iminium catalysis as like first step. The following sixth step is bio-mimetic hydrogenation of the active olefin 75 by Hantzsch ester 15 to produce 72 through self-catalysis by decreasing HOMO-LUMO energy gap between 75 and 15 respectively.\textsuperscript{11-12,16}

**Scheme 13**: Proposed Catalytic Cycle for the Double Cascade Reactions.

Taking into account the recent applications of amine-catalyzed olefination reactions\textsuperscript{6-8,16} and based on the different experiments performed (Tables 15-18), we proposed that the most likely reaction course for the organocatalyzed direct epimerization at β-position to carbonyl of trans-isomer 68 and three-component reductive alkylation of cis-isomer 69 is the one outlined through amino acid-catalysis as shown in Scheme 14.
**Scheme 14**: Proposed Mechanisms for the L-proline 4c Catalyzed Epimerization and Three-component Reductive Alkylation reactions.

*Epimerization at β-position to carbonyl via enamine catalysis*

*Olefination via iminium catalysis*
Epimerization of trans-isomer 68 or the diastereospecific synthesis of cis-isomer 69 in the cascade O/DA/E reaction of enone 1, aldehyde 2 and CH-acid 3 can be explained as illustrated in Scheme 14. The energy difference (ΔH) between the two isomers 68bbq and 69bbq is 3.085 kcal/mol based on PM3 calculations. The energy difference (ΔH) between the two isomers of 68bbn and 69bbn is 3.081 kcal/mol based on PM3 calculations. Minimized structures of 68bbq, 69bbq, 68bbn, and 69bbn are depicted in the Scheme 15. Since the differences in ΔH’s between the two isomers of 68bbq/69bbq and 68bbn/69bbn are greater than 3 kcal/mol, the minor kinetic isomers 68bbq and 68bbn are epimerized to the thermodynamically more stable cis-isomers 69bbq and 69bbn, respectively, at room temperature under mild organocatalysis. The minor kinetic isomer trans-isomer 68 was epimerized to the thermodynamically stable cis-isomer 69 via deprotonation/reprotonation or retro-Michael/Michael reactions catalyzed by amino acid. This is in agreement with the previously proposed retro-Michael/Michael reaction mechanism7a at the epimerization step (Scheme 14). As shown in Scheme 14, the amino acid reacts with trans-isomer 68 to generate the enamine 76. The retro-Michael reaction to form the ring-opened imine/enolate 77 should be accelerated by hydrogen bonding with protic/polar solvents. Imine/enolate 77 then undergoes Michael reaction to form the enamine of the thermodynamically stable cis-isomer 78, which undergoes hydrolysis in situ to furnish the cis-isomer 69.

The possible reaction mechanism for the cascade TCRA reactions of 69, 3, 15 and 4c is illustrated in Scheme 14. First, the reaction of proline 4c with cis-isomer 69 generates the iminium cation 81, an excellent electrophile that undergoes Mannich type reactions with CH-acid 3 to generate the Mannich product 83. Base induced elimination reaction of the amine 83 would furnish the active olefin 75. The next hydrogen transfer reactions are dependent upon the electronic nature of the in situ generated conjugated system or, more precisely, the HOMO-LUMO gap of the reactants 15 and 75.11-12,16
**Scheme 15**: Minimized Structure of $68_{bbq}/69_{bbq}$ and $68_{bbn}/69_{bbn}$ Based on MOPAC Calculations

Observed high regio-selectivity in the cascade products $72$ can be explained by the approach of the hydride source (Hantzsch ester $15$) to olefins $75$ which is the main controlling factor than the thermodynamic stability of the resulting hydrogenated products $72$. Approach of the Hantzsch ester $15$ to the olefin $75$ through the equatorial position is more favourable than the axial position, may be due to the existence of more steric hindrance in an axial approach. Steric strain control (SSC) is the main controlling factor than the product stability control (PSC) in bio-mimetic cascade reductions, because thermodynamically stable isomer *cis*-72 is formed as very minor product. This selectivity trend can be easily understood by the approach of bulk hydride source $15$ to highly functionalized olefins $75$. 
5.4 Conclusions

In summary, we have developed the first amino acid catalyzed direct cascade O/DA/E, O/DA/E/TCRA and O/DA/E/TCRA/TE reactions. This astonishingly simple and atom-economic approach can be used to construct highly functionalized prochiral 1-cyano-4-oxo-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters 69 and 1-cyano-4-(cyano-alkoxycarbonyl-methyl)-2,6-diaryl-cyclohexanecarboxylic acid alkyl esters 72 in a diastereospecific fashion. Selective multi-step reactions of this type inspire analogies with biosynthetic pathways and compliment traditional multi-component synthetic methodologies. As we have suggested previously, the synthesis of poly-functionalized molecules under amino acid-catalysis provides a unique and under explored perspective on pre-biotic synthesis. A complete understanding of the scope of amino acid-catalysis should not only empower the synthetic chemist but also provide a new perspective on the origin of complex molecular systems.