Memory of Chirality (MOC) Concept in Imino-Aldol Reaction: Enantioselective Synthesis of \( \alpha,\beta \)-Diamino Esters and Aziridines

Manas K. Ghorai, Koen Ghosh, A. K. Yadav, Y. Nanaji, Sandipan Halder, and Masthanvali Sayyad

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

ABSTRACT: A simple strategy for the synthesis of chiral \( \alpha,\beta \)-diamino- and \( \alpha \)-amino,\( \beta \)-hydroxy ester derivatives in high yields with moderate to high ee has been developed via asymmetric imino-aldol and aldol reactions, respectively, starting from protected aminoesters employing memory of chirality concept for chiral induction. This strategy has been extended for the enantioselective synthesis of aziridines (ee up to 92%). The absolute configuration of the imino-aldol adducts has been determined. The stereochemical outcome of the products has been explained by a suitable mechanism and supported by computational studies.

INTRODUCTION

The asymmetric aldol and imino aldol reactions of enolates with aldehydes (or equivalents) and imines, respectively, are synthetically very important for the construction of \( \beta \)-amino esters, \( \alpha,\beta \)-diamino ester derivatives, nonproteogenic \( \beta \)-amino acids, different polyfunctionalized chiral building blocks, and \( \beta \)-lactam antibiotics, etc. The enantioselective synthesis of many of these bioactive compounds were achieved by the addition of chiral enolates with imines where a chiral auxiliary or an untouched stereogenic center of the ester enolate controls the stereoselectivity. Other approaches for asymmetric imino-aldol reactions either involve achiral enolates and chiral imines along with achiral Lewis acids or chiral enolate complexes generated from achiral enolates with chiral Lewis acids. However, there is no report other than ours for asymmetric imino-aldol reaction without using any external chiral source, for example, chiral auxiliary or a catalyst. To induce asymmetry in imino-aldol reaction without the aid of an external chiral source, we anticipated that a conformationally chiral enolate could be added to an imine following Memory of Chirality (MOC) concept. The phenomenon of MOC was first demonstrated in the field of enolate chemistry by Fuji and Kawabata where enantioselective alkylation of chiral ketones, amides and amino acid esters were achieved through enolate carbamions with a high degree of selectivity. A number of synthetically and biologically important compounds including substituted \( \alpha \)-amino acids, quaternary amino acids, cyclic amino acids, N-heterocycles, etc. were synthesized utilizing this concept. Recently, we have explored MOC in an asymmetric imino-aldol reaction to obtain \( \alpha,\beta \)-diamino esters with consecutive quaternary and tertiary stereogenic centers in high yields and stereoselectivities. Optically active \( \alpha,\beta \)-diamino acids are found in a variety of antibiotics and natural products. A number of synthetic routes are available in the literature for the synthesis of \( \alpha,\beta \)-diamino acids and their derivatives including direct catalytic asymmetric Mannich reaction, opening of aziridine rings, \( \alpha,\beta \)-imino-aldol reaction, catalytic asymmetricaza-Henry reaction, etc. In this article, we report our detailed study for the synthesis of chiral \( \alpha,\beta \)-diamino ester derivatives via the imino-aldol protocol following MOC concept. This methodology was further explored for aldol reaction.

RESULTS AND DISCUSSION

To begin our study, the enolate was generated from N-benzyl-N-tert-butoxycarbonylphenylalanine ethyl ester as a mixture of diastereomers in 88% yield with dr 62-64% (Scheme 1). The imino-aldol adduct 4a was isolated as an inseparable mixture of diastereomers. However, 3 did not cyclize to produce the corresponding \( \beta \)-lactam 5 since the negative charge developed on nitrogen was highly delocalized over the sulfonyl group. The \( ^1 \)H NMR spectrum of the imino-aldol adduct 4a showed broad signals at room temperature possibly because of its existence as a mixture of rotamers. However, the formation of the product 4a was confirmed by \( ^13 \)C NMR, DEPT NMR and mass spectral analysis. To restrict the interconversion of possible rotamers of the imino-aldol adduct 4a at room temperature, extensive low temperature NMR study was carried out at \(-25, -40 \) and \(-55 \) °C (in CDCl\(_3\)) with an idea that one of the rotamers might be frozen at lower temperature (see Supporting Information). Resolution of the \( ^1 \)H NMR spectrum was improved to some extent upon lowering the temperature, although it was not completely resolved even at \(-55 \) °C (in CDCl\(_3\)). \( ^1 \)H NMR spectrum of 4a recorded at higher temperature (60 °C in DMSO-\( \text{d}_6 \)) showed similar broad spectrum as discussed earlier. To simplify the \( ^1 \)H NMR spectrum, N-Boc group of 4a was removed using 1:2 trifluoroacetic acid and dichloromethane to give 6a as a mixture of diastereomers in 88% yield with dr 75:25 (based on \( ^1 \)H NMR study of the crude reaction mixture) (Scheme 2). The diastereomers were separated...
by flash column chromatography. Compound 6a was characterized by spectroscopic and analytical data.

The reaction of 1a with N-tosylphenylaldimine was studied in different solvents using KHMDS as the base (Table 1, entries 1–4). In all cases, compound 4a was obtained in moderate yield but with low enantioselectivity (up to 28% for the major diastereomer, based on chiral HPLC analysis of 6a). The reaction was studied with other bases such as LDA, LiHMDS, NaHMDS, and LTMP etc. as shown in Table 1 (entries 5–8). When NaHMDS or LiHMDS was used, the reaction did not proceed (Table 1, entry 5) at all. The best result was obtained using LDA as the base and THF as the solvent where 4a was obtained with d.r. 83:17 (ee 92% for the major diastereomer) (Table 1, entry 6). When toluene was used as the solvent, only a trace amount of 4a was formed (Table 1, entry 7). However, using LTMP, 4a was obtained with high yield (80%) and selectivity (based on ee 80% for the major diastereomer of 6a) (Table 1, entry 8). In all the cases, stereoselectivity was determined only after removal of the Boc group from 4a.

Recently Kawabata et al.13a have reported enantioselective cyclization of α-amino acid derivatives at ambient temperature using powdered KOH in DMSO or DMF. Encouraged by this report, we carried out the imino-aldol reaction using KOH in DMSO or DMF at ambient temperature. The addition reaction (imino-aldol) did not proceed under this condition; instead, the corresponding acid 7 was produced by the hydrolysis of the ester group of 1a (Scheme 3).

On the basis of the above results, further studies were carried out using LDA as the base. Although the reaction proceeded smoothly with 1.2 equivalent of enolate, for obtaining better yield and selectivity the use of 2.2 equivalents of enolate was found to be the best. This optimized condition was used in all the subsequent reactions. The reaction was nearly completed within 2 h; however, for further improvement in yield and ee, the reaction was continued for 10 h. To extend the scope of this reaction, a variety of N-activated imines with electron donating as well as electron withdrawing aryl substituents were reacted with amino acid ester 1a to afford the substituted nonracemic α,β-diamino ester derivatives 4b–j (based on optical rotation) as a mixture of diastereomers in 62–81% yields (Scheme 4).

Although 1H NMR signals of imino-aldol adducts 4b–j were found to be wavy as discussed earlier (low temperature 1H NMR spectra are provided in the Supporting Information), the formation of all the compounds 4b–j were fully confirmed by 13C NMR, DEPT NMR and HRMS data. The stereoisomers of the imino-aldol products 4b–j could not be separated at this stage.

To confirm the diastereoselectivity as well as the enantiomeric excess, the imino-aldol adducts 4b–j were subjected

**Scheme 1. Addition of N-BenzyI-N-tert-butoxycarbonylphenylalanine Ethyl Ester Enolate to 2-Phenyl-N-tosyl Aldimines**

**Scheme 2. Boc Deprotection of α,β-Diamino Ester Derivatives 4a**

**Scheme 3. Addition of 1a to 2-Phenyl-N-tosyl Aldimines at Ambient Temperature**

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield 4a (%)</th>
<th>yield 6a (%)</th>
<th>ee (%)</th>
<th>d.r (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KHMDS</td>
<td>THF</td>
<td>6.0</td>
<td>55</td>
<td>89</td>
<td>4</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>KHMDS</td>
<td>THF/Toluene 4:1</td>
<td>2.0</td>
<td>71</td>
<td>94</td>
<td>16</td>
<td>58:42</td>
</tr>
<tr>
<td>3</td>
<td>KHMDS</td>
<td>THF/Toluene 1:4</td>
<td>2.5</td>
<td>70</td>
<td>92</td>
<td>26</td>
<td>64:36</td>
</tr>
<tr>
<td>4</td>
<td>KHMDS</td>
<td>Toluene</td>
<td>2.5</td>
<td>56</td>
<td>87</td>
<td>28</td>
<td>74:26</td>
</tr>
<tr>
<td>5</td>
<td>LiHMDS/NaHMDS</td>
<td>THF</td>
<td>14.0</td>
<td>Trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>LDA</td>
<td>THF</td>
<td>10.0</td>
<td>84</td>
<td>88</td>
<td>92</td>
<td>83:17</td>
</tr>
<tr>
<td>7</td>
<td>LDA</td>
<td>Toluene</td>
<td>10.0</td>
<td>Trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>LTMP</td>
<td>THF</td>
<td>2.0</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>64:36</td>
</tr>
</tbody>
</table>

*Combined yield of both the diastereomers after purification. HPLC separation was done using Chiral AD-H column (95:5 Hexane/Isopropanol as mobile phase and 1.0 mL/min flow rate). ee was determined from HPLC analysis of 6a. d.r based on crude 1H NMR analysis of 6a.
to BOC-group deprotection following the aforementioned condition to afford 6b−j as a mixture of diastereomers with 70−91% yields (Scheme 5, Table 2). Diastereoselectivity was determined by 1H NMR spectrum of the crude reaction mixture and the maximum $\text{dr}$ ($83:17$) was achieved in the cases of compounds 6a and 6c (Table 2, entries 1, 4). At this stage, the major diastereomers of the $\alpha,\beta$-diamino ester derivatives 6a−j could be separated by flash column chromatography on silica gel (Table 2). The minor diastereomers of 6b, 6d, and 6h could not be obtained in pure forms; their $\text{ees}$ were determined by chiral HPLC analysis comparing the peaks of the mixture with that of the pure major diastereomer. All of the compounds (6a−j) were fully characterized by spectral and analytical data.

The substrate scope of the reaction was studied by replacing the benzyl group of 1a with a less sterically demanding methyl group. When the ester enolate generated from the alanine derivative 1b was reacted with 2-phenyl-$N$-tosylaldimine, the corresponding addition product 4k was obtained with 72% yield. Its Boc group was removed to produce the compound 6k as a mixture of diastereomers in 79% yield (Scheme 6). In this case, lower stereocontrol was observed (major/minor = 55:45 and $\text{ee}$ 33% for the major diastereomer) probably due to the rapid racemization of the chiral enolate during the course of the reaction. This result is consistent with the work reported by Kawabata et al. where such type of chirality loss was overruled by rapid cyclization in the case of intramolecular reaction, however, in the case of intermolecular reaction lower $\text{ee}$ ($\sim 33\%$) of the product was observed.12a

To provide evidence in support of the MOC concept in imino-aldol reaction, ester enolate generated from (S)-methyl 2-[bis(tert-butoxycarbonyl) amino]-3-phenylpropanoate (1c) was treated with 2-phenyl-N-tosylaldimine to produce the corresponding addition product 4l.16 In this case, the enolate having no axial chirality along C−N axis was expected not to induce any chirality into the product (Scheme 7). Although the corresponding addition product 4l could not be separated in chiral HPLC column (Chiralcel OD-H or AD-H), the Boc deprotected derivative 6l was well separated in chiracel AD-H column and obtained as a racemate.20 This interesting result unambiguously supports that the MOC is operating in our imino-aldol reaction with substrates 1a−b.

After successful demonstration of the memory of chirality in imino-aldol reaction we intended to explore the concept in aldol reaction. Although in recent years memory of chirality concept has become a conceptually new strategy in the field of asymmetric synthesis, surprisingly, MOC based aldol reaction
remained unexplored. Stoodley and co-workers demonstrated the memory of chirality effect in intramolecular aldol cyclization of 1-(3-oxabutyryl) derivatives of L-4-oxaproline and proline isopropyl esters via the involvement of an axially chiral enolate intermediate.\textsuperscript{19a,b} Very recently Kawabata and co-workers demonstrated the application of MOC concept in asymmetric

Table 2. Imino-aldol Adducts \(6\) Generated after Boc Removal from \(4a-h\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product ((6))\textsuperscript{a}</th>
<th>Yield (6) (%)\textsuperscript{b}</th>
<th>(dr) (%)\textsuperscript{c}</th>
<th>ee (%)</th>
<th>(6a-h) major (anti) diastereomer</th>
<th>ee (%)</th>
<th>(6a-h) minor (syn) diastereomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Image] (6a)</td>
<td>88</td>
<td>83:17</td>
<td>92</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>![Image] (6b)</td>
<td>70</td>
<td>71:29</td>
<td>80</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>![Image] (6c)</td>
<td>84</td>
<td>83:17\textsuperscript{d}</td>
<td>88</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>![Image] (6d)</td>
<td>87</td>
<td>71:29</td>
<td>84</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>![Image] (6e)</td>
<td>80</td>
<td>79:21\textsuperscript{d}</td>
<td>56</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>![Image] (6f)</td>
<td>86</td>
<td>73:27</td>
<td>75</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>![Image] (6g)</td>
<td>91</td>
<td>75:25</td>
<td>96</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>![Image] (6h)</td>
<td>87</td>
<td>67:33</td>
<td>80</td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>![Image] (6i)</td>
<td>88</td>
<td>75:25</td>
<td>57</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>![Image] (6j)</td>
<td>85</td>
<td>62:38</td>
<td>60</td>
<td>33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Corresponding imino-aldol adducts (a mixture of major and minor isomers of \(6\)) obtained after 10 h. \textsuperscript{b}Combined yield of both the diastereomers after purification. \textsuperscript{c}\(dr\) based on crude \(^1\)H NMR analysis. \textsuperscript{d}Minor diastereomer could not be separated in available chiral HPLC columns.
aldol reaction followed by cyclization to form cyclic 2-oxooxazolidine derivatives in high ee starting from amino acid ester enolate and aldehyde using KHMDS as the base. To begin our study in aldol reaction, the ester enolate was generated from N-benzyl-N-tertbutoxycarbonylphenylalanine ethyl ester 1a using LDA as the base at −78 °C and was reacted with an electron withdrawing aldehyde (4-nitrobenzaldehyde) at the same temperature to afford the corresponding α-amino, β-hydroxy ester derivative 8a as a mixture of diastereomers (dr 3:2.4) in 65% yield (Scheme 8). The formation of the aldol product was confirmed by 1H NMR, 13C NMR, DEPT NMR and HRMS analysis. The diastereoselectivity of 8a was confirmed by 1H NMR of the crude reaction mixture after removal of the unreacted starting material by flash column chromatography. Although the major diastereomer could be isolated in pure form in small amount, the minor isomer could not be obtained in pure form. The ee of the minor diastereomer was found to be 68%, however, the major isomer was produced with low ee (16%). The methodology of making α-amino, β-hydroxy ester derivatives 8a–d with a variety of aldehydes to afford the corresponding α-amino, β-hydroxy ester derivatives 8a–d in 51–66% yields (Scheme 8, Table 3).

In the case of another electron withdrawing aromatic aldehyde (3-nitrobenzaldehyde), the corresponding addition product 8b was obtained in 66% yield as a mixture of diastereomers (Table 3, entries 2). Both of the isomers of 8b could be isolated in pure forms by column chromatography. The ee of the major and the minor isomers were found to be 30 and 76%, respectively. On increasing the reaction temperature to −70 °C, the diastereomeric ratio of 8b changed to 3:2. The major and the minor diastereomers of 8b were obtained with reduced ee (14 and 67%, respectively). Using electron rich aromatic aldehydes (e.g., 4-methoxybenzaldehyde and 3,4-dimethoxybenzaldehyde), the corresponding addition products (8c and 8d, respectively) were obtained with reduced yields (51–52%) (Table 3, entries 3–4) probably due to the reduced electrophility of the carbonyl carbon. All of the compounds were characterized by spectroscopic and analytical data. These results are summarized in Table 3.19d

The major and the minor diastereomers of the products 8a–d were produced with syn and anti relative stereochemistry, respectively, as determined by the NOE experiments of both the diastereomers of 8b.20

The N-Boc group of 8a (as a mixture of diastereomers) was deprotected using TFA/DCM (1:2) to give the corresponding NH-free aldol product 9 (Scheme 9). Both the isomers of compound 9 were separated by column chromatography. The major isomer was obtained with very poor ee (9%), although the minor isomer was obtained with good ee (67%) based on chiral HPLC analysis. In the same fashion, other α-amino/β-hydroxy ester derivatives 8c–d were subjected to Boc group removal step as discussed earlier but even after the Boc group deprotection the diastereomers could not be separated in column chromatography and the enantiomers remained inseparable in available chiral HPLC columns.

The formation of the nonracemic aldol products 8 suggests that memory of chirality concept is operating in the aldol reaction. Unfortunately, in most of the cases, the pure diastereomer could not be isolated by column chromatography and the ee also could not be determined. At this stage, the stereocenter in aldol reaction was further investigated using KHMDS as a base.

When ester enolate generated from 1a was generated by using KHMDS at −78 °C and reacted with benzaldehyde at the same temperature (Scheme 10), ethyl 3,4-dibenzyl-2-oxo-5-phenyloxazolidine-4-carboxylate (10a) was obtained in 55% yield. The intermediate aldolate anion, instead of giving the corresponding aldol product, underwent intramolecular cyclization with the carbamate group to produce 10a as a single diastereomer with low ee (16%). Very similar recent aldol reaction followed by cyclization has been reported by Kawabata et al.19e with excellent enantioselectivities (ee up to 94%).

This finding was generalized with a variety of aromatic aldehydes having electron donating (e.g., 3,4-dimethoxybenzaldehyde) and electron withdrawing (2-chlorobenzaldehyde, 3-nitrobenzaldehyde) substituents (Scheme 10). In the case of electron withdrawing aldehydes, compound 10 was obtained in higher yield (up to 59%) as compared to the electron donating ones. However, all of the compounds 10b–d were obtained as single diastereomers but with very poor ees (4–16%).19d Formation of 10 with poor ees from our substrate 1a using KHMDS as the base is consistent with our earlier observation in imino-aldol reaction. It is interesting to note that using LDA as the base, the substrate 1a undergoes intramolecular aldol reaction to produce the free aldol products 8, whereas ethyl 3,4-dibenzyl-5-aryl-oxooxazolidine-4-carboxylates 10 were obtained via aldol followed by intramolecular cyclization with N-Boc group when KHMDS was used as the base.

Different reactivity patterns of the enolates generated from 1a using LDA or KHMDS as the base could be explained by considering the chelating ability of the counterion Li⁺ or K⁺ as shown in Scheme 11. In the case of LDA, the counterion Li⁺ is strongly coordinating and hence the intermediate aldolate anion remained in chelated form as shown in 12a–b, whereas K⁺, being a less coordinating metal ion, makes the alkoxy anion 15 more available for further attack to carbamate to form the cyclized product 10. Possible retroaldol reaction from the aldolate anion 15 would regenerate the K-enolate 14. Probably because of faster racemization of K-enolate 14 being in
nonchelated form compared to chelated Li-enolate 11a–b, the aldolate anion intermediate 15 gets racemized easily and further cyclizes to produce 10 with poor ees.

After successful demonstration of the memory of chirality concept in imino-aldol reaction, we attempted to determine the absolute con

figuration of α,β-diamino ester derivatives. For this purpose the pure major and minor diastereomers of 6a were separately crystallized out using 9:1 CHCl3 in hexane. On the basis of X-ray crystallographic analysis, the major diastereomer of 6a was assigned to be anti having relative con

figuration (2S,3R) and that of the minor diastereomer of 6a was found to be syn with relative configuration (2S,3S). Unfortunately, in both the cases the crystals were obtained as a racemate (based on centrosymmetric point group and HPLC analysis) and the mother liquor contained the pure enantiomer. Unfortunately, the pure enantiomer of 6a (obtained from the mother liquor) in combination of various solvents could not be crystallized and hence we were unable to determine its absolute configuration. However, using our imino-aldol protocol α,β-diamino ester derivatives (e.g., 6a) could be obtained in enantiomerically pure forms.

Other α,β-diamino ester derivatives 6b, 6e, 6g and 6j after crystallization from their diastereomeric mixtures resulted the crystals of pure major diastereomers as racemates with anti relative stereochemistry (see Supporting Information). In general, the major diastereomer of α,β-diamino ester derivatives were obtained with anti geometry following our imino-aldol protocol. Recently, anti/syn selectivity of α,β-diamino ester derivatives has been nicely explained independently by Davis21 and de Kimpe et al.18c

Next, different derivatization processes were attempted with enantiopure 6a (major diastereomer). Initially, the ester moiety of 6a was reduced with lithium borohydride in tetrahydrofuran at room temperature to give the corresponding alcohol 16a without loss of enantioselectivity (Scheme 12).23 In this case, the enantiomerically pure alcohol 16a could not be crystallized from different combination of solvents.

In another attempt, when compound 4a was subjected to acid group hydrolysis using LiOH in THF or THF/MeOH or THF/MeOH/H2O or dioxane/H2O, the racemic amino acid 7 was formed via the C–C bond breaking followed by hydrolysis of the ester group (Scheme 13).

Table 3. Synthesis of α-Aminoβ-hydroxy Ester Derivatives 8a–d

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product (8a–d)</th>
<th>Yield (%)</th>
<th>Dr (syn:anti)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="8a" alt="Image" /></td>
<td>65</td>
<td>3:2 (syn:anti)</td>
</tr>
<tr>
<td>2.</td>
<td><img src="8b" alt="Image" /></td>
<td>66</td>
<td>3:1 (syn:anti)</td>
</tr>
<tr>
<td>3.</td>
<td><img src="8c" alt="Image" /></td>
<td>52</td>
<td>3:1 (syn:anti)</td>
</tr>
<tr>
<td>4.</td>
<td><img src="8d" alt="Image" /></td>
<td>51</td>
<td>4:1 (syn:anti)</td>
</tr>
</tbody>
</table>

"Dr based on 1H NMR of the crude reaction mixture after removal of the unreacted ester 1a, ee (%) for the minor and the major diastereomers of 8 based on chiral HPLC analysis. ee (%) for 8a: 68 (minor isomer), 16 (major isomer). ee (%) for 8b: 76 (minor isomer), 30 (major isomer)."
Furthermore, when enantiopure alcohol 16a was treated with various alcohol protecting groups in basic medium (TBDMSCl or TBDPSCl in imidazole or p-nitrobenzylchloride in the presence of triethylamine in dichloromethane), the reaction did not proceed. Next, the diphenyl acetate ester of enantiopure 16a was prepared using diphenylacetic acid and DCC in dichloromethane to give the corresponding coupling product, which could not be crystallized. As discussed earlier, the absolute configuration of α,β-diamino ester derivatives could not be assigned on the basis of X-ray crystallographic data of 6 or its derivatives; hence, other indirect methods were employed to determine the absolute stereochemistry of both stereogenic centers. First, the recovered starting material 1a after imino-aldol reaction (Table 1, entry 6) at −78 °C showed retention in configuration with partial racemization (based on chiral HPLC analysis). Second, the enolate generated from 1a using LDA at −78 °C was quenched with water at the same temperature where the regenerated starting material was obtained with retention in configuration along with partial racemization (based on chiral HPLC analysis, Figure 1). These experiments revealed that the stereogenic center of the starting ester (S)-1a remained unchanged during the course of the reaction. Third, the enolate of 1a was formed using LDA as the base at −78 °C and was quenched with water at 0 °C, which showed complete racemization of the starting amino acid ester (based on chiral HPLC analysis, Figure 2). This result evidenced that the enolization was completed at −78 °C. On the basis of these observations, plausible intermediates 18 and 19 were proposed where intermediate 18 was a configurationally stable carbanion stabilized by N-Boc group and intermediate 19 was a chiral enolate in which the chiral nitrogen was strongly coordinated with the lithium ion. Formation of anti isomer as the major diastereomer in imino-aldol reaction with retention of configuration was rationalized by the abstraction of proton from the bottom face of the NBenzyl-N-tert-butoxycarbonylphenylalanine ethyl ester 1a to give intermediate 18 or 19. The anionic species thus generated had a chance to react with the imines from the same face (in the intermediate 18) to produce the major diastereomer of the imino-aldol adduct 4 with retention in configuration (Figure 3). Removal of the Boc group from 4 produced 6 where the stereogenic centers remained unaltered. However, the absolute configuration at the quaternary stereogenic center (C2) becomes R as priority order at this center being changed in 4 or 6 compared to 1a (H of 1a was replaced by PhCHNHTs).
The stereochemistry of both the stereogenic centers in 4 or 6 was compared with the crystal structures of 6 and the absolute stereochemistry was assigned.

From the above discussion it is evident that absolute configuration of quaternary stereogenic center in the imino aldol product 4 is R. The X-ray crystallographic analysis revealed that the relative configuration of the major diastereomer of 6a was (2R,3S) and hence the absolute configuration of its tertiary stereocenter is S. Thus, the absolute configuration of the major diastereomer of the addition product 4 is (2R,3S).

The stereochemical assignment of the product 6 was further supported by computational studies taking 6a as an example. For this purpose all the possible structures of the enolate 19 (obtained from the starting material 1a) with different geometry of the double bond (E and Z) and the orientation of the protecting groups (Boc and benzy) attached with nitrogen were modeled and optimized using Gaussian 03 program. The Z-enolate was found to be more stable in comparison with E-enolate. In the presence of the counter-cation (Li+) in THF solvent, the possible geometries of the enolate 19 with different orientation of the protecting groups attached with nitrogen were also modeled and optimized, and we found that enolate 19 Z-1 is more stable in comparison to the enolate 19 Z-2 by 8.08 kcal mol$^{-1}$.

Next, the imino aldol strategy has been utilized for the enantioselective synthesis of substituted aziridines. The ester group of 6a was reduced to the corresponding alcohol 16a as mentioned earlier. 16a on cyclization in the presence of mesyl chloride and triethyl amine produced the substituted aziridine 20a in good yield with high enantioselectivity ($ee$ 92%) (Scheme 14). This strategy was successful in the case of 6d as well and the reaction went smoothly to afford the corresponding aziridine 20b in 71% yield with $80\% ee$ (Scheme 14). 20a–b were characterized by $^1$H NMR, $^{13}$C NMR, IR and mass spectral analysis. Following our methodology, aziridines 20a–b could be synthesized in almost enantiopure form with contiguous quaternary and tertiary stereogenic centers.

**CONCLUSION**

The memory of chirality concept has been successfully demonstrated in imino-aldol and aldol reactions. Using KHMDS as the base imino-aldol reaction produced $\alpha\beta$-diamino ester derivatives with poor $ee$ whereas in aldol reaction 2-oxazolidinone derivatives were obtained as a single diastereomer with low $ee$. Interestingly, when LDA was used as a base, the imino-aldol adduct was obtained in good to excellent yield with moderate to high $ee$ (up to 96%). Enantiopure $\alpha\beta$-diamino derivatives could be obtained using our imino-aldol protocol. Similar results were observed in the case of aldol reaction where $\alpha$-amino$\beta$-hydroxyl ester derivatives were formed in moderate yield with up to 76% $ee$ using LDA as the base. Thus, utilizing MOC concept higher stereocentral was achieved from our substrate when LDA was used as the base. The absolute configuration of the major isomer of the imino-aldol product was assigned to be (2R,3S). This methodology was further extended for the asymmetric synthesis of substituted aziridines.

### EXPERIMENTAL SECTION

**General Procedures.** Unless otherwise noted, all reactions were carried out in oven-dried glassware under nitrogen atmosphere using anhydrous solvents. Wherever appropriate, all reagents were purified prior to use following Vogel’s or Perrin and Armarego guidelines.

$^1$H NMR spectra were recorded on 400 or 500 MHz in CDCl$_3$ as the solvent and TMS as an internal standard. $^{13}$C NMR spectra were recorded on 100 or 125 MHz. Melting points were measured using hot stage apparatus and were uncorrected. Infrared spectra were recorded in chloromethane for liquid compounds and KBr for solid compounds. HRMS were obtained using (ESI) mass spectrometer (TOF). Optical rotations were measured using a 2.0 mL cell with a 1.0 dm path length and reported as $[\alpha]_D$ ($c$ in g per 100 mL solvent) at 25 $^\circ$C. Enantiomeric excess ($ee$) was determined using chiralcel OD-H, AD-H or cellulose-2 analytical column (detection at 254 nm). Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F$^{254}$ precoated plates, (0.25 mm thickness). Visualization was performed using UV lamp or I$_2$ stain. Silica gel 230–400 mesh size was used for flash column chromatography using the combination of ethyl acetate and petroleum ether as eluent. Relative stereochemistry of the major diastereomer was assigned on the basis of X-ray crystallography.

All the N-sulfonylamidines were prepared in the laboratory for the corresponding sulfonamide and aldehyde in the presence of Lewis acid catalyst following a reported procedure.

**General Procedure for the Synthesis of N-Benzylated Amino Acid Ester**

To a solution of amino acid ester hydrochloride (20.0 mmol) in MeOH (10 mL), were added triethylamine (20.0 mmol) and benzenesulfonyl chloride (50.0 mmol). The reaction mixture was stirred at room temperature for 1.5 h, cooled to 0 $^\circ$C and NaHCO$_3$ (40.0 mmol) was added in portions. After stirring at room temperature for additional 2 h, the solvent was evaporated to dryness and the residue was extracted with ethyl acetate (3 × 50.0 mL) and washed with H$_2$O and brine. The organic layer was dried over Na$_2$SO$_4$ and the solvent was evaporated. The residue was purified by flash column chromatography on silica gel (230–400 mesh) using 4% ethyl acetate in petroleum ether as eluent.

General procedure described above was followed to obtain (S)-Ethyl 2-(N-benzylamino)-3-phenylpropanoate as a colorless liquid in 92% ($5.2$ g) yield; IR $\nu_{max}$ (CH$_2$Cl$_2$, cm$^{-1}$): 3323, 3062, 3028, 2990, 2929, 2851, 2713, 1603, 1494, 1454, 1372, 1337, 1185, 1130, 1027; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 1.09 ($t$, $J$ = 7.1 Hz, 3H), 2.92 ($d$, $J$ = 6.6 Hz, 2H), 3.46–3.49 (m, 1H), 3.61 ($d$, $J$ = 13.2 Hz, 1H), 3.76 ($d$, $J$ = 13.2 Hz, 1H), 4.02 ($q$, $J$ = 7.1 Hz, 2H), 7.17–7.30 (m, 10H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 13.9, 39.4, 53.1, 60.1, 61.7, 126.2, 126.6, 127.9, 128.0, 129.0, 137.1, 139.4, 141.5, 153.2, 157.9, 192.0.

General procedure described above was followed to obtain (S)-Methyl 2-(N-benzylamino)-3-phenylpropanoate as a colorless liquid in 87% ($3.36$ g) yield; IR $\nu_{max}$ (CH$_2$Cl$_2$, cm$^{-1}$): 3324, 3086, 3063, 3028, 2977, 2950, 2850, 1736, 1603, 1494, 1454, 1374, 1334, 1200, 1152, 1065, 1044, 1026; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 1.30 ($d$, $J$ = 7.1 Hz, 3H), 3.75 ($q$, $J$ = 7.1 Hz, 1H), 3.64 ($d$, $J$ = 12.4 Hz, 1H), 3.71 ($s$, 3H), 3.77 ($d$, $J$ = 12.9 Hz, 1H), 4.70 ($s$, 1H), 7.21–7.35 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 19.0, 52.0, 55.9, 65.3, 127.1, 128.2, 128.4, 139.7, 176.2.
**General Procedure for the Synthesis of (1a-b).** To a solution of N-benzylated amino acid ester (7.06 mmol) in dry dichloromethane (15.0 mL) were added di-tert-butylperoxide (8.75 mmol) and triethylamine (7.9 mmol) and the mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with 0.5 M aqueous HCl and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extract was washed with water and dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography over silica gel (230–400 mesh) using 4% ethyl acetate in petroleum ether as eluent to provide 1a–b.

**(S)-Ethyl 2-[(N-Benzyl)-(N-t-butoxycarbonyl)amino]-3-phenylpropanoate (1a).** General procedure described above was followed to obtain 1a as a colorless liquid in 75% (2.03 g) yield as a mixture of two conformers major M and minor m in a ∼5:3 ratio; [α]23 = +910 (c 1.30, CHCl₃); IR ν max (CH₂Cl₂ cm⁻¹): 3087, 3063, 3029, 2977, 2932, 1740, 1698, 1494, 1453, 1425, 1392, 1366, 1250, 1164, 1079, 1048, 1030, 982; For mixture of rotamers: 1H NMR (500 MHz, CDCl₃): δ (ppm) 1.17 (6H, M+m), 1.40 (6H, M), 1.50 (6H, M), 3.06–3.13 (m, H, M), 3.17–3.22 (m, H, M), 3.30–3.50 (m, J = 5.50 Hz, H, M), 3.32 (J = 5.50 Hz, H, M), 3.78 (J = 15.3 Hz, H, M), 3.88–3.90 (m, H, M), 3.98–4.08 (m, M, 2H, M), 4.21–4.27 (m, H, M), 4.40 (d, J = 15.58 Hz, H, M), 4.62 (d, J = 15.3 Hz, H, M), 7.02–7.14 (m, 10H, M), 7.21–7.28 (m, 10H, M); 13C NMR (125 MHz, CDCl₃): δ (ppm) 14.1 (m, M), 28.4 (m, M), 35.7 (m, M), 36.6 (m, M), 51.9 (m, M), 61.2 (m, M), 61.3 (m, M), 80.5 (m, M), 126.5 (m, M), 127.1 (m, M), 127.4 (m, M), 127.8 (m, M), 128.2 (m, M), 128.3 (m, M), 128.5 (m, M), 128.7 (m, M), 129.4 (M, M), 137.3 (M, M), 138.1 (m, M), 155.2 (M, M), 171.0 (M, M), 171.1 (m, M); HRMS (ESI) m/z: Calcd. for C₂₅H₂₃N₃O₃M+Na+: 406.1994, Found: 406.1994.

**(S)-Methyl 2-[(N-Benzyl)-(N-t-butoxycarbonyl)amino]-3-phenylpropanoate (1b).** General procedure described above was followed to obtain 1b as a viscous liquid in 60% (1.24 g) yield. [α]23 = +910 (c 1.30, CHCl₃); IR ν max (KBr, cm⁻¹): 3302, 2978, 2930, 1743, 1671, 1529, 1544, 1391, 1349, 1165, 1089; 13C NMR for mixture of diastereomers (100 MHz, CDCl₃): δ (ppm) 13.6, 27.9, 40. 1, 49, 61, 64, 75.0, 82.1, 123.3, 125.5, 126.0, 126.4, 127.6, 127.9, 128.1, 128.2, 130.6, 130.9, 134.0, 139.2, 1468, 149.1, 157.8, 169.9; HRMS (ESI) m/z: Calcd. for C₂₃H₂₁N₂O₃M+(Na+Na): 69.26285, Found: 69.2550.

**Ethyl 2-Benzyl-2-[(N-benzyl)-(N-t-butoxycarbonyl)amino]-3-(4-nitrophenylsulfonamido)-3-phenylpropanoate (4a).** General procedure described above was followed to afford 4a as a yellow solid in 80% (0.21 g) yield. Eluent: EtOAc/petroleum ether 10/90; Rf 0.37 (ethyl acetate/petroleum ether 15/85); [α]23 = +90.0 (c 0.30, CHCl₃); IR ν max (KBr, cm⁻¹): 3302, 2978, 2930, 1743, 1671, 1529, 1544, 1391, 1349, 1165, 1089; 13C NMR for mixture of diastereomers (100 MHz, CDCl₃): δ (ppm) 13.6, 27.9, 40. 1, 49, 61, 64, 75.0, 82.1, 123.3, 125.5, 126.0, 126.4, 127.6, 127.9, 128.1, 128.2, 130.6, 130.9, 134.0, 139.2, 1468, 149.1, 157.8, 169.9; HRMS (ESI) m/z: Calcd. for C₂₃H₂₁N₂O₃M+(Na+Na): 692.6285, Found: 692.2350.

**Ethyl 2-benzyl-2-[(N-benzyl)-(N-t-butoxycarbonyl)amino]-3-(3-bromophenylsulfonylamido)-3-phenylpropanoate (4d).** General procedure described above was followed to afford 4d as a white solid in 68% (0.21 g) yield. Eluent: EtOAc/petroleum ether 10/90; Rf 0.45 (ethyl acetate/petroleum ether 10/90, 13C NMR for mixture of diastereomers (100 MHz, CDCl₃): δ (ppm) 13.4, 21.3, 27.9, 29.6, 37.1, 40.6, 49.5, 61.2, 61.4, 61.9, 71.0, 80.9, 81.1, 125.5, 125.8, 126.2, 127.0, 127.2, 127.8, 128.6, 128.0, 128.1, 128.5,128.7, 128.8, 129.4, 130.9, 131.2, 134.6, 135.7, 136.8, 138.1, 139.6, 141.9, 142.3, 156.1, 157.1, 169.5; HRMS (ESI) m/z: Calcd. for C₂₄H₂₂N₂O₃S(M+Na+Na): 643.2842, Found: 643.2834.

**Ethyl 2-Benzyl-2-[(N-benzyl)-(N-t-butoxycarbonyl)amino]-3-phenyl-3-sulfonylamido-propanoate (4b).** General procedure described above was followed to afford 4b as a white solid in 62% (0.15 g) yield; Eluent: EtOAc/petroleum ether 10/90; Rf 0.32 (ethyl acetate/petroleum ether 15/85); Optical rotation: [α]23 = +3.70 (c 0.415, CHCl₃); IR ν max (KBr, cm⁻¹): 3380, 2976, 2926, 1739, 1697, 1451, 1388, 1330, 1253, 1160, 1090, 1021; 13C NMR for mixture of diastereomers (100 MHz, CDCl₃): δ (ppm) 13.4, 27.9, 37.2, 40.5, 49.5, 61.2, 61.4, 61.9, 71.0, 80.9, 81.5, 125.5, 125.7, 126.2, 126.7, 127.3, 127.8, 129.0, 129.4, 129.8, 130.7, 131.1, 131.4, 131.6, 134.5, 135.6, 136.6, 139.5, 139.8, 141.2, 156.0, 157.2, 169.4; HRMS (ESI) m/z: Calcd. for C₂₄H₂₂N₂O₃S(M+H): 629.2685, Found: 629.2887.
Ethyl 2-[(N-Benzyl)-(N-t-butoxycarbonyl)amino]-3-(4-chlorophenyl)-3-(4-methylsulfonfonyl)propanoate (6b). General procedure described above was followed to afford 6a (major) and 6a (minor) as a white solid in 88% (0.0048 g) overall yield (combined yield of both the diastereomers). It was obtained as a mixture of diastereomers with δr 83:17 (based on 1H NMR analysis of crude reaction mixture) where the diastereomers were separated through flash column chromatography (eluent: EtOAc/petroleum ether 10/90).

For the Major Diastereomer 6a. Rf 0.45 (ethyl acetate/petroleum ether: 20/80); mp: 158–160 °C; Optical rotation: [α]_D^25 = +10.25 ((c 0.335, CHCl₃) for a 92% ee sample; Optical purity was determined by chiral HPLC analysis (Chiral AD-H column) using 95/5 hexane/isopropanol, flow rate = 1.0 mL/min, Tₚ 1: 72.6 min (major), Tₚ 2: 97.3 min (minor); IR νmax (KBr, cm⁻¹): 3347, 3296, 2925, 2854, 2354, 1732, 1600, 1454, 1263, 1161, 1091, 1019; 1H NMR (400 MHz, CDCl₃); δ (ppm) 1.08 (t, J = 7.2 Hz, 3H), 2.25 (s, 3H), 3.04 (d, J = 14.8 Hz, 1H), 3.51 (d, J = 12.4 Hz, 1H), 3.71 (j, J = 7.7 Hz, 1H), 6.87–6.98 (m, 2H), 7.08–7.23 (m, 13H), 7.31 (j, J = 8.0 Hz, 2H); 13C NMR (100 MHz, CDCl₃); δ (ppm) 13.7, 21.2, 38.7, 46.9, 61.6, 61.7, 68.8, 68.9, 126.8, 127.0, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 128.9, 129.8, 130.9, 131.0, 131.3, 131.4, 137.8, 138.4, 139.7, 141.9, 142.2, 150.5, 151.2, 155.6, 168.3, 169.0; HRMS (ESI) m/z Calcld. for C₃₇H₄₂N₃O₈S (M⁺ + H⁺): 673.2394, Found: 673.2397.

Ethyl 2-(N-Benzyl)-(N-t-butoxycarbonyl)amino]-3-(2-furanyl)-3-(4-methylsulfonfonyl)propanoate (4a). General procedure described above was followed to afford 4i as a white solid in 70% (0.037 g) overall yield (combined yield of both the diastereomers). 1H NMR (400 MHz, CDCl₃): δ (ppm) 1.03 (t, J = 7.2 Hz, 3H), 2.20 (s, 3H), 3.04 (d, J = 14.8 Hz, 1H), 3.35 (d, J = 14.8 Hz, 1H), 3.51 (d, J = 12.4 Hz, 1H), 3.66 (d, J = 12.4 Hz, 1H), 3.93 (q, J = 7.2 Hz, 2H), 4.83 (d, J = 6.6 Hz, 1H), 6.2 (brs, 1H), 6.87–7.06 (m, 4H), 7.08–7.23 (m, 11H), 7.31 (j, J = 8.0 Hz, 2H); 13C NMR (100 MHz, CDCl₃); δ (ppm) 13.4, 21.1, 27.7, 28.1, 38.6, 40.5, 54.7, 61.9, 61.2, 71.0, 81.6, 81.9, 122.4, 125.0, 125.5, 126.7, 127.6, 128.0, 128.7, 128.9, 129.0, 130.7, 131.3, 131.4, 137.8, 138.4, 139.7, 141.9, 142.2, 150.5, 151.2, 155.6, 168.3, 169.0; HRMS (ESI) m/z Calcld. for C₃₂H₃₄N₂O₄S (M⁺): 543.2329, Found: 543.2329.

For the Minor Diastereomer 6a. Rf 0.44 (ethyl acetate/petroleum ether: 20/80); mp: 118–120 °C; Optical rotation: [α]_D^25 = −10.77 ((c 0.65, CHCl₃) for a 80% ee sample; Optical purity was determined by chiral HPLC analysis (Chiral AD-H column) using 95/5 hexane/isopropanol, flow rate = 1.0 mL/min, Tₚ 1: 35.1 min (major), Tₚ 2: 43.2 min (minor); IR νmax (KBr, cm⁻¹): 3347, 3296, 2925, 2854, 2354, 1730, 1661, 1600, 1454, 1264, 1161, 1090, 1019; 1H NMR (500 MHz, CDCl₃); δ (ppm) 1.08 (t, J = 7.7 Hz, 3H), 2.25 (s, 3H), 3.04 (d, J = 15.2 Hz, 1H), 3.34 (d, J = 15.2 Hz, 1H), 3.73 (j, J = 11.8 Hz, 1H), 3.81 (d, J = 11.8 Hz, 1H), 7.71 (m, 4H), 7.74 (m, 4H), 7.48 (d, J = 7.7 Hz, 1H), 6.10 (d, J = 7.7 Hz, 1H), 6.85–6.88 (m, 2H), 6.98–7.09 (m, 4H), 7.22–7.33 (m, 11H), 7.70 (d, J = 8.3 Hz, 2H); 13C NMR (125 MHz, CDCl₃); δ (ppm) 13.9, 21.5, 38.7, 48.9, 61.7, 62.4, 71.1, 72.7, 127.5, 127.8, 128.2, 128.3, 128.8, 128.9, 129.8, 130.9, 131.3, 131.4, 134.5, 135.4, 137.9, 139.3, 139.7, 142.5, 142.8, 156.7, 169.5; HRMS (ESI) m/z Calcld. for C₃₂H₃₄N₂O₄S (M⁺ + Na): 699.2939, Found: 699.2939.
Ethyl 2-Benzyl-2-(N-benzylamino)-3-(4-nitrophenylsulfonamido)-3-phenylpropanoate 6c. General procedure described above was followed to afford 6c (major) and 6f (minor) as a pale yellow solid in 84% (0.052 g) overall yield (combined yield of both the diastereomers). It was obtained as a mixture of diastereomers with dr 73:27 (based on 1H NMR analysis of crude reaction mixture) where the major diastereomer 6c was separated through flash column chromatography (eluent: EtOAc/petroleum ether 10:90). Its optical rotation was [α]D20 = +43.0° (c 0.66, CHCl3) for a 4% ee sample; Optical purity was determined by chiral HPLC analysis (Ciraciel AD-H column) using 95/5 hexane/isopropanol, flow rate = 0.8 mL/min, T 1: 21.4 min (major), T 2: 26.5 min (minor).

Ethyl 2-Benzyl-2-(N-benzylamino)-3-(2-chlorophenyl)-3-(4-methylphenylsulfonamidopropionate 6e. General procedure described above was followed to afford 6e (major) and 6f (minor) as a white solid in 79% (0.051 g) overall yield (combined yield of both the diastereomers). It was obtained as a mixture of diastereomers with dr 71:29 (based on 1H NMR analysis of crude reaction mixture) where the major diastereomer was separated through flash column chromatography (eluent: EtOAc/petroleum ether 10:90). Its optical rotation was [α]D20 = +25.0° (c 0.25, CHCl3) for a 10% ee sample; Optical purity was determined by chiral HPLC analysis (Ciraciel AD-H column) using 95/5 hexane/isopropanol, flow rate = 0.8 mL/min, T 1: 21.4 min (major), T 2: 26.5 min (minor).
Ethyl 2-Benzyl-2-(N-benzylamino)-3-(2-furanyl)-3-(4-methylphenylsulfonamidoo)propanoate 6h (Table 2, entry 8). General procedure described above was followed to afford 6h (0.046 g) as a white solid in 87% overall yield (combined yield of both the diastereomers). The compound was isolated as a mixture of diastereomers with $\delta$ 67.33 (based on $^1$H NMR analysis of the crude reaction mixture) where a little amount of pure major diastereomer was isolated through flash column chromatography (eluent: EtOAc/petroleum ether 10/90) which was injected in chiral HPLC condition (see below) to identify pair of peaks for each diastereomer; $R_1$ 0.30 (ethyl acetate/petroleum ether: 15/85).

For the Major Diastereomer $6g$.

The Journal of Organic Chemistry

The Journal of Organic Chemistry

For the Minor Diastereomer 6j.

ee $78\%$; Optical purity was determined by chiral HPLC analysis (Lux 5u Cellulose-2 column) using 95/5 hexane/isopropanol, flow rate = 1.0 mL/min, $T_R$ 1: 113.8 min (major), $T_R$ 2: 78.2 min (minor).
reaction (monitored with TLC), it was quenched with saturated aqueous ammonium chloride solution and extracted with 2 × 5.0 mL of ethyl acetate. The combined organic extract was dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure.

The residue was purified by flash column chromatography on a silica gel using ethyl acetate in petroleum ether as the eluent to afford 7 as a colorless liquid in 66% (0.2 g) yield as a 1:1 mixture of rotamers (R and r); IR ν_{max} (CHCl₃, cm⁻¹): 2977, 2928, 2853, 1744, 1699, 1454, 1367, 1250, 1161; For mixture of rotamers: 1H NMR (500 MHz, CDCl₃): δ (ppm) 1.43 (s, 9H, R), 1.51 (s, 9H, r), 3.08–3.12 (m, 1H, r), 3.27–3.28 (m, 3H, 2R+r), 3.48 (d, J = 15.0 Hz, 1H, R), 3.71 (d, J = 16.0 Hz, 1H, r), 3.88–3.89 (m, 1H, R), 4.13–4.15 (m, 1H, r), 4.37 (d, J = 16.0 Hz, 1H, R), 4.61 (d, J = 15.0 Hz, 1H, R), 7.04–7.09 (m, 7H, r), 7.21–7.28 (m, 13H, 10R+3r); 13C NMR (125 MHz, CDCl₃): δ (ppm) 28.1, 36.8, 48.0, 52.1, 52.9, 61.0, 62.6, 81.4, 81.5S, 126.8, 127.3, 127.5, 127.8, 128.4, 128.7, 128.8, 129.4, 136.9, 137.4, 137.7, 138.0, 155.2, 156.1, 175.6, 176.9; HRMS (ES⁻) m/z: Calcd. for C₁₂H₁₀NaNO₄ (M⁻ + Na): 378.1681, Found: 378.1654.

**Attemed Hydrolysis of Compound 4a.** To a suspension of LiOH (0.848 mmol) in 2 mL dry THF (MeOH or THF/MeOH or H₂O or dioxane/H₂O etc.) was added a solution of N-benzyl-N-tert-butoxycarbonyl amino acid esters 4a (0.884 mmol) in 1.0 mL dry THF at 0 °C. The reaction was monitored by TLC. The reaction was acidified with 2(N) HCl up to pH 2 and was extracted with 3 × 5.0 mL of diethyl ether. The combined organic extract was washed with water, dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The residue was purified on a silica gel column by flash column chromatography using ethyl acetate in petroleum ether as the eluent to afford 7 as a colorless liquid in 66% (0.2 g) yield. Spectrum was same as above.

**General Procedure for the Aldol Reaction of N-Benzyl-N-tert-butoxycarbonyl Phenylalanine Ethyl Ester 1a with a Variety of Aldehydes in the Presence of LDA.** To a solution of disopropylamine (0.10 mL, 0.75 mmol) in 2 mL dry THF was added n-ButLi (1.6 M in hexane, 0.50 mL, 0.75 mmol) at 0 °C and stirred for 20 min. It was cooled to −78 °C and a solution of N-benzyl-N-tert-butoxycarbonyl phenylalanine ethyl ester 1a (0.75 mmol) in 1.0 mL dry THF was added to it and allowed to stir for 1 h. Aldehydes (0.50 mmol) dissolved in 1.0 mL dry THF was slowly added into the reaction mixture and stirring was continued at the same temperature for 10 h. The reaction (monitored with TLC) was quenched with saturated aqueous ammonium chloride solution and extracted with 5.0 mL of ethyl acetate in two portions. The combined organic extract was dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on a silica gel column using ethyl acetate in petroleum ether as the eluent to afford 8a–d.

**Ethyl 2-Benzyl-2-(benzyl(tert-butoxy carbonyl)amino)-3-hydroxy-3-(4-nitrophenyl)propanoate 8a.** General procedure described above was followed to afford 8a as a white solid in 65% (0.17 g) overall yield. It was obtained as a mixture of diastereomers with dr 3:1 (based on 1H NMR analysis of crude reaction mixture) where little amount of pure major diastereomer was separated by flash column chromatography (eluent: EtOAc/petroleum ether 10:90; Rf 0.26 (ethyl acetate/petroleum ether: 15/85); IR ν_{max} (CHCl₃, cm⁻¹): 3489, 2977, 2928, 1742, 1692, 1513, 1453, 1386, 1366, 1252, 1159; For the major diastereomer: 1H NMR (500 MHz, CDCl₃): δ (ppm) 1.25 (brs, 12H), 2.63 (d, J = 13.2 Hz, 1H), 3.24 (d, J = 18.3 Hz, 1H), 3.42 (d, J = 13.2 Hz, 1H), 3.79 (s, 3H), 3.79–3.83 (m, 1H), 4.06–4.15 (m, 2H), 5.63 (s, 1H), 6.69 (d, J = 8.0 Hz, 2H), 7.05–7.14 (m, 7H), 7.17–7.23 (m, 4H), 7.36 (d, J = 8.0 Hz, 2H); 13C NMR (125 MHz, CDCl₃): δ (ppm) 13.9, 28.3, 35.8, 48.7, 55.4, 61.1, 70.0, 73.8, 78.0, 82.1, 113.6, 125.9, 126.4, 126.9, 127.7, 128.1, 129.3, 131.3, 131.4, 136.2, 140.7, 155.9, 172.0; HRMS (ES⁻) m/z: Calcd. for C₁₆H₁₅NO₂ (M⁻ + Na): 252.0999, Found: 252.0995.

**Ethyl 2-Benzyl-2-(benzyl(tert-butoxy carbonyl)amino)-3-hydroxy-3-(3,4-dimethoxyphenyl)propanoate 8d.** General procedure described above was followed to afford 8d as a thick liquid in 51% (0.14 g) overall yield. It was obtained as a inseparable mixture of diastereomers with dr 4:1 (based on 1H NMR analysis of crude reaction mixture) where little amount of pure major diastereomer was separated by flash column chromatography (eluent: EtOAc/petroleum ether 10:90; Rf 0.29 (ethyl acetate/petroleum ether: 30/70); IR ν_{max} (CHCl₃, cm⁻¹): 3456, 2926, 2854, 1741, 1693, 1516, 1453, 1388, 1367, 1262, 1157, 1029. For the major diastereomer: 1H NMR (400 MHz, CDCl₃): δ (ppm) 1.25 (brs, 12H), 2.65 (d, J = 13.4 Hz, 1H), 3.26 (d, J = 18.3 Hz, 1H), 3.45 (d, J = 13.4 Hz, 1H), 3.80–3.84 (m, 1H), 3.89 (brs, 6H), 4.09–4.13 (m, 4H), 4.16 (d, J = 13.4 Hz, 1H), 5.63 (s, 1H), 7.04–7.13 (m, 6H), 7.18–7.22 (m, 4H); 13C NMR (100 MHz, CDCl₃): δ (ppm) 13.7, 28.1, 35.7, 48.7, 55.9, 56.0, 60.9, 70.2, 73.8, 80.9, 110.9, 111.5, 120.6, 125.8, 126.3, 126.8, 127.0, 130.8, 131.3, 131.6, 136.1, 140.0, 148.6, 148.8, 155.7, 173.6; HRMS (ES⁻) m/z: Calcd. for C₁₆H₁₅NO₂ (M⁻ + H): 250.2804, Found: 250.2803.
in dry dichloromethane (1.0 mL) was added trifluoroacetic acid (0.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. It was neutralized with aq. saturated NaHCO₃ solution and the aqueous layer was extracted with CH₂Cl₂ (3 × 5.0 mL). The combined organic extract was washed with brine and dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (100–200 mesh) using ethyl acetate in petroleum ether (20:80) as eluent to provide 9 as a pale yellow paste in 85% (0.04 g) yield. Optical purity was determined by chiral HPLC analysis (Cellulose-2 column). 95/5 hexane/isopropanol, flow rate = 1.0 mL/min, Tₚk = 35.5 min (major), Tₚk = 2: 42.5 min (minor); IR νmax (KBr, cm⁻¹): 3065, 3032, 2925, 2853, 1765, 1719, 1533, 1451, 1390, 1353, 1276, 1202, 1095, 1048; 1H NMR (500 MHz, CDCl₃): δ (ppm) 0.77 (t, J = 7.2 Hz, 3H), 3.32–3.29 (m, 1H), 4.11–4.05 (m, 3H), 5.45 (AB quartet, J_gem = 15.2 Hz, 2H), 5.42 (s, 1H), 7.18–7.20 (m, 2H), 7.27–7.35 (m, 6H), 7.42–7.49 (m, 4H), 8.05 (s, 1H), 8.14 (dd, J = 7.9, 2.1 Hz, 1H); 13C NMR (125 MHz, CDCl₃): δ (ppm) 13.6, 37.3, 47.8, 55.9, 56.0, 61.9, 73.5, 71.9, 109.1, 110.7, 118.8, 126.6, 127.8, 127.9, 128.6.

Ethyl 3,4-Dibenzy1-5-(2-chlorophenyl)-2-oxooxazolidine-4-carboxylate 10c. General procedure described above was followed when 1a reacted with 2-chlorobenzaldehyde to afford 10c as a white solid in 49% (0.11 g) yield as a single diastereomer (based on 1H NMR analysis of crude reaction mixture). The compound was purified through flash column chromatography (eluents: EtOAc/petroleum ether 20:80). Rf 0.20 (ethyl acetate/petroleum ether: 20:80); 4% ee; Optical purity was determined by chiral HPLC analysis (Chiral OD-H column) using 95/5 hexane/isopropanol, flow rate = 1.0 mL/min, Tₚk = 18.3 min (minor), Tₚk = 2: 27.4 min (major); IR νmax (KBr, cm⁻¹): 3065, 3032, 2924, 2854, 1764, 1749, 1444, 1395, 1355, 1279, 1208, 1024; 1H NMR (500 MHz, CDCl₃): δ (ppm) 7.5 (t, J = 7.2 Hz, 3H), 3.24 (dq, J = 7.2, 7.3 Hz, 1H), 3.44 (dq, J = 6.9, 7.3 Hz, 1H, 1H), 3.61 (AB quartet, J_gem = 15.5 Hz, 2H), 4.50 (AB quartet, J_gem = 15.5 Hz, 2H), 3.56 (s, 1H), 7.14–7.15 (m, 2H), 7.21–7.25 (m, 2H), 7.26–7.36 (m, 8H), 7.40–7.42 (m, 2H); 13C NMR (125 MHz, CDCl₃): δ (ppm) 13.1, 38.9, 47.6, 61.9, 73.2, 76.6, 126.7, 127.7, 127.9, 128.5, 128.8, 128.9, 129.4, 130.2, 130.3, 132.5, 133.8, 133.9, 135.6, 137.9, 168.8; HRMS (ESI⁺) m/z: Calculd for C₁₅H₁₄NO₃ (M⁺ + H): 249.1472, Found: 249.1474.

Ethyl 3,4-Dibenzy1-2-oxo-5-(4-methoxyphenyl)-oxazolidine-4-carboxylate 10d. General procedure described above was followed when 1a reacted with 4-methoxybenzaldehyde to afford 10d as a white solid in 49% (0.11 g) yield as a single diastereomer (based on 1H NMR analysis of crude reaction mixture). The compound was purified through flash column chromatography (eluents: EtOAc/petroleum ether 20:80). Rf 0.20 (ethyl acetate/petroleum ether: 20:80); 4% ee; Optical purity was determined by chiral HPLC analysis (Chiral OD-H column) using 95/5 hexane/isopropanol, flow rate = 1.0 mL/min, Tₚk = 18.3 min (minor), Tₚk = 2: 27.4 min (major); IR νmax (KBr, cm⁻¹): 3065, 3032, 2924, 2854, 1764, 1749, 1444, 1395, 1355, 1279, 1208, 1024; 1H NMR (500 MHz, CDCl₃): δ (ppm) 7.5 (t, J = 7.2 Hz, 3H), 3.24 (dq, J = 7.2, 7.3 Hz, 1H), 3.44 (dq, J = 6.9, 7.3 Hz, 1H, 1H), 3.61 (AB quartet, J_gem = 15.5 Hz, 2H), 4.50 (AB quartet, J_gem = 15.5 Hz, 2H), 3.56 (s, 1H), 7.14–7.15 (m, 2H), 7.21–7.25 (m, 2H), 7.26–7.36 (m, 8H), 7.40–7.42 (m, 2H); 13C NMR (125 MHz, CDCl₃): δ (ppm) 13.1, 38.9, 47.6, 61.9, 73.2, 76.6, 126.7, 127.7, 127.9, 128.5, 128.8, 128.9, 129.4, 130.2, 130.3, 132.5, 133.8, 133.9, 135.6, 137.9, 168.8; HRMS (ESI⁺) m/z: Calculd for C₁₅H₁₄O₃N (M⁺ + H): 249.1472, Found: 249.1474.
129.0, 129.1, 130.7, 134.1, 136.5, 148.9, 149.4, 158.5, 169.4; HRMS (ES+) m/z: Calcd. for C30H29BrN2O2S (M+ + H): 571.1211, Found: 571.1210.

**ASSOCIATED CONTENT**

**S Supporting Information**

Experimental procedures, characterization, X-ray crystallographic data of some of the compounds, computational results and related data, copies of 1H NMR, 13C NMR spectra of all new compounds and HPLC chromatograms for optical determination. This material is available free of charge via the Internet at http://pubs.acs.org.

**AUTHOR INFORMATION**

**Corresponding Author**

E-mail: mkghoria@iitk.ac.in.

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

M.K.G. is grateful to IIT-Kanpur and DST, India. K.G., A.K.Y., and M.S. thank CSIR, India and S.H. thanks UGC, India for research fellowships.

**REFERENCES**


(10) Zhao, H.; Hsu, D. C.; Carlier, P. R. Synthesis 2005, 1, 1.


(20) For details see Supporting Information.


(23) Racemization is observed in 16a was reported. Viso, A.; de la Pradilla, R. F.; García, A.; Guerrero-Strachan, C.; Marta, A.; Tortosa, M.; Flores, A.; Martín-Martínez, P.; Fonseca, I.; André, I.; Rodriguez, A. Chem.—Eur. J. 2003, 9, 2867.


(25) The compound 21 could not be crystallized.


