CHAPTER-III

SECTION- A: LiClO₄ – catalyzed highly diastereoselective synthesis of Cis-aziridine carboxylates.
INTRODUCTION

The scientific community is constantly involved in the development of efficient methodologies, novel reactions and processes that will lead to the synthesis of desired target molecules and their derivatives with ease. During the last decades much effort has been devoted to the development of efficient catalysts for the synthesis, and enantioselective synthesis, of organic building blocks such as epoxides and aziridines. As an ongoing research program, our group has constantly involved in development of new methodologies on synthesis of aziridine derivatives. The following two sections explore the detailed study of investigations.

Aziridines are useful building blocks for the synthesis of many biologically active compounds such as amino alcohols, unnatural amino acids and nitrogenous heterocycles. Aziridines are carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo regioselective ring opening leads to many biologically active compounds such as α, β-unsaturated amino esters, β-lactam antibiotics and alkaloids.

Classical methods for the synthesis of aziridines are ring closure of amino alcohols, ring opening of epoxides with sodium azide, and addition of α-halo ester enolates to N-(trimethyl silyl) imines. In 1995, a conceptually new synthesis of aziridines via catalyzed carbine-transfer reactions of α-diazoacetates with imines, appeared in the literature.

Aziridine-2-carboxylates are interesting compounds in view of their structural relationship with α- as well as β-amino acids and the intrinsic high reactivity.
of the three-membered ring. Although there is an extensive literature on aziridines in
general, their carboxylic acids received limited attention\(^7\).

**Previous synthetic approaches:**

Espenson and Zhu\(^8\) reported that a catalytic amount of MTO with ethyl diazoacetate
(EDA) converted aromatic imines to aziridines. (Scheme 1)

\[
\text{ArCH=NR} + \text{N}_2\text{CHCO}_2\text{Et} \xrightarrow{\text{cat. MTO} + \text{-N}_2} \text{ArCH=CH} + \text{HCO}_2\text{Et}
\]

\((R = \text{Ph, Bun, HXn})\)

**Scheme 1**

Sengupta and Mondal\(^9\) discovered InCl\(_3\) can catalyze the reaction of ethyl diazoacetate
with aldimines to give aziridine carboxylates under mild conditions with low catalyst
loading and high \textit{cis}-selectivity. (Scheme 2)

\[
\text{PhNHCO}_2\text{Et} + \text{N}_2\text{CHCO}_2\text{Et} \xrightarrow{\text{InCl}_3, \text{solvent}} \text{PhNHCO}_2\text{Et} + \text{N}_2\text{CHCO}_2\text{Et}
\]

**Scheme 2**

George Wang et al.\(^{10}\) reported that lanthanide triflates were effective to catalyze the
aziridination reaction of diazo compounds with a variety of imines. (Scheme 3)
Joseph L. Templeton et al. reported the reaction of imines with EDA catalyzed by BF$_3$·Et$_2$O. (Scheme 4)

Anker Jorgensen and co-workers developed the metal catalyzed aziridation of imines with ethyl diazoacetate as the carbine fragment donor using various Lewis acids (Scheme 5). The catalytic properties of different Lewis acid complexes have been tested and it has been found that both main-group complexes, such as BF$_3$·OEt$_2$, early- and late-transition metal complexes, such as TiCl$_3$(O-Pr$^+$)$_2$, Cu(OTf)$_2$ and Zn(OTf)$_2$ and rare-earth metal complexes, such as Yb (OTf)$_3$, can catalyze the formation of aziridines.
Eric N. Jacobsen\textsuperscript{13} reported the catalytic method for the preparation of aziridines from imines and diazoacetate using copper complexes as a catalyst. The synthetic, diastereo- and enantio-selective scope of the reaction were presented. (Scheme 6)
In this part of work we explored the facile synthesis of highly diastereoselective cis-aziridine carboxylates by the reaction of aldimines generated in situ from aldehydes, amines and EDA in the presence of a catalytic amount of lithium perchlorate. (Scheme 7).

In recent years, LiClO₄ in diethyl ether (LPDE) has emerged as a mild Lewis acid importing high region- chemo- and stereoselectivity in various organic transformations. Lithium perchlorate is found to retain its activity even in the presence of amines and has also been found to activate effectively nitrogen-containing compound such as imines.

Accordingly, treatment of benzaldehyde and aniline with ethyl diazoacetate in the presence of 10 mol% of lithium perchlorate gave the corresponding ethyl 1,3-diphenylaziridine-2-carboxylate (3a) in 87% yield with high cis-selectivity. The cis stereochemistry of the aziridine 3a was confirmed by the large coupling constant ($J = 6.9 \text{ Hz}$) of the aziridine ring hydrogen's at $\delta 3.20$ and $3.59$ (the ring protons of trans-3a appear at $\delta 3.20$ and $3.80$ with a smaller coupling constant, ($J = 2.0–3.0 \text{ Hz}$).

The reaction probably proceeds through the activation of the imine by complexation with lithium perchlorate followed by nucleophilic addition of EDA on the C=N double bond and subsequent ring closing with loss of N₂ resulting in the formation of the aziridine 3 (Scheme 8).
A variety of aldimines (derived in situ from aldehydes and amines) reacted smoothly with ethyl diazoacetate to produce the corresponding aziridines in high yields (Table 1). Treatment of an ether solution of \(N\)-benzylideneaniline with variable amounts of lithium perchlorate and 1 equiv. of ethyl diazoacetate also resulted in the formation of an aziridine. The use of 10 mol\% of \(\text{LiClO}_4\) in acetonitrile or in nitro methane was found to be the most ideal. A lower loading of catalyst resulted in both a prolonged reaction time and lower yields. Among various lithium salts such as lithium perchlorate, lithium triflate and lithium tetrafluoroborate, \(\text{LiClO}_4\) was found to be the best catalyst of those tested for the aziridination.

The influence of solvent in this reaction has also been investigated with the best results being obtained in acetonitrile or nitro methane. Aryl imines derived from aromatic amines and aromatic aldehydes and \(N\)-benzyl aryl imines and imines derived from aromatic amines and aliphatic aldehydes worked well. Aryl imines possessing either electron-donating or electron-withdrawing groups reacted readily with EDA in acetonitrile in the presence of lithium perchlorate affording the corresponding aziridines with high \(cis\)-selectivity. Not only aromatic aldehydes but also aliphatic aldehydes reacted smoothly under these reaction conditions to afford the corresponding aziridines in excellent yields with high diastereoselectivity.
### Table 1 LiClO₄⁻ catalyzed synthesis of cis-aziridine carboxylates from imines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Amine</th>
<th>Product*</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Cis-trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>R = Ph</td>
<td>R' = Ph</td>
<td>3a</td>
<td>4.5</td>
<td>89</td>
<td>cis only</td>
</tr>
<tr>
<td>b</td>
<td>R = 4-Me-Ph</td>
<td>R' = 4-Cl-Ph</td>
<td>3b</td>
<td>5.0</td>
<td>91</td>
<td>cis only</td>
</tr>
<tr>
<td>c</td>
<td>R = 2-Naphthyl</td>
<td>R' = Ph</td>
<td>3c</td>
<td>6.5</td>
<td>84</td>
<td>cis only</td>
</tr>
<tr>
<td>d</td>
<td>R = Ph</td>
<td>R' = 4-F-Ph</td>
<td>3d</td>
<td>5.5</td>
<td>87</td>
<td>cis only</td>
</tr>
<tr>
<td>e</td>
<td>R = 4-NO₂-Ph</td>
<td>R' = Ph</td>
<td>3e</td>
<td>6.0</td>
<td>75</td>
<td>85:15</td>
</tr>
<tr>
<td>f</td>
<td>R = 3-NO₂-Ph</td>
<td>R' = 4-Br-Ph</td>
<td>3f</td>
<td>6.5</td>
<td>79</td>
<td>82:18</td>
</tr>
<tr>
<td>g</td>
<td>R = 4-Cl-Ph</td>
<td>R' = 4-Cl-Ph</td>
<td>3g</td>
<td>5.0</td>
<td>86</td>
<td>cis only</td>
</tr>
<tr>
<td>h</td>
<td>R = 4-Me-Ph</td>
<td>R' = Ph</td>
<td>3h</td>
<td>4.5</td>
<td>90</td>
<td>cis only</td>
</tr>
<tr>
<td>i</td>
<td>R = 4-Me-Ph</td>
<td>R' = 4-Br-Ph</td>
<td>3i</td>
<td>5.5</td>
<td>85</td>
<td>cis only</td>
</tr>
<tr>
<td>j</td>
<td>R = 4-HO-Ph</td>
<td>R' = Ph</td>
<td>3j</td>
<td>6.0</td>
<td>80</td>
<td>cis only</td>
</tr>
<tr>
<td>k</td>
<td>R = Ph</td>
<td>R' = [\text{O} \text{C} \text{R}, \text{O} \text{LH}2]</td>
<td>3k</td>
<td>5.0</td>
<td>87</td>
<td>97:3</td>
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<tr>
<td>l</td>
<td>R = 4-Cl-Ph</td>
<td>R' = [\text{O} \text{C} \text{R}, \text{O} \text{LH}2]</td>
<td>3l</td>
<td>5.5</td>
<td>89</td>
<td>95:5</td>
</tr>
<tr>
<td>m</td>
<td>R = Ph</td>
<td>R' = PhCH₂-</td>
<td>3m</td>
<td>6.0</td>
<td>85</td>
<td>cis only</td>
</tr>
<tr>
<td>n</td>
<td>R = 4-Cl-Ph</td>
<td>R' = Ph</td>
<td>3n</td>
<td>4.5</td>
<td>90</td>
<td>cis only</td>
</tr>
<tr>
<td>o</td>
<td>R = 4-MrO-Ph</td>
<td>R' = Ph</td>
<td>3o</td>
<td>5.0</td>
<td>86</td>
<td>cis only</td>
</tr>
<tr>
<td>p</td>
<td>R = n-C₅H₁₁-</td>
<td>R' = Ph</td>
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<td>78</td>
<td>92:8</td>
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<tr>
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<td>R' = Ph</td>
<td>3q</td>
<td>7.5</td>
<td>75</td>
<td>89:11</td>
</tr>
<tr>
<td>r</td>
<td>R = PhCH₂CH₂-</td>
<td>R' = Ph</td>
<td>3r</td>
<td>5.5</td>
<td>80</td>
<td>87:13</td>
</tr>
</tbody>
</table>

a. All products were characterized by 'H NMR, IR and mass spectroscopy.
b. Yield refers to pure products after column chromatography.
In summary, lithium perchlorate was found to be a highly efficient and convenient catalytic medium for the synthesis of cis-aziridine carboxylates from aldehydes, amines and ethyl diazoacetate in a single-step operation. In addition to its simplicity and milder reaction conditions, this method provides high yields of products with high cis-selectivity which makes it a useful and attractive strategy for the preparation of cis-aziridine carboxylates of synthetic importance.

**Experimental procedure:** A mixture of the aldehyde (1 mmol), amine (1 mmol), ethyl diazoacetate (1.2 mmol) and LiClO₄ (10 mol %) in acetonitrile (10 mL) was stirred at 28°C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water (15 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100-200 mesh, ethyl acetate-hexane 1:9) to afford pure cis-aziridine.

**Cis-Ethyl 1, 3-diphenylaziridine-2-carboxylate (3a)**

Solid, Mp 64-66°C;

**¹H NMR (200 MHz, CDCl₃)**

\[
\begin{align*}
\delta & \quad \text{ppm} \\
0.99 & (t, 3H, J = 7.0 \text{ Hz}), \\
3.20 & (d, 1H, J = 6.8 \text{ Hz}), \\
3.60 & (d, 1H, J = 6.8 \text{ Hz}), \\
3.99-4.05 & (m, 2H), \\
7.06 & (d, 2H, J = 8.4 \text{ Hz}), \\
7.20-7.40 & (m, 6H), \\
7.55 & (d, 2H, J = 8.1 \text{ Hz}).
\end{align*}
\]

**EI MS**

\[
\begin{align*}
\text{m/z} & \quad \text{ppm} \\
335 & M^+ 267, 194.
\end{align*}
\]

**¹³C NMR (50 MHz, CDCl₃)**

\[
\begin{align*}
\delta & \quad \text{ppm} \\
13.9, 45.5, 47.1, 61.0, 119.9, 123.6, 127.7, 127.9, 128.0, 129.2, 134.6, 152.4, 167.8.
\end{align*}
\]
Cis-Ethyl 1-(4-Chlorophenyl)-3-(4-methylphenyl) aziridine-2-carboxylate (3b)

Pale yellow solid, mp 73-75 °C.

\[ \text{IR (KBr)} \quad 3050, 2931, 2865, 1749, 1600, 1543, 1369, 1190 \text{ cm}^{-1} \]

\[ \text{C} \] _7\text{s-Ethyl 1-(4-Chlorophenyl)-3-(4-methylphenyl) aziridine-2-carboxylate (3b)}

\[ \text{H NMR (200 MHz, CDCl}_3) \quad \delta \ 1.28 (t, 3H, J = 6.9 \text{ Hz}), 2.34 (s, 3H), 3.20 (d, J = 6.7 \text{ Hz, 1H}), 3.60 (d, J = 6.7 \text{ Hz, 1H}), 3.93-4.13(m, 2H), 7.01 (m, 2H) 7.14-7.37 (m, 6H).

\[ \text{C} \] _o-Ethyl 1,3-di (p-chlorophenyl) aziridine-2-carboxylate (3g)

Solid, mp 60-62°C

\[ \text{H NMR (200 MHz, CDCl}_3) \quad \delta \ 1.0 (t, 3H, J = 7.0 \text{ Hz}), 3.10 (d, 1H, J = 6.7 Hz), 3.45 (d, 1H, J = 6.7 Hz), 3.98-4.08 (m, 2H), 6.90 (d, 2H, J = 7.9 Hz), 7.25 (d, 2H, J = 8.0 Hz), 7.35 (d, 2H, J = 7.9 Hz), 7.45 (d, 2H, J = 8.0 Hz),

\[ \text{EIMS} \quad m/z 335 M^+ , 267, 194.

\[ \text{C} \] _o-Ethyl 1, 3-di (p-chlorophenyl) aziridine-2-carboxylate (3g)

Solid, mp 60-62°C

\[ \text{H NMR (200 MHz, CDCl}_3) \quad \delta \ 14.0, 45.7, 46.6, 61.3, 121.2, 128.3, 128.5, 129.0, 129.2, 133.8, 136.3, 151.6, 166.9.

\[ \text{IR (KBr)} \quad 3050, 2931, 2865, 1749, 1600, 1543, 1369, 1190 \text{ cm}^{-1} \]
Chapter III

Section A

Ethyl 1-(2-furylmethyl)-3-phenyl-2-aziridine-2-carboxylate (3k)

Liquid

$^1$H NMR (200 MHz, CDCl$_3$) : $\delta$ 0.98 (t, 3H, $J = 6.9$ Hz), 2.60 (d, 1H, $J = 6.7$ Hz), 3.05 (d, 1H, $J = 6.7$ Hz), 3.75-3.87 (ABq, 2H, $J = 13.7$ Hz), 3.90-4.0 (m, 2H), 6.25-6.30 (m, 2H), 7.20-7.40 (m, 6H).

EIMS : m/z 271 M$^+$, 269, 188, 143, 116, 89, 53.

IR (KBr) : 2982, 2930, 1745, 1667, 1500, 1374, 1189, 744 cm$^{-1}$.

Ethyl 1-benzyl-3-phenyl-2-aziridine-2-carboxylate (3m)

Liquid

$^1$H NMR (200 MHz, CDCl$_3$) : $\delta$ 1.0 (t, 3H, $J = 7.0$ Hz), 2.60 (d, 1H, $J = 6.8$ Hz), 3.0 (d, 1H, $J = 6.8$ Hz), 3.65 (d, 1H, $J = 13.9$ Hz), 3.85-4.0 (m, 3H), 7.20-7.45 (m, 10H).


IR (KBr) : 2925, 2865, 1747, 1655, 1505, 1453, 1173 cm$^{-1}$.
Cis-Ethyl 1-Phenyl-3-(4-methoxyphenyl) aziridine-2-carboxylate (3o)

Pale yellow oil.

$^1$H NMR (200 MHz, CDCl$_3$)

: $\delta$ 1.09 (t, 3H, $J = 6.8$ Hz), 3.21 (d, $J = 6.8$ Hz, 1H),
3.74 (d, $J = 6.8$ Hz, 1H), 3.80 (s, 3H), 3.96–4.04 (m, 2H), 6.83–7.72 (m, 9H).

$^{13}$C NMR (CDCl$_3$)

: $\delta$ 14.1, 45.6, 46.7, 55.6, 61.2, 114.0, 114.2, 121.1,
126.3, 129.2, 129.8, 130.2, 152.1, 167.0.

EIMS

: $m/z$ 297 (M$^+$, 18), 224 (100).
Reference:


CHAPTER-III

SECTION- B: Enzymatic resolution of N-aryl aziridine carboxylates.
INTRODUCTION

The technique of kinetic resolution of racemic substrates with enzymes is now a well-established tool in preparative organic chemistry. Books and reviews abound in this area,¹ and the commercial impact of this methodology is rising.² While the traditional focus in utilizing enzymes has been centered on food processing, detergent additives, and diagnostic applications, new companies are gearing up their attention to supply new enzymes and to make single enantiomers for the pharmaceutical industry on a large scale. Biocatalytic synthesis of optically active compounds is well established³ and used for the synthesis of optically active aziridinecarboxylates,⁴ amino acids⁵ and β-lactams.⁶

Aziridine carboxylates are important chiral synthons, which can generate a plethora of useful organic intermediates such as α- and β-amino acids and β-lactams.⁷ Furthermore, enantiomerically pure aziridine carboxylates may be used as precursors for the generation of chiral building blocks and enantioselective routes to unusual amino acids can be envisaged through regioselective ring opening reactions involving aziridinoesters.⁸ Regio- and stereo selective ring opening with many types of nucleophiles provide access to a great variety of useful synthetic intermediates. In addition to being attractive substrates or building blocks for organic chemists, aziridine carboxylates can also act as chiral auxiliaries, chiral reagents and chiral ligands for asymmetric synthesis.⁹ Various chiral aziridines are available in enantiomerically pure form either through asymmetric synthesis¹⁰ or kinetic resolution of racemates.¹¹
Candida rugosa lipase (CRL) is an extracellular protein, inexpensive and accepts a broad range of substrates. It is extensively used for the hydrolysis and esterification of organic compounds\textsuperscript{12} and the knowledge\textsuperscript{13} of its crystal structure has greatly contributed to understand the mechanism of its selective recognition of substrates.\textsuperscript{14} In order to improve the chemo-, regio- and diastereoselectivity of the enzyme, commercial CRL as well as conventional purifications, \textsuperscript{15} have been subjected to several treatments that cause molecular or conformational changes. Structural analysis reveals that the catalytic trait is not exposed to the reaction medium, and the polypeptide lid, which covers the active site of the native enzyme, is displaced before the substrate approaches the active site.\textsuperscript{16} Scattered data indicate that the method of CRL purification and the reaction medium\textsuperscript{17} strongly influence the activity and selectivity of lipase but systematic studies in this area are rare.\textsuperscript{18}
Previous Approaches

Cipiciani and co-workers\textsuperscript{19} reported the kinetic resolution of racemic methyl 2-aryloxypropionates in water and in a series of two-phase aqueous organic media in the presence of Candida rugosa lipase (CRL). The biocatalytic material used was the enzyme of commercial CRL purified by treatment with different alcohols. The purification of CRL and the reaction medium play an important role in the enantioselection of race mates.

Ennio Valentin reported\textsuperscript{20} the kinetic resolution of an $\alpha$-methylene-$\gamma$-lactone. The probe molecule, ethyl 2-methyl-4-methylene-tetrahydro-5-oxo-2-flurancarboxylate\textsuperscript{3} was successfully resolved with Porocine pancreatic lipase and Candida rugosa lipase, in the presence of acosolvent, led to a both enantiomers of the corresponding acid with high enantiomeric excesses. (Scheme 9)

\begin{equation}
\text{EtO}_2\text{C} \quad \text{O} \quad \text{EtO}_2\text{C} \\
(\pm)-3 \\
\begin{array}{c}
\text{PPL} \\
\text{pH 7.4} \\
10\% \text{ acetone}
\end{array}
\end{equation}

\begin{eqnarray}
\text{EtO}_2\text{C} \quad \text{O} \quad \text{EtO}_2\text{C} + \\
(\pm)-3 + \\
\text{HO}_2\text{C} \quad \text{O} \\
(+)\text{-}4
\end{eqnarray}

Scheme 9
Maurice C. R. Franssen\textsuperscript{21} achieved an efficient chemo enzymatic synthesis of \((-\))-3-methyl 5-(2-propxyethyl) (4\textit{R})-4-[2-(difluoromethoxy) phenyl]-2, 6-dimethyl-1, 4-Dihydro-3, 5-pyridinedicarboxylate. (Scheme 10) The key step is a highly stereoselective \textit{Candida rugosa} lipase (CRL)-mediated asymmetrisation of the prochiral bis (isobutyryloxy)-4-[2-(difluoromethoxy) phenyl]-1, 4-dihydro-2, 6-dimethyl-3, 5-pyridinedicarboxylate.

\begin{center}
\textbf{Scheme 10}
\end{center}

Kurt Konigsberger and co-workers reported\textsuperscript{22} the kinetic resolution of 1, 1, 1-trifluoro-2-alkanone cyanohydrin acyl derivatives with \textit{Candida rugosa} lipase afforded the remaining \((\textit{R})\)-enantiomer in high selectivity (E from 30 >200). (Scheme 11) \textit{Candida rugosa} lipases from several suppliers were compared and found to differ remarkably in their selectivity.
Chapter III

Irene Moretti reported that N-substituted aziridine-2-carboxylates and 2,3-dicarboxylates have been resolved with good to excellent stereochemical purity by enzymatic hydrolysis catalysed by lipase from *Candida cylindracea*. (Scheme 12)

\[
\text{Scheme 12}
\]

Christoph Tamm reported the hydrolysis of the racemic dimethyl aziridine-2,3-dicarboxylates with pig liver esterase (PLE). (Scheme 13)

\[
\text{Scheme 13}
\]
PRESENT WORK

In this part of work we report the kinetic resolution of racemic N-arylaziridine-2-carboxylates via enantioselective hydrolysis by C. rugosa lipase (CRL). (Scheme 14)

Racemic aziridines were prepared by the ring contraction of precursor triazoline carboxylates, which were readily obtained through 1, 3-dipolar cycloadditions of various aryl azides with methyl acrylates (Scheme 15).

Hydrolysis was conducted in pH 7.5 phosphate buffer (0.1 M) and due to the low solubility of the substrates in buffer solution, dioxane was used as the co-solvent. The hydrolysis was terminated at around 45–50% conversion by extraction with EtOAc. The crude optically active esters obtained after evaporation of the solvent were flash chromatographed on silica gel (EtOAc/n-hexane gradient) to afford pure N-arylaziridine carboxylates. The enantiomeric purity was determined by chiral HPLC and $^1H$ NMR-shift reagent methods. Moderate to high enantiomeric purity (70–99%) was observed.
among the substrates (see Table 2) studied. The absolute configuration of all the unhydrolyzed N-arylaziridine carboxylates was determined as S by comparing the sign of the specific rotation, based on a literature precedent.

Table 2: Enantioselective hydrolysis of aziridine-2-carboxylate by C. rugosa

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (Ar)</th>
<th>Reaction conditions</th>
<th>Unchanced ester</th>
<th>Absolute configuration</th>
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<tr>
<td></td>
<td></td>
<td>t (h)</td>
<td>E/S*</td>
<td>Conversion (%)</td>
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<tr>
<td>1</td>
<td>Ar</td>
<td>4</td>
<td>1/2</td>
<td>48</td>
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<tr>
<td>2</td>
<td>Br</td>
<td>5</td>
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<td>50</td>
</tr>
<tr>
<td>3</td>
<td>O$_2$N-</td>
<td>3</td>
<td>1/2</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>H$_2$C-</td>
<td>4.5</td>
<td>1/2</td>
<td>48</td>
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<tr>
<td>5</td>
<td>F-</td>
<td>5.5</td>
<td>1/4</td>
<td>44</td>
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<td>6</td>
<td>Br</td>
<td>5.5</td>
<td>1/4</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>MeO-</td>
<td>5</td>
<td>1/2</td>
<td>46</td>
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</table>
We have successfully demonstrated herein, the kinetic resolution of synthetically important N-arylaziridine-2-carboxylates in moderate to high enantiomeric purity using C. rugosa lipase. All the unhydrolyzed esters were found to be of an (S)-configuration.

**Experimental procedure:**

Racemic N-arylaziridine carboxylate (25 mg) was added to a phosphate buffer (pH 7.5 mL, 0.1 M) and treated with C. rugosa lipase (Sigma 0.890 units/mg) with vigorous stirring at room temperature (25 °C). The ratio of enzyme/aziridine carboxylate (E/S) employed is reported in Table 1. The pH was adjusted at 7.5 and kept constant by the intermittent addition of 0.1 M NaOH. Dioxane (1-2 mL, 4-8% v/v) was used as the co-solvent to improve the solubility of N-arylaziridine carboxylates. The progress of hydrolysis was monitored by TLC and the reaction terminated at 45-5-% conversion via simple extraction with ethyl acetate (2 x 20 mL) after which the organic extract was dried and purified by flash chromatography (ethyl acetate/n-hexane gradient mixture) to afford the pure N-arylaziridine carboxylate.

**Methyl N-(phenyl) aziridine-2-carboxylate**

\[ ^1H \text{NMR} \]

\[ \delta \ 2.30 \text{ (dd, 1H)}, \ 2.66 \text{ (dd, 1H)}, \ 2.81 \text{ (dd, 1H)}, \ 3.80 \text{ (s, 3H)}, \ 7.02-7.05 \text{ (m, 3H)}, \ 7.22-7.26 \text{ (m, 2H)}. \]

\[ \text{MS} \]

\[ \text{m/z} \ (%) \ 177 (M^+, 32), \ 163 (26), \ 119 (18), \ 104 (100), \ 90 (55), \ 77 (44). \]
Chapter III

Section B

IR (KBr) : 1750 cm⁻¹
Optical rotation [α]D²⁵ : (-)173.2 (c 0.25, CHCl₃);
Found : C, 67.69; H, 6.57; N, 7.97%.

Methyl N-(p-bromophenyl) aziridine-2-carboxylate

¹H NMR : δ 2.26 (d, 1H), 2.63 (s, 1H), 2.75 (dd, 1H), 3.79 (s, 1H), 6.84 (d, 2H), 7.29 (d, 2H).
MS : m/z (%) 255 (M⁺, 91), 182 (96), 169 (53), 117 (100), 90 (76), 63 (43).
IR (KBr) : 1754 cm⁻¹
Optical rotation [α]D²⁵ : (-)156.3 (c 0.25, CHCl₃)
Anal. Calcd for C₁₀H₁₀BrNO₂ : C, 46.90; H, 3.94; Br, 31.20; N, 5.47.
Found : C, 46.98; H, 3.86; Br, 31.32; N, 5.37%.

Methyl N-(p-nitrophenyl) aziridine-2-carboxylate

¹H NMR : δ 2.24 (d, 1H), 2.78 (s, 1H), 2.95 (dd, 1H), 3.82 (s, 3H), 7.06 (d, 2H), 8.18 (d, 2H).
MS : m/z (%) 222 (M⁺, 82), 206 (70), 163 (28), 149 (100), 117 (54), 90 (43), 45 (30).
IR (KBr) : 1758 cm⁻¹
Optical rotation [α]D²⁵ : (-)40.3 (c 0.5, CHCl₃)
Anal. Calcd for C₁₀H₁₀N₂O₄ : C, 54.06; H, 4.54; N, 12.61;
Found : C, 54.15; H, 4.42; N, 12.73%. 

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**Methyl N-(p-methyl phenyl) aziridine-2-carboxylate**

$^1$H NMR

\[ \delta 2.25-2.28 \text{ (m, 4H), } 2.59 \text{ (dd, 1H), } 2.71 \text{ (dd, 1H), } 3.79 \text{ (s, 3H), } 6.85 \text{ (d, 2H), } 7.03 \text{ (d, 2H).} \]

MS

\[ m/z \% 191 (M^+, 66), 177 (30), 133 (35), 119 (100), 106 (65), 92 (60). \]

IR (KBr)

\[ 1756 \text{ cm}^{-1} \]

Optical rotation $[\alpha]_D^{25}$

\[ (-) 195.5 \text{ (c 0.25, CHCl}_3) \]

Anal. Calcd for C$_{11}$H$_{13}$NO$_2$ : C, 69.09; H, 6.86; N, 7.32.

Found : C, 69.15; H, 6.80; N, 7.4%.

**Methyl N-(p-fluoro phenyl) aziridine-2-carboxylate**

$^1$H NMR

\[ \delta 2.24 \text{ (d, 1H), } 2.62 \text{ (s, 1H), } 2.76 \text{ (dd, 1H), } 3.80 \text{ (s, 3H), } 6.85 \text{ (d, 2H), } 6.92 \text{ (d, 2H).} \]

MS

\[ m/z \% 196 (M^+ + 1, 100), 180 (12), 136 (30), 122 (15), 83 (14), 69 (14), 55 (28). \]

IR (KBr)

\[ 1756 \text{ cm}^{-1} \]

Optical rotation $[\alpha]_D^{25}$

\[ (-) 18.4 \text{ (c 1.5, CHCl}_3) \]

Anal. Calcd for C$_{10}$H$_{10}$FNO$_2$ : C, 61.53; H, 5.16; F, 9.73; N, 7.18.

Found : C, 61.60; H, 5.11; F, 9.78; N, 7.26%.

**Methyl N-(2-bromo-4-methylphenyl) aziridine-2-carboxylate**

$^1$H NMR

\[ \delta 2.24 \text{ (s, 3H), } 2.38 \text{ (dd, 1H), } 3.81 \text{ (s, 3H), } 6.79 \text{ (d, 1H), } 6.95 \text{ (d, 1H), } 7.32 \text{ (s, 1H).} \]
MS : m/z (%) 196 (M⁺, 30), 198 (36), 107 (100), 79 (62).

IR (KBr) : 1755 cm⁻¹

Optical rotation [α]D²⁵ : (-)15.9 (c 0.025, CHCl₃)

Anal. Calcd for C₅H₁₁BrNO₂ : C, 48.91; H, 4.48; Br, 29.58; N, 5.19.

Found : C, 48.83; H, 4.57; Br, 29.68; N, 5.22%.

**Methyl N-(p-methoxy phenyl) aziridine-2-carboxylate**

¹H NMR : δ 2.23 (d, 1H), 2.59 (s, 1H), 2.69 (dd, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 6.75 (d, 2H), 6.84 (d, 2H).

MS : m/z (%) 207 (M⁺, 95), 192 (26), 134 (100), 121 (62), 77 (24).

IR (KBr) : 1754 cm⁻¹

Optical rotation [α]D²⁵ : (-)184.3 (c 0.5, CHCl₃)

Anal. Calcd for C₁₁H₁₃NO₃ : C, 63.76; H, 6.32; N, 6.76.

Found : C, 63.68; H, 6.40; N, 6.89%.
Reference:


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SPECTRA
SPECTRUM OF COMPOUND 3g ppm

'H NMR SPECTRUM OF COMPOUND 3g

0.863

-7.84.528
-3.9.2.73
-0.413.272
-5.562.585
'H NMR SPECTRUM OF COMPOUND 3m
NCMS, IICT
02-06-2003

Operator : NCMS

FURFURYL LRP M. SESHU, FURFURYL

Scan 5 RT = 0:20 No. ions = 320 Base = 80.5% F TIC = 212899

MASS SPECTRUM OF COMPOUND 3k
BENZYL.LRP  P.N.REDDY, BENZYL


Scan 2  RT= 0:11  No.ions= 365  Base= 95.4%F  TIC=215664

![Mass Spectrum of Compound 3m](image)
$^1$H NMR spectrum of COMPOUND 2
$^1$H NMR SPECTRUM OF COMPOUND 3
1H NMR SPECTRUM OF COMPOUND 4
1H NMR SPECTRUM OF COMPOUND 6
H NMR SPECTRUM OF COMPOUND 7

Current Data Parameters
NAME Feb 18-2003
EXPNO 46
PROCNO 1

F2 - Acquisition Parameters
Date 20030218
Time 17.06
INSTRUM av300
PROBMD 5 mm DUL 13C-1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SW 6188.115 Hz
FDores 0.188846 Hz
AG 2.647852 sec
RG 405.4
ON 80.000 usec
DE 6.000 usec
TE 300.0 K
G1 1.00000000 sec

****** CHANNEL f1 ******

H NMR plot parameters
CX 20.00 cm
CY 12.50 cm
FP1 11.000 ppm
F1 3301.43 Hz
FP2 -1.000 ppm
F2 -300.13 Hz
PPMCM 0.60000 ppm/cm
HZCM 180.07800 Hz/cm

PROTON CDCl3 D: /u routine 46

MeOOC

OMe
Scan 8  RT= 1:0  No.ions= 358  Base= 40.3%F  TIC=177934

MASS SPECTRUM OF COMPOUND 3
MASS SPECTRUM OF COMPOUND 6

Scan 10  RT= 0:39  No. ions= 485  Base= 29.0%F  TIC=180198
WAVENUMBER IR SPECTRUM OF COMPOUND 6