Chapter 4

DIASTEREOSELECTIVE AZIDATION
REACTIONS MEDIATED BY
CERIUM(IV) AMMONIUM NITRATE

4.1 INTRODUCTION

Addition of free radicals to carbon-carbon double bonds has emerged as an important reaction in organic chemistry (see Chapter 1). Because of their high reactivity, organic free radicals have historically been regarded as intermediates poorly suited for selective reactions. Recently, however, remarkable progress has been made in stereochemical control in radical carbon-carbon bond formation.¹ Developments in diastereoselective radical reactions began in the 1980s and have culminated in guidelines for the use of auxiliaries and the understanding of substrate controlled processes.

Chiral auxiliary methodology continues to offer an effective approach in asymmetric synthesis.² An important condition for the success of the approach is that the chiral auxiliary must be efficiently introduced and it must be easily removed without disrupting the newly formed stereogenic centres. Currently, the most useful chiral auxiliaries are those which function by controlling the diastereoselectivity of attached acyl fragments. In this context, perhaps the most widely used auxiliaries are the versatile oxazolidin-2-ones 1 and 2 discovered by Evans³ (Figure 1). The N-acyl derivatives of Evans' auxiliaries 1 and 2 have been utilized in numerous highly diastereoselective reactions including alkylation, amination, azidation, bromination, hydroxylation, aldol addition, Diels-Alder cycloadditions and conjugate additions.⁴
With the development of chiral enolate systems, it has been found that amide and imide enolates of 1 and 2 exhibit excellent levels of asymmetric induction for alkylation reactions (Scheme 1).\(^5\)

The electrophilic introduction of azide with chiral imide enolate has been used to synthesize α-amino acids with high diastereoselection. The reaction can be performed with either the enolate directly\(^6\) or through a halo intermediate,\(^7\) the resultant azide can be reduced to the corresponding amine (Scheme 2).
Although there are numerous examples of diastereoselective Diels-Alder, Aldol and other reactions that are directed by chiral auxiliaries, there are only a few reports of diastereoselective radical reactions. The reaction of alkyl iodides, electron-deficient alkenes and allyl tributyl stannane has been used extensively to test the efficacy of auxiliary groups in free radical additions. The auxiliary can be used in a propagation sequence that involves radical addition to the acrylimide followed by trapping of the adduct radical with allyl stannane and this is exemplified in Scheme 3.\(^8\)

\[\text{Scheme 3}\]

The diphenyloxazolidinone in combination with Lewis acids provides a general solution for diastereoselective reactions (Scheme 4).\(^9\)
Recent work in our laboratory has shown that CAN mediated addition of azide to \( \alpha, \beta \)-unsaturated carboxylic acid under an atmosphere of argon leads to a facile synthesis of \( \alpha \)-azido-\( \beta \)-nitrato compounds that can serve as precursors to \( \alpha \)-amino-\( \beta \)-hydroxy acids (Scheme 5).\(^7\) It is worthy of mention that the latter are of considerable biological importance.\(^8\) Inter alia, they are components of various peptides possessing a wide range of biological activities such as antibiotic and immunosuppressive properties.

In this case, the reaction proceeded to afford the product as a 1:1 mixture of \textit{syn} and \textit{anti} isomers. Intrigued by the possibility of diastereoselective radical reactions, it was of interest to undertake the addition of azide radical to \( \alpha, \beta \)-unsaturated N-acyl oxazolidin-2-ones.

4.2 RESULTS AND DISCUSSION

The cinnamyloxazolidinone required for our study was synthesized according to the procedure as outlined in Scheme 6.\(^9\)
A deoxygenated solution of cinnamyloxazolidinone and sodium azide in anhydrous acetonitrile, on treatment with a deoxygenated solution of CAN in the same solvent afforded only the anti isomer 26 in 52% yield (Scheme 7).

The product was purified by silica gel column chromatography and characterized by the usual spectroscopic methods. The IR spectrum of 26 showed the characteristic absorption of azide at 2115 cm\(^{-1}\). The absorptions due to carbonyl groups were visible at 1781 and 1707 cm\(^{-1}\) respectively. The absorption due to ONO\(_2\) group was visible at 1645 cm\(^{-1}\). In the \(^1\)H NMR spectrum, the proton attached C-1 was visible as doublet at \(\delta 6.22\) (d, \(J = 9.9\) Hz). The proton on C-2 also appeared as doublet at \(\delta 5.47\) (d, \(J = 7.2\) Hz). In the \(^{13}\)C NMR spectrum, the carbonyl carbons were discernible at \(\delta 166.24\) and 152.78. The C-1 carbon resonated at \(\delta 81.55\) and the C-2 carbon resonated at \(\delta 66.60\). All other signal were in good agreement with the assigned structure.
When we attempted the exocyclic cleavage of the chiral auxiliary using lithium hydroxide, the product obtained was the 2-azidocinnamic acid (Scheme 8).

Scheme 8

Subsequently, we tried the Lewis acid mediated cleavage of the chiral auxiliary for which a solution of the product in anhydrous methanol was treated with scandium triflate under an atmosphere of argon and was refluxed for 24 hours. The reaction proceeded to afford 80% of 28 with 58% of ee and 86% of 23 (Scheme 9). Enantiomeric excess of the product was determined by using chiral shift reagent, tris[3-heptafluoropropylhydroxymethylene(+)-camphorato]europium(III), Eu(hfc)$_3$.

Scheme 9

4-Methylcinnamyloxazolidinone also gave the anti isomer of the $\alpha$-azido-$\beta$-nitrato product under similar reaction conditions (Scheme 10).

Scheme 10
The structure of the product 30 was established on the basis of spectroscopic data. The IR spectrum showed the absorption due to $N_3$ at 2118 cm$^{-1}$ and $\text{ONO}_2$ group at 1642 cm$^{-1}$. The absorptions due to the carbonyl groups were visible at 1787 and 1715 cm$^{-1}$. In the $^1$H NMR spectrum, the proton attached to C-1 appeared as a doublet at $\delta$ 6.14 (d, $J = 9.9$ Hz) and the proton on C-2 also appeared as doublet at $\delta$ 5.76 (d, $J = 7.2$ Hz). In the $^{13}$C NMR spectrum, the carbonyl peaks were discernible at $\delta$ 166.22 and 152.46. The C-1 carbon resonated at $\delta$ 81.76 and the C-2 carbon resonated at $\delta$ 79.62. All other signals were in good agreement with the assigned structure.

The reaction was found to proceed well with other substituted cinnamyloxazolidin-2-ones 31, 33 and 35 and the results are presented in Table 1. The products were characterized on the basis of spectroscopic data.

Table 1: Azidation of cinnamyloxazolidin-2-ones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product/Yield(%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 31" /></td>
<td><img src="image2" alt="Product 32" /> (51%)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 33" /></td>
<td><img src="image4" alt="Product 34" /> (48%)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 35" /></td>
<td><img src="image6" alt="Product 36" /> (50%)</td>
</tr>
</tbody>
</table>

$^a$ Reaction Conditions: $\text{NaN}_3$, CAN, dry CH$_3$CN, argon, rt, 50 min

4.3 MECHANISTIC DETAILS

A working hypothesis for the stereoselectivity observed for the CAN mediated azidations with chiral auxiliary can be depicted as shown in Scheme
11. The success of the oxazolidinone template in providing high diastereoselectivity is attributed to the availability of two donor sites for chelation. In the first step Cerium(IV) co-ordinates with the oxygen atoms of the oxazolidinone to form the six membered chelated intermediate 37 (Figure 2).

![Figure 2](image)

A model 37 can account for the observed selectivity. The oxazolidinone 4-substituent provides shielding of the diastereotopic face and thus the azido radical formed by the oxidation of azide anion by CAN would add to this complex preferentially from only one face thus leading to the observed stereoselectivity. This radical can be oxidized to benzylic cation 40 by a second equivalent of CAN and the cation is then quenched by ONO₂ or by ligand transfer from CAN to yield the product.

![Scheme 11](image)
4.4 CONCLUSION

In conclusion, the preliminary results presented above suggest that the stereoselectivity achieved in the radical carbon-heteroatom bond forming reactions mediated by CAN makes further exploration obligatory. It is quite likely that such studies will result in much interesting results. Further work in this direction will be undertaken by other members of our research group.

4.5 EXPERIMENTAL DETAILS

For general information, see section 2.6 of Chapter 2 page 64.

4.5.1 CAN mediated addition of azide to cinnamyloxazolidin-2-ones under deoxygenated conditions: General Procedure

A mixture of cinnamyloxazolidin-2-one (1 mmol) and sodium azide (1.2 mmol) was taken in anhydrous acetonitrile (5 mL) in a two necked round-bottomed flask fitted with a pressure equalizing funnel containing CAN (2.3 mmol) dissolved in anhydrous acetonitrile (10 mL). Both the solutions were simultaneously bubbled with argon, which was deoxygenated by passing through Fieser's solution for 15 minutes. Then the solution of CAN in CH₃CN was added dropwise at room temperature and the reaction mixture was stirred vigorously under argon atmosphere for 50 minutes. When the starting material was fully consumed as shown by tlc, acetonitrile was evaporated off, the reaction mixture was diluted with water (75 mL) and extracted using dichloromethane (3 x 25 mL). The combined organic extracts were washed with water, then with saturated brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to obtain the crude residue, which was subjected to column chromatography on silica gel. Elution with an appropriate mixture of hexane-ethyl acetate afforded the products.
3-(2-Azido-3-nitrato-3-phenyl-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (26)

To a deoxygenated solution of sodium azide (78 mg, 1.2 mmol) and cinnamyl oxazolidin-2-one 25 (307 mg, 1 mmol) in anhydrous acetonitrile (5 mL) was added dropwise a deoxygenated solution of CAN (1.26 g, 2.3 mmol) in acetonitrile (10 mL) at room temperature over a period of 50 minutes. On completion of the reaction, it was processed as described in the general procedure. The residue on column chromatography on silica gel using hexane-ethyl acetate (80:20) afforded 214 mg (52%) of the product.

colourless viscous liquid

IR (neat) $\nu_{\text{max}}$ : 3024, 2918, 2115, 1781, 1707, 1645, 1458, 1390, 1273, 1211, 1111, 842, 700 cm$^{-1}$.

$^1$H NMR : $\delta$ 7.51-7.44 (m, 5H, ArH), 7.33-7.25 (m, 3H, ArH), 7.21-7.18 (m, 2H, ArH), 6.22 (d, 1H, CHONO$_2$, $J = 9.9$ Hz), 5.47 (d, 1H, CHN$_3$, $J = 7.2$ Hz) 4.73-4.68 (m, 1H, CH), 4.28-4.20 (m, 1H, CH$_2$), 3.24 (dd, 1H, CH$_2$, $J = 2.9$ Hz, $J = 13.3$ Hz), 2.87 (dd, 1H, CH$_2$, $J = 9.1$ Hz, $J = 13.5$ Hz).

$^{13}$C NMR : $\delta$ 166.24, 152.78, 134.35, 133.59, 130.12, 129.36, 129.13, 128.98, 127.78, 127.53, 81.55, 66.60, 60.82, 55.29, 37.45.

3-(2-Azido-3-nitrato-3-(4'-methylphenyl)-1-oxopropyl)-4-(methyl)-2-(phenyl)-2-oxazolidinone (30)

To a deoxygenated solution of sodium azide (78 mg, 1.2 mmol) and 4-methyl cinnamyl oxazolidin-2-one 29 (321 mg, 1 mmol) in anhydrous acetonitrile (5 mL) was added dropwise a deoxygenated solution of CAN (1.26 g, 2.3 mmol) in acetonitrile (10 mL) at room temperature over a period of 50 minutes. On completion of the reaction, it was processed as described in the general procedure. The residue on column chromatography on silica gel using hexane-ethyl acetate (80:20) afforded 213 mg (50%) of the product.
colourless viscous liquid

IR (neat) ν<sub>max</sub> : 2989, 2921, 2118, 1787, 1715, 1642, 1458, 1384, 1276, 1155, 1007, 852, 737 cm<sup>-1</sup>.

<sup>1</sup>H NMR : δ 7.43-7.38 (m, 5H, ArH), 7.32-7.24 (m, 4H, ArH), 6.14 (d, 1H, CHONO<sub>2</sub>, <i>J</i> = 10.0 Hz), 5.76 (d, 1H, CHN<sub>3</sub>, <i>J</i> = 7.2 Hz), 5.49 (d, 1H, CH, <i>J</i> = 10.0 Hz) 4.83-4.79 (m, 1H, CH), 2.39 (s, 3H, CH<sub>3</sub>), 0.96 (d, 3H, CH<sub>3</sub>).

<sup>13</sup>C NMR : δ 166.22, 152.46, 140.28, 132.66, 130.62, 129.90, 129.09, 128.87, 127.84, 125.65, 81.76, 79.62, 60.86, 55.27, 21.40, 14.33.

3-(2-Azido-3-nitrato-3(4'-methylphenyl-1-oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (32)

To a deoxygenated solution of sodium azide (78mg, 1.2 mmol) and 4-methyl cinnamyl oxazolidin-2-one 31 (321 mg, 1 mmol) in anhydrous acetonitrile (5 mL) was added dropwise a deoxygenated solution of CAN (1.26 g, 2.3 mmol) in acetonitrile (10 mL) at room temperature over a period of 50 minutes. On completion of the reaction, it was processed as described in the general procedure. The residue on column chromatography on silica gel using hexane-ethyl acetate (80:20) afforded 217 mg (51%) of the product.

colourless viscous liquid

IR (neat) ν<sub>max</sub> : 3020, 2116, 1779, 1705, 1644, 1457, 1398, 1275, 1210, 1101, 850, 740 cm<sup>-1</sup>.

<sup>1</sup>H NMR : δ 7.40-7.38 (m, 2H, ArH), 7.36-7.30 (m, 3H, ArH), 7.28-7.21 (m, 5H, ArH), 6.16 (d, 1H, CHONO<sub>2</sub>, <i>J</i> = 10.0 Hz), 5.49 (d, 1H, CHN<sub>3</sub>, <i>J</i> = 10.0 Hz) 4.76-4.71 (m, 1H, CH), 4.35-4.24 (m, 1H, CH<sub>2</sub>), 3.29 (dd, 1H, CH<sub>2</sub>, <i>J</i> = 3.3 Hz, <i>J</i> = 13.5 Hz), 2.88 (dd, 1H, CH<sub>2</sub>, <i>J</i> = 9.2 Hz, <i>J</i> = 13.5 Hz), 2.40 (s, 3H, CH<sub>3</sub>).
$^{13}$C NMR : δ 166.55, 152.65, 140.30, 134.47, 130.66, 129.93, 129.51, 129.14, 127.90, 127.69, 81.69, 66.69, 60.81, 55.38, 37.54, 21.42.

3-(2-Azido-3-nitrato-3-(phenyl)-1-oxopropyl)-4-(methyl)-2-(phenyl)-2-oxazolidinone (34)

To a deoxygenated solution of sodium azide (78 mg, 1.2 mmol) and methyl cinnamyl oxazolidin-2-one 33 (307 mg, 1 mmol) in anhydrous acetonitrile (5 mL) was added dropwise a deoxygenated solution of CAN (1.26 g, 2.3 mmol) in acetonitrile (10 mL) at room temperature over a period of 50 minutes. On completion of the reaction, it was processed as described in the general procedure. The residue on column chromatography on silica gel using hexane-ethyl acetate (80:20) afforded 197 mg (48%) of the product.

colourless viscous liquid

IR (neat) $v_{\text{max}}$ : 3012, 2104, 1783, 1702, 1645, 1450, 1390, 1256, 1230, 1103, 864, 710

$^1$H NMR : δ 7.50-7.32 (m, 10H, ArH), 6.18 (d, 1H, CHONO$_2$, $J = 10.0$ Hz), 5.76 (d, 1H, CHN$_3$, $J = 7.2$ Hz), 5.49 (d, 1H, CH, $J = 10.0$ Hz) 4.84-4.79 (m, 1H, CH), 0.97 (d, 3H, CH$_3$).

$^{13}$C NMR : δ 165.97, 152.50, 136.44, 132.58, 132.34, 129.56, 129.21, 128.96, 125.69, 80.99, 79.78, 79.09, 55.28, 14.42.

3-(2-Azido-3-nitrato-3-(4'-chlorophenyl)-1-oxopropyl)-4-(methyl)-2-(phenyl)-2-oxazolidinone (36)

To a deoxygenated solution of sodium azide (78 mg, 1.2 mmol) and 4-chloro methyl cinnamyl oxazolidin-2-one 35 (341.5 mg, 1 mmol) in anhydrous acetonitrile (5 mL) was added dropwise a deoxygenated solution of CAN (1.26 g, 2.3 mmol) in acetonitrile (10 mL) at room temperature over a period of 50 minutes. On completion of the reaction, it was processed as described in the general procedure. The residue on column chromatography on silica gel using hexane-ethyl acetate (80:20) afforded 223 mg (50%) of the product.
colourless viscous liquid

IR (neat) \( \nu_{\text{max}} \) : 2989, 2124, 1790, 1708, 1650, 1506, 1391, 1283, 1202, 1155, 1094, 1000, 852, 771, cm\(^{-1}\).

\(^1\)H NMR : \( \delta \) 7.45-7.39 (m, 9H, ArH), 6.14 (d, 1H, CHONO\(_2\), \( J = 10.0 \) Hz), 5.78 (d, 1H, CHN\(_3\), \( J = 7.2 \) Hz), 5.47 (d, 1H, CH, \( J = 10.0 \) Hz) 4.86-4.77 (m, 1H, CH), 0.96 (d, 3H, CH\(_3\)).

\(^{13}\)C NMR : \( \delta \) 165.92, 152.48, 136.39, 132.57, 132.26, 129.53, 129.21, 129.14, 128.89, 125.64, 80.91, 79.69, 60.84, 55.27, 14.35.

2-Azido-3-nitrato-3-phenyl-methylpropanoate(27)

A solution of azido oxazolidinone 26 (205 mg, 0.5 mmol) and scandium triflate (10 mol%) in methanol (2 mL) was heated under reflux under an atmosphere of argon for 24 hours. The reaction mixture was filtered through a silica gel pad to remove the catalyst. The filtrate was evaporated and the residue was subjected to column chromatography on silica gel to afford 213 mg (80%) of methyl cinnamate 28 and 152 mg (86%) of oxazolidinone 23.

IR (neat) \( \nu_{\text{max}} \) : 2990, 2119, 1735, 1647, 150, 1361, 1273, 1155, 1080, 1010, 842, 761, cm\(^{-1}\).

\(^1\)H NMR : \( \delta \) 7.41 (s, 5H, ArH), 6.13 (d, 1H, CHONO\(_2\), \( J = 7.0 \) Hz), 4.34 (d, 1H, CHN\(_3\), \( J = 7.0 \) Hz), 3.84 (s, 3H, OCH\(_3\)).

\(^{13}\)C NMR : \( \delta \) 170.46, 132.81, 129.90, 128.99, 127.00, 82.02, 63.70.

Enantiomeric excess of the product was determined by chiral shift reagent, tris[3-heptafluoro propyl hydroxy methylene(+)-camphorato]europium(III), Eu(hfc)\(_3\). For this racemic \( \alpha \)-azido-\( \beta \)-nitrato ester was prepared and 5 mg of the ester was dissolved in 0.5 ml of CDCl\(_3\). To this shift reagent was added in 5 mg lots until a good separation of the methoxy signals were obtained. The two COOCH\(_3\) groups shifted on adding shift reagent and a good separation of one of the methoxy groups were obtained with 40 mg
of the shift reagent. Similarly, in the case of 28 the ee was determined using 30 mg Eu(hfc)_3.

4.6 REFERENCES