The synthesis of novel nitrogen containing heterocycles

Arife Yazici
University of Wollongong
NOTE

This online version of the thesis may have different page formatting and pagination from the paper copy held in the University of Wollongong Library.

UNIVERSITY OF WOLLONGONG

COPYRIGHT WARNING

You may print or download ONE copy of this document for the purpose of your own research or study. The University does not authorise you to copy, communicate or otherwise make available electronically to any other person any copyright material contained on this site. You are reminded of the following:

Copyright owners are entitled to take legal action against persons who infringe their copyright. A reproduction of material that is protected by copyright may be a copyright infringement. A court may impose penalties and award damages in relation to offences and infringements relating to copyright material. Higher penalties may apply, and higher damages may be awarded, for offences and infringements involving the conversion of material into digital or electronic form.
The Synthesis of Novel Nitrogen Containing Heterocycles

A thesis submitted in (partial) fulfillment of the requirements for the award of the degree

DOCTOR OF PHILOSOPHY

From

UNIVERSITY OF WOLLONGONG

By

Arife YAZICI, Org. Chem. (Hons., M.Sc.)

Supervisor: Prof. Stephen G. Pyne

School of Chemistry
January 2010
THESIS CERTIFICATION

I, Arife Yazici, hereby declare that all material in this thesis, submitted in partial fulfillment of the requirements of the award of Doctor of Philosophy, in the Department of Chemistry, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. This document has not been submitted for qualifications at any other academic institution.

Arife YAZICI
Date:
To my husband and son.
ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisor, Prof. Stephen Pyne, for his wisdom, kindness and patience throughout the whole period of my PhD project. Without his knowledge, desire, drive and encouragement this degree would never have been completed. My special thanks for the support and patience during and after my pregnancy.

Secondly, I would like to thank my dearest husband Veysel Yazici for his love, support and help.

I would like to thank the technical staff in the School of Chemistry, particularly Dr. Wilford Lie, Dr. John Korth, Roger Kanitz and Roza Dimeska.

Special thanks to past and present members of the Pyne group, namely Dr Ian Morgan for induction and his help at the beginning of my project, Morwenna for her help and friendship, all Thai people, Chris, Kumara, Marc, Minyan, Uta, Sarah, and Andrew for their friendship.
PUBLICATIONS ARISING FROM THIS THESIS


ABSTRACT

This thesis reports on the development of new methods for the synthesis of functionalized pyrrolidines. These compounds are of important since they are the common ring structure that forms the bicyclic, heterocyclic core structure of the pyrrolizidine, indolizidine and Stemona alkaloids.

In Chapter 2 we report our efforts to develop a general method for preparing 4-hydroxy-5-substituted pyrrolidin-2-ones from the borono-Mannich reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones with boronic acids in the presence of BF$_3$·Et$_2$O. The 4,5-dihydroxypyrrolidin-2-one gave in two cases 4,5-
 cis adducts with very high $cis$ selectivity but in relatively low yields, while the 4-benzyloxy-5-hydroxypyrrolidin-2-one gave 4,5- $trans$ adducts with good $trans$ selectivity and in good to moderate yields. Unfortunately the desired dienyl 4,5-
 $cis$ adduct, required for the synthesis of the Stemona alkaloids, could only be obtained in the low yield of 33%. A RCM reaction of this compound gave the desired pyrrolo[1,2-$a$]azepine in 72% yield.

In Chapter 2 we also report the formation of a novel, Ritter reaction product, a pyrrolo[3,2-$b$]oxazole as an unwanted side product in the borono-Mannich reaction when acetonitrile was used as a solvent.

In Chapter 3 we describe an efficient synthesis of pyrrolo[3,2-$b$]oxazoles from the Ritter reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones with nitriles in the presence of BF$_3$·Et$_2$O. When 4-benzyloxy-5-hydroxypyrrolidin-2-one was used as the substrate the corresponding pyrrolo[3,2-$b$]oxazoles were formed along with the corresponding $N$-benzyl amides, which were formed from the Ritter reactions of benzyl cation and the nitrile. The isolation of these amide compounds were consistent with our proposed reaction mechanism. Two of the pyrrolo[3,2-$d$]oxazole compounds were hydrolyzed to novel 5-acylaminopyrrolidinones.

In Chapter 4 we report the metal-catalyzed cycloisomerization reactions of 3-hydroxy-2-alkynylpyrrolidine which was obtained from the borono-Mannich reaction of 2,3-dihydroxypyrrolidine and potassium phenylethynyltrifluoroborate. The cycloisomerization reaction of this pyrrolidine afforded a 2,5-disubstituted furan when Ag(I), Au(I) or Pd(II)/Cu(I) were used as a catalyst. While 3-halo-2,5-disubstituted furans were synthesized from the corresponding CuCl or CuBr
mediated reactions. Novel 3-iodo, 3-phenyl and 3-cyano substituted furo[3,2-
\textit{b}]pyrroles were synthesized from the reactions of the 3-hydroxy-2-
alkynylpyrrolidine with CuI, CuCN and PhI/Pd(dba)$_2$, respectively.

In Chapter 5 a novel method for the synthesis of 3-cyanoindoles is reported. This
method showed good tolerance to electron-donating and electron withdrawing
substituents on the starting \textit{ortho}-alkynylaniline and allowed 3-cyanoindoles to be
obtained in a single step. While the method of Wang provides 3-bromo and 3-chloro
indoles in one step from \textit{ortho}-alkynylaniline this method has not been extended to
make 3-cyanoindoles. Future studies could involve the examination of Wang’s
conditions using CuCN/O$_2$ instead of CuBr$_2$ or CuCl$_2$ to prepare 3-cyanoindoles.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>[α]_D</td>
<td>Specific Rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Ac_2O</td>
<td>Acetic anhydride</td>
</tr>
<tr>
<td>amu</td>
<td>Atomic mass unit</td>
</tr>
<tr>
<td>ArC</td>
<td>Aromatic carbon</td>
</tr>
<tr>
<td>ArCH</td>
<td>Aromatic methine</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>br. s</td>
<td>Broad singlet</td>
</tr>
<tr>
<td>CAN</td>
<td>Cerium ammonium nitrate</td>
</tr>
<tr>
<td>Cbz</td>
<td>Benzyloxy carbonyl</td>
</tr>
<tr>
<td>C_6D_6</td>
<td>Deuterated benzene</td>
</tr>
<tr>
<td>CDCl_3</td>
<td>Deuterated chloroform</td>
</tr>
<tr>
<td>CHCl_3</td>
<td>Chloroform</td>
</tr>
<tr>
<td>CH_2Cl_2</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>CH_3CN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>CH_3NO_2</td>
<td>Nitromethane</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlation spectroscopy</td>
</tr>
<tr>
<td>d</td>
<td>Day</td>
</tr>
<tr>
<td>d</td>
<td>Doublet (NMR)</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublets (NMR)</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>de</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EE</td>
<td>Ethoxyethyl</td>
</tr>
<tr>
<td>eq</td>
<td>Molar equivalents</td>
</tr>
<tr>
<td>Et_2O</td>
<td>Diethylether</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear multiple bond correlation</td>
</tr>
<tr>
<td>HREIMS</td>
<td>High resolution electron impact mass spectrometry</td>
</tr>
<tr>
<td>HRESIMS</td>
<td>High resolution electrospray ionization mass spectrometry</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear single quantum correlation</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared spectroscopy</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant (NMR)</td>
</tr>
<tr>
<td>Lit.</td>
<td>Literature</td>
</tr>
<tr>
<td>LREIMS</td>
<td>Low resolution electron impact mass spectrometry</td>
</tr>
<tr>
<td>LRESIMS</td>
<td>Low resolution electrospray ionization mass spectrometry</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet (NMR)</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>min</td>
<td>Minutes</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>Mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>NIS</td>
<td>N-Iodosuccinimide</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser enhancement spectroscopy</td>
</tr>
<tr>
<td>φ</td>
<td>Dihedral angle</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-Methoxybenzyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million (NMR)</td>
</tr>
<tr>
<td>q</td>
<td>Quartet (NMR)</td>
</tr>
<tr>
<td>RCM</td>
<td>Ring closing metathesis</td>
</tr>
<tr>
<td>Rf</td>
<td>Retardation factor</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet (NMR)</td>
</tr>
<tr>
<td>sat.</td>
<td>Saturated</td>
</tr>
<tr>
<td>TBS</td>
<td><em>tert</em>-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td><em>tert</em>-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>td</td>
<td>Triplet of doublets</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>(N,N,N,N)-Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane</td>
</tr>
</tbody>
</table>
TABLE OF CONTENTS

THESIS CERTIFICATION ................................................................. i
ACKNOWLEDGEMENTS ............................................................... iii
PUBLICATIONS ARISING FROM THIS THESIS ......................... iv
ABSTRACT ................................................................. v
ABBREVIATIONS .............................................................. vii
TABLE OF CONTENTS ........................................................ x
LIST OF FIGURES ................................................................. xiii
LIST OF SCHEMES ................................................................. xv
LIST OF TABLES ................................................................. xix

1. INTRODUCTION ........................................................................ 1
   1.1. Definition of Alkaloids ...................................................... 1
   1.2. History of Alkaloids .......................................................... 1
   1.3. Classification of Alkaloids .................................................. 2
   1.4. Occurrence and Distribution of Alkaloids ......................... 4
   1.5. Pyrrolizidine Alkaloids ....................................................... 5
   1.6. Indolizidine Alkaloids ......................................................... 8
   1.7. *Stemona* Alkaloids .......................................................... 10
   1.8. Alkaloids having a Furo[3,2-b]pyrrole Nucleus ................. 12
   1.9. Aims of the Project ......................................................... 13

2. DIASTEREOSELECTIVE BORONO MANNICH REACTIONS OF
   PYRROLIDINONES .............................................................. 16
   2.1. The Borono-Mannich Reaction ......................................... 20
   2.2. Borono-Mannich Reaction of Pyrrolidinones ..................... 24
       2.2.1. Borono-Mannich Reaction of (4S)-1-Benzyl-4,5-dihydroxy-
              pyrroolidin-2-one .............................................................. 24
       2.2.2. Borono-Mannich Reaction of (4S)-1-Benzyl-4-benzyloxy-5-
              hydroxypyrrolidin-2-one ....................................................... 35
       2.2.3. Borono-Mannich Reaction of (4S)-4,5-Dihydroxy-1-(pent-4-
              enyl)pyrroolidin-2-one .......................................................... 39
   2.3. Grignard Reaction of Succinimide 125 .................................. 44

3. DIASTEREOSELECTIVE RITTER REACTIONS OF
   PYRROLIDINONES .............................................................. 48
3.1. The Ritter Reaction ................................................................. 49
  3.1.1. Ritter Reactions of (4S)-1-Benzyl-4,5-dihydroxypyrrolidin-2-one ... 54
  3.2. Hydrolysis of Pyrrolo[2,3-\textit{d}]oxazoles ...................................................... 60

4. METAL CATALYZED CYCLOISOMERIZATION REACTIONS AND 
COPPER MEDIATED CYCLIZATION-HALOGENATION AND 
CYCLIZATION-CYANATION REACTIONS OF 2-ALKYNYL-3-HYDROXY 
PYRROLIDINES ..................................................................................................... 63
  4.1. Borono-Mannich Reactions of Benzyl 2,3-Dihyroxypyrrolidine-1- 
carboxylate ............................................................................................................. 68
  4.2. Metal-Catalyzed Cycloisomerization Reactions of the 2,3-\textit{cis} Pyrrolidine72
  4.3. Copper Mediated Cyclization-Halogenation and Cyclization-Cyanation 
Reactions of 2,3-\textit{cis} Pyrrolidine ............................................................................. 75

5. COPPER MEDIATED CYCLIZATION-CYANATION REACTIONS OF 
\textit{ORTH}-ALKYNYLANILINES ............................................................................. 88
  5.1. Synthesis of Indoles ................................................................................... 88
  5.2. Synthesis of 3-Cyanoindoles ...................................................................... 95
  5.3. Preparation of \textit{ortho}-Alkynylaniline Derivatives \textit{via} the Sonogashira 
Reaction .................................................................................................................. 96
    5.3.1. The Sonogashira Reaction ................................................................. 96
    5.3.2. Sonogashira Reactions of \textit{ortho}-Iodoaniline Derivatives ............... 98
  5.4. Protection Reactions of \textit{ortho}-Alkynylanilines ......................................... 101
  5.5. Cyclization-Cyanation Reactions of \textit{ortho}-Alkynylanilines .................... 104
    5.5.1. Attempts to Synthesise 3-Haloindoles ............................................. 110

6. CONCLUSIONS ............................................................................................ 112

7. EXPERIMENTAL .......................................................................................... 114
  7.1. General Experimental............................................................................... 114
    7.1.1. Reaction Conditions ......................................................................... 114
    7.1.2. Nuclear Magnetic Resonance (NMR) Spectroscopy ....................... 114
    7.1.3. Chromatography ........................................................................... 114
    7.1.4. Melting Points ................................................................................ 115
    7.1.5. Polarimetry ..................................................................................... 115
    7.1.6. Mass Spectrometry .......................................................................... 115
    7.1.7. Infrared Spectrometry .................................................................... 115
  7.2. Experimental for Chapter 2 ...................................................................... 115
LIST OF FIGURES

Figure 1.1. Structures of atropine 1, berberine 2, colchicine 3 and indicine N-oxide 4.................................................................3

Figure 1.2. Structures of morphine 5, caffeine 6, aconitine 7 and coniine 8. ....3

Figure 1.3. Structures of pederin 9, pederone 10 and pseudopederin 11 and a photo of the Paederus. .................................................................4

Figure 1.4. Structures of samandarine 12 and samandenone 13 and a photo of the alpine salamander.................................................................4

Figure 1.5. Structures of retrocine 14, rosmarinine 15 and monocrotaline 16........5

Figure 1.6. Pyrrolizidine alkaloids from legumes 17-21......................................................6

Figure 1.7. The seeds of Castanospermum australe (picture taken from Wikipedia).20 .................................................................6

Figure 1.8. a) Hyacinthoides non-scripta (bluebells)24 b) Scilla campanulata25 c) Muscari armeniacum26 d) Scilla sibirica27 (pictures taken from Wikipedia)......7

Figure 1.9. Structures of hyacinthacines 22-35……………………………………………………8

Figure 1.10. Structures of polyhydroxylated indolizidine alkaloids 36-43.…………………9

Figure 1.11. Astragalus lentiginosus (picture taken from Wikipedia)34 ..................10

Figure 1.12. Classification of Stemona alkaloids………………………………………………11

Figure 1.13. Structures of stemocurtisine 44, stemocurtisinol 45 and oxyprotostemonine 46...........................................................................11

Figure 1.14. Structures of lucilactaene 47, fusarin A 48 and UCS1025A 49. ........12

Figure 2.1. 1H NMR spectrum (500 MHz, CDCl3) of 127. ........................................29

Figure 2.2. 1H NMR spectrum (500 MHz, CDCl3) of 132 without purification........30

Figure 3.1. Structures of odorine 186 and odorinol 187. ........................................48

Figure 3.2. 1H NMR (500 MHz, CDCl3) spectrum of 129...........................................55

Figure 3.3. 13C NMR (125 MHz, CDCl3) spectrum of 129. ......................................56

Figure 3.4. Calculated dihedral angles of 129 using Spartan 04 (AMI). ..................56

Figure 3.5. The observed NOE correlations of 129. ...............................................57

Figure 3.6. 1H NMR (500 MHz, CD3OD) spectrum of 185. ......................................61

Figure 3.7. 1H NMR (500 MHz, CDCl3) spectrum of 236........................................62

Figure 4.1. 1H NMR (500 MHz, CDCl3) spectrum of 270........................................73

Figure 4.2. 13C NMR (125 MHz, CDCl3) spectrum of 270. ......................................73

Figure 4.3. 1H NMR (500 MHz, CDCl3) spectrum of 280........................................78
Figure 4.4. $^1$H NMR (500 MHz, CDCl$_3$) spectrum of 284................................. 81
Figure 5.1. $^1$H NMR (500 MHz, CDCl$_3$) spectrum of 368................................. 105
Figure 5.2. $^1$H NMR (500 MHz, CDCl$_3$) spectrum of 369................................. 105
LIST OF SCHEMES

1. Proposed synthesis of pyrrolidine based alkaloids
2. Proposed synthesis of the furo[3,2-b]pyrroles
3. General Scheme for Chapters 2 and 3
4. General Scheme for Chapter 4
5. General Scheme for Chapter 5
6. Retrosynthetic analysis for 2-alkyl-3-hydroxypyrrolidines
7. Reactions of pyrrolidinones with TMSCN
8. Reactions of pyrrolidinones with organosilyl compounds
9. Synthesis of 4,5-cis pyrrolidinones
10. Reactions of with indoles
11. Reaction of with 2-naphthol
12. Reaction of pyrrolidinone with tributylstannane cyanide
13. Reactions of pyrrolidinones with allyltributyltin
14. Reaction of with vinylmagnesium bromide
15. Reactions of with Grignard reagents
16. Proposed mechanism of the Petasis reaction
17. Alternative proposed mechanism of the borono-Mannich reaction
18. Synthesis of (-)-cytoxazone
19. Synthesis of castanospermine
20. Retrosynthetic analysis for 119
21. Synthesis of 124 and 126
22. Formation of boronate complex
23. Attempts to synthesize 5-styrylpyrrolidine from boronate complex
24. Proposed mechanism for the synthesis of 127 from 128
25. Synthesis of 127 and 132
26. Synthesis of epoxide
27. Epimerization of 124
28. Formation of the dimer
29. Comparison of the C4 and C5 $^{13}$C NMR chemical shifts of 132 and 135
30. Reactions of epoxide
Scheme 2.26. Results of Borono-Mannich reactions of 124 ........................................... 33
Scheme 2.27. Formation of cis and trans pyrrolidinones and boronate complex .... 33
Scheme 2.28. Debenzylation of 149 .............................................................................. 36
Scheme 2.29. Mechanism of formation of trans product ............................................. 37
Scheme 2.30. Borono-Mannich adducts of 126 ............................................................ 38
Scheme 2.31. Alternative synthesis of 151 ..................................................................... 38
Scheme 2.32. RCM reaction of 52 ................................................................................ 39
Scheme 2.33. Retrosynthetic analysis for N-pentenyl derivative 157 ......................... 40
Scheme 2.34. Synthesis of 164 ..................................................................................... 40
Scheme 2.35. Deprotection reaction of 164 .................................................................... 41
Scheme 2.36. Synthesis of 167 ..................................................................................... 41
Scheme 2.37. Synthesis of 157 ..................................................................................... 42
Scheme 2.38. RCM reaction of 171 ............................................................................... 43
Scheme 2.39. Two ways for the reparation of 5-substituted pyrrolidines .................. 44
Scheme 2.40. Result of reaction of 125 with phenylvinylmagnesium bromide ...... 46
Scheme 2.41. Proposed mechanism for the formation of 180 ...................................... 46
Scheme 2.42. Debenzylation of 180 and 149 ................................................................. 47
Scheme 3.1. Synthetic pathway to 185 ........................................................................... 48
Scheme 3.2. Synthesis of odorine 186 ........................................................................... 49
Scheme 3.3. Ritter reactions of alkenes 195 and alcohols 197 .................................... 49
Scheme 3.4. Mechanism of the Ritter reaction ............................................................. 50
Scheme 3.5. Ritter reaction of 205 and 206 ................................................................. 51
Scheme 3.6. Proposed mechanism for the formation of imidazoles 210 .................. 52
Scheme 3.7. Synthesis of 2-oxazoles 217 ..................................................................... 52
Scheme 3.8. Synthesis of oxazolines 219 ..................................................................... 53
Scheme 3.9. Proposed mechanism for the formation of oxazolines 219 ............... 53
Scheme 3.10. The Holy reaction of arabinose 223 with cyanamide. ......................... 53
Scheme 3.11. Proposed mechanism for the formation of 129 .................................... 57
Scheme 3.12. Reaction of 126 with CH$_3$CN ............................................................... 58
Scheme 3.13. Proposed mechanism for the Ritter reaction of 129 and formation of 230 .............................................................................................................................. 59
Scheme 3.14. Attempted oxidation reactions of 229a and 229b .............................. 60
Scheme 3.15. Acidic hydrolysis of 129 .......................................................................... 60
Scheme 3.16. Acidic hydrolysis of 229a ...................................................................... 61
Scheme 4.1. Proposed synthesis of furo[3,2-b]pyrroles 57 ........................................ 63
Scheme 4.2. Mechanism of metal-catalyzed cycloisomerization reactions of alkynes 237 ............................................................................................................. 64
Scheme 4.3. Utimoto’s synthesis of furans 242 ................................................... 64
Scheme 4.4. Synthesis of 244 ............................................................................. 64
Scheme 4.5. Synthesis of furopyridines 246a and 246b ................................. 65
Scheme 4.6. Synthesis of 2,3-dihydroisoxazoles 248 ....................................... 65
Scheme 4.7. Preparation of bicyclic ketals 250 .................................................. 66
Scheme 4.8. Proposed mechanism for the formation of bicyclic ketals 250 ...... 66
Scheme 4.9. Synthesis of 2-substituted benzofurans 256 .................................. 67
Scheme 4.10. Synthesis of diol 116 ................................................................... 68
Scheme 4.11. Synthesis of 262 .......................................................................... 69
Scheme 4.12. Synthesis of racemic trans-263 ................................................... 71
Scheme 4.13. Formation of the 2,3-trans product 268 ....................................... 72
Scheme 4.14. Synthesis of 2,5-disubstituted furan 270 ..................................... 73
Scheme 4.15. Results of the treatment of trans-263 with Ag(I) or Au(I) ....... 75
Scheme 4.16. Synthesis of 3-iodobenzofurans and indoles ............................ 76
Scheme 4.17. Synthesis of iodofurans 274 ....................................................... 76
Scheme 4.18. Synthesis of 3-iodobenzofurans 276 ........................................... 76
Scheme 4.19. Synthesis of 3-halo-2-substituted benzofurans ......................... 77
Scheme 4.20. The proposed mechanism for the formation of 270 and 280 ...... 79
Scheme 4.21. Reaction of cis-263 with I2 and NaHCO3 .................................... 79
Scheme 4.22. Reaction of cis-263 with NIS ....................................................... 80
Scheme 4.23. Reaction of cis-263 with CuBr ...................................................... 80
Scheme 4.24. Reaction of cis-263 with CuCl ....................................................... 81
Scheme 4.25. Reaction of cis-263 with CuCN ..................................................... 82
Scheme 4.26. Reaction of cis-263 with CuI under an O2 atmosphere ............. 82
Scheme 4.27. Reaction of 280 with CuI .............................................................. 83
Scheme 4.28. Treatment of 270 with NIS ......................................................... 83
Scheme 4.29. Treatment of 270 with NBS .......................................................... 84
Scheme 4.30. Reaction of cis-263 with CuCN under O2 atmosphere ............. 85
Scheme 4.31. Treatment of trans-263 with CuI and CuCN .............................. 85
Scheme 4.32. Reaction of cis-263 with CuBr2 .................................................... 86
Scheme 4.33. Tandem cyclization-cross coupling reaction of cis-263 ............. 86
Scheme 5.1. Proposed synthesis of 3-halo and 3-cyano indoles

Scheme 5.2. Three methods for the synthesis of indole ring.

Scheme 5.3. Synthesis of 5,6-difluorindole

Scheme 5.4. Synthesis of oxygen-bearing substituted indoles

Scheme 5.5. Synthesis of 2-substituted-NH-indoles

Scheme 5.6. The proposed mechanism of Pd(II)-catalyzed cyclization of 2-alkynylanilines.

Scheme 5.7. One-pot synthesis of indoles.

Scheme 5.8. One-pot synthesis of 2,3-disubstituted indoles

Scheme 5.9. Palladium catalyzed reactions of 321 with 322.

Scheme 5.10. Microwave-assisted synthesis of indoles.

Scheme 5.11. Synthesis of 3-haloindoles.

Scheme 5.12. The proposed mechanism for the formation of 3-haloindoles

Scheme 5.13. Solid phase synthesis of 3-cyano indoles.


Scheme 5.15. PIDA-mediated synthesis of 3-cyanoindoles

Scheme 5.16. Synthesis of 5-cyanoindole.

Scheme 5.17. The Sonogashira reaction.

Scheme 5.18. The mechanism of the Sonogashira coupling reaction.

Scheme 5.19. Sonogashira reaction of ortho-iodoaniline

Scheme 5.20. Synthesis of 2-bromo-4-methoxyaniline

Scheme 5.21. Sonogashira reactions of 353 and 355.

Scheme 5.22. The Sonogashira reaction of 2-iodoaniline 347 and 1-heptyne.

Scheme 5.23. Treatment of 349 with CuCN.

Scheme 5.24. The reaction of 349 with TsCl and (CF₃CO)₂O.

Scheme 5.25. Reaction of 357 with TsCl and (CF₃CO)₂O.


Scheme 5.27. Cyclization-cyanation reactions of 363 and 364.

Scheme 5.28. Cyclization-cyanation reaction of 365.

Scheme 5.29. Synthesis of 3-cyano-2-pentylindole.

Scheme 5.30. Reaction of 366 with CuCN.

Scheme 5.31. Attempts to synthesize 3-cyanoindole by using 10 mol% of CuCN.

Scheme 5.32. Attempts to make 3-haloindoles.
LIST OF TABLES

Table 2.1. Selected results from Petasis’s paper^59^.................................................................... 21
Table 2.2. Selected results from Batey’s paper^66^........................................................................ 23
Table 2.3. Yields of boronate ester 128 and Ritter product 129.............................................. 26
Table 2.4. Comparison of selected ^1^H NMR chemical shifts of 132 and 133........... 31
Table 2.5. Selected J$_{4,5}$ values for cis and trans pyrrolidines from the literature^68-70^........................................................................................................................................... 34
Table 2.6. J$_{4,5}$ values of pyrrolidinones.............................................................................. 34
Table 2.7. Optimization of borono-Mannich reaction of 126 ........................................... 36
Table 2.8. J$_{4,5}$ values of products of Borono-Mannich reaction of 126. ...................... 37
Table 2.9. Results of borono-Mannich reaction of 157........................................................ 43
Table 2.10. Results of treatment of 125 with organoboron compounds. ......................... 45
Table 3.1. Results of the Ritter reaction of alkenes 195 and alcohols 197^76^.................... 50
Table 3.2. Synthesis of imidazoles.......................................................................................... 51
Table 3.3. Results of reaction of 124 with CH$_3$CN.............................................................. 54
Table 3.4. Ritter reactions of 124.............................................................................................. 58
Table 3.5. Results of Ritter reaction of 126.............................................................................. 59
Table 4.1. Synthesis of 2-methylene-oxolanes 254a-e................................................................ 67
Table 4.2. Optimization of borono-Mannich reaction of 116 and 262.......................... 70
Table 4.3. Cycloisomerization of cis-263 with Ag(I).............................................................. 74
Table 4.4. Cycloisomerization of cis-263 with Au(I) or Pd(II)/Cu(I) catalysts................. 75
Table 4.5. Synthesis of 270 and 280...................................................................................... 78
Table 4.6. Reactions of cis-263 with copper salts under O$_2$ atmosphere........................... 84
Table 5.1. Results of protection of ortho-alkynylanilines...................................................... 103
Table 5.2. Optimization of cyclization-cyanation reaction of 359...................................... 105
Table 5.3. Optimization of cyclization-cyanation reaction of 360...................................... 106
1. INTRODUCTION

1.1. Definition of Alkaloids
Meissner first proposed the word “alkaloid” in 1819.\(^1\) He described alkaloids as plant-derived substances that react like alcalis. His definition was put forward at a time when only few plant bases were known.\(^1,2\) In 1896 Guareschi described the alkaloids as basic organic compounds whether obtained from animal or plant materials, or prepared artificially. His definition is synonymous with organic base or organic alkali. In 1910 Winterstein and Trier described alkaloids as compounds with nitrogen atoms bound in a heterocyclic fashion, with a greater or lesser degree of basic character, marked physiological effects, complicated molecular structure, which are found in plants, and, with a few exceptions, are characteristic for particular plant families, genera or species.\(^1,2\) Another definition was made by Stoll in 1953 which described alkaloids as nitrogen-containing bases of vegetable origin. In 1983, Pelletier described alkaloids as cyclic organic compounds containing nitrogen in a negative oxidation state which are of limited distribution among living organisms. Although many definitions of alkaloids have been made, none of them are fully satisfactory. For instance, it is clear that not all alkaloids are heterocyclic or even cyclic and they are not necessarily physiologically active. Moreover, it is now accepted that the occurrence of alkaloids is not restricted to plants. It is obvious that alkaloids are most commonly found in plants but they are also found in animals. Hydroxylated tyrosine or tryptamine derivatives are the most common alkaloids found in mammals. Thus alkaloids occur in all types of living organisms. In view of all this information the general definition may be “Alkaloids are nitrogen-containing organic substances of natural origin with a greater or lesser degree of basic character”.\(^1\)

1.2. History of Alkaloids
Humans have been using alkaloids as drugs, medicines, teas and poisons for 4000 years. They used plants which contained arrow poisons in hunting or in dealing with enemies. These poisons are still in use in Africa and South America. Alkaloids that were isolated from arrow poison have been used in the treatment of glaucoma and myasthenia gravis, as a muscle relaxant in anesthesia and as an antihypertensive.\(^3\) The first crude drug was from the opium poppy, which had been used for its
analgesic and narcotic properties for centuries. In 1805 Serturner isolated morphine from opium. Between the years 1817 and 1820 many biologically active compounds were isolated from plants, including styrchnine, emetine, brucine, caffeine, quinine, cinchocine and colchicine. This pioneering work formed the cornerstone of all that has occurred in alkaloid chemistry to the present. The number of alkaloids that had been isolated and identified was 200 in 1939 and by 1989, 10,000 alkaloids were known. Currently there are over 27000 known alkaloids.

1.3. **Classification of Alkaloids**

Alkaloids can be classified according to the nature of the nitrogen atom or according to their biogenetic origins. They have been classified into four groups according to the nature of the nitrogen atom (Figure 1.1). These four groups include:

1. Secondary or tertiary amines which are protonated and therefore hydrophilic at pH < 7.0, and lipophilic at pH > 8.0. e.g., atropine 1;
2. Quaternary amino compounds which are very polar and charged at all pH values. e.g., berberine 2;
3. Neutral amino compounds which include the amide-type alkaloids. e.g., colchicine 3;
4. N-oxides, which are generally highly soluble in water, the pyrrolizidine group of alkaloids being rich in this alkaloid type. e.g., indicine N-oxide 4.

Alkaloids can also be classified into four groups according to their biogenetic origins (Figure 1.2). These four groups include:

1. Alkaloids derived from amino acids. e.g., morphine 5, ornithine, arginine, lysine, histidine and phenylalanine;
2. Purine alkaloids. e.g., caffeine 6 and xanthine;
3. Aminated terpenes. e.g., aconitine 7 and the triterpene solanine;
4. Polyketide alkaloids. e.g., coniine 8 and the coccinellines.

The number of new alkaloids continues to increase as more insect and marine organisms are investigated.
Figure 1.1. Structures of atropine 1, berberine 2, colchicine 3 and indicine N-oxide 4.

Figure 1.2. Structures of morphine 5, caffeine 6, aconitine 7 and coniine 8.
1.4. Occurrence and Distribution of Alkaloids

In the past the major source of alkaloids were flowering plants, the *Angiospermea*. In recent years a large number of alkaloids have been isolated from animals, insects, marine organisms, microorganisms and lower plants. Alkaloids in animals can act as defensive compounds or as chemical signals. A powerful cytotoxin, pederin 9 was isolated from the genus *Paederus* (Figure 1.3). It is toxic when digested and causes dermatoxic wounds when it is applied to the skin of animals. Two close derivatives, pseudopederin 10 and pederone 11 were also isolated from the same genus (Figure 1.3).

![Paederus](https://example.com/paederus.png)

**Figure 1.3.** Structures of pederin 9, pederone 10 and pseudopederin 11 and a photo of the *Paederus*.

Salamanders are known to be toxic. The alpine salamander toxins have been found to be the steroidal alkaloids, samandarine 12 and samandenone 13 (Figure 1.4).

![Samandarine](https://example.com/samandarine.png)

![Samandenone](https://example.com/samandenone.png)

**Figure 1.4.** Structures of samandarine 12 and samandenone 13 and a photo of the alpine salamander.
While there are a large number of different structural classes of alkaloids this Chapter will only discuss the alkaloid classes that are relevant to this thesis.

1.5. **Pyrrolizidine Alkaloids**

Pyrrolizine alkaloids are a diverse class of naturally occurring compounds. Over 350 pyrrolizidine alkaloids have been isolated from more than 6000 plant species belonging to Boraginaceae, Leguminoseae and Asteraceae families.\(^7\),\(^12\) The main groups of pyrrolizidine alkaloids are based on necines. They are mono or diesters of the 1-hydroxymethyl-7-hydroxy-1,2-dehydropyrrolizine structure. They may have 1, 2 or 3 hydroxyl groups and 1 or 2 double bonds. Typical alkaloids are retrocine \(^{14}\), rosmarine \(^{15}\) and monocrotaline \(^{16}\) that were isolated from the *Senecio* genus (Figure 1.5).

![Figure 1.5. Structures of retrocine 14, rosmarinine 15 and monocrotaline 16.](image)

More recently several 3-hydroxymethylpyrrolizidines alkaloids have been isolated. In 1988, the polyhydroxylated pyrrolizidine alkaloid alexine \(^{17}\) was isolated from the pods of the legume *Alexa leiopetala* (Figure 1.6).\(^{13}\) It was the first example of a pyrrolizidine alkaloid having a carbon substituent at the C-3 position.\(^{14},^{15}\) At about the same time australine \(^{18}\) was isolated from the seeds of *Castanospermum australe* (Figure 1.7), which was found to be 7-epi-alexine by X-ray crystallographic analysis.\(^{16}\) Later, 1-epi-australine \(^{19}\), 3-epi-australine \(^{20}\) and 7-epi-australine \(^{21}\)
(Figure 1.6) were isolated from the same plant. The structures of 1-epi-australine 19 and 3-epi-australine 20 were also identified by X-ray crystallographic analysis.\textsuperscript{17-19} The structure of 7-epi-australine 21 was assigned based on NMR spectroscopic studies. The synthesis of australine 18 and 7-epi-australine 21 and extensive studies on both natural and synthetic australine 18 isomers elucidated that the natural product reported as 7-epi-australine 21 was actually australine. As a result, 7-epi-australine 21 has not yet been found as a natural product. These polyhydroxylated pyrrolizidine alkaloids are of medicinal chemistry interest as they are inhibitors of glycosidases.\textsuperscript{7}

![Pyrrolizidine alkaloids from legumes 17-21.](Please see print copy for image)

**Figure 1.6.** Pyrrolizidine alkaloids from legumes 17-21.

![The seeds of *Castanospermum australe* (picture taken from Wikipedia).](Please see print copy for image)

**Figure 1.7.** The seeds of *Castanospermum australe* (picture taken from Wikipedia).\textsuperscript{20}
Alexine and the australines have also been isolated from two small genera of Leguminose (Castanospermum and Alexia). It was initially thought that the occurrence of polyhydroxylated 3-hydroxypyrrolizidine alkaloids would be restricted. However, many such alkaloids were found from a different family, Hyacinhaceae. In 1999, several new pyrrolizidine alkaloids were isolated from this family and named as hyacinthacines. Hyacinthacines B₁ 22 and B₂ 23 (Figure 1.9) were isolated from the immature fruits and stalks of Hyacinthoides non-scripta (Figure 1.8) and hyacinthacine C₁ 24 (Figure 1.9) was isolated from the bulbs of Scilla campanulata (Figure 1.8). 21 Four novel hyacinthacines, A₁ 25, A₂ 26, A₃ 27 and B₃ 28 (Figure 1.9) were isolated from the bulbs of Muscari armeniacum (Figure 1.8). 22 Seven new hyacinthacines, A₄ 29, A₅ 30, A₆ 31, A₇ 32, B₄ 33, B₅ 34, and B₆ 35 (Figure 1.9), were found from the GC-MS analysis of extract of S. sibirica (Figure 1.8). 23 Many of these species are common as garden plants, for example “bluebells” (Hyacinthoides non-scripta) (Figure 1.8).

Figure 1.8. a) Hyacinthoides non-scripta (bluebells) 24 b) Scilla campanulata 25 c) Muscari armeniacum 26 d) Scilla sibirica 27 (pictures taken from Wikipedia).
Figure 1.9. Structures of hyacinthacines 22-35.

1.6. Indolizidine Alkaloids

Indolizidine alkaloids have a fused 5- and 6-membered ring. Over 170 indolizidine alkaloids have been isolated from a diverse group of organisms. They are also known to occur in frogs, toads and orchidaceae species.28,29 Like the polyhydroxylated
pyrrolizidine alkaloids, the polyhydroxylated indolizidine alkaloids also are known
to inhibit glycosidases. The polyhydroxylated indolizidine alkaloid swainsonine 36
(Figure 1.10), was detected in two members of the genus Ipomoea which were I. sericophylla and I. riedelli. Mezher reported the first total synthesis of swainsonine
and confirmed its absolute configuration in 1984. The polyhydroxylated
indolizidine alkaloid, castanospermine 37, was isolated from the immature seeds of
Castanospermum australe (Figure 1.7) in 1981 (Figure 1.10). Four indolizidine
alkaloids, 6-epi-castanospermine 38, 7-deoxy-6-epi-castanospermine 39, 6,7-diepi-
castanospermine 40 and 6,8-diepi-castanospermine 41 (Figure 1.10) were also
isolated from the seeds of the same plant. Lentiginosine 42 and 2-epi-lentiginosine
43 (Figure 1.10) were found in the leaves of Astragalus lentiginosus (Figure 1.11).
These two indolizidine alkaloids were shown to be biosynthesized from (1R)-1-
hydroxyindolizidine by hydroxylation at C-2.

Figure 1.10. Structures of polyhydroxylated indolizidine alkaloids 36-43.
1.7. **Stemona Alkaloids**

The *Stemona* alkaloids have been isolated from the monocotyledonous family *Stemonaceae*. The *Stemonaceae* comprises three genera, *Croomia, Stemona*, and *Stichoneuron*, mainly distributed in China, Japan and South-East Asia. *Stemona* is the largest genus with 25 species and can be easily distinguished by tetramerous flowers. Many of the *Stemona* alkaloids have biological and insecticidal activities. The tuberous roots and herbal extracts of *S. japonica, S. sessilifolia* and *S. tuberosa* have been used in Chinese, Japanese and Vietnamese traditional medicine for the treatment of respiratory diseases and have also been used against *Enteric helminths* and ectoparasites on humans.\(^{35,36}\) The roots of these plants are also widely used as insecticides and for medicinal purposes. In Thailand the roots of *S. cutisii* are used to protect pepper plants against insects.\(^{35,36}\)

In 1973 only seven *Stemona* alkaloids had been described with a defined structure. In 2000 Pilli and Ferreira listed 42 structures which they separated into five structural groups.\(^{36}\) In the meantime the number of *Stemona* alkaloids has been nearly doubled, now containing 82 derivatives. Among these alkaloids only four alkaloids had been isolated from the *Croomia* and *Stichoneuron* species, all the other derivatives were isolated from the *Stemona* species.\(^{36}\) Based on structural considerations and their species of origin the *Stemona* alkaloids have more recently been classified into three skeletal types, the stichoneurine-, protostemonine-, and croomine-type alkaloids (Figure 1.12). The three groups can be distinguished by different carbon chains attached to C-9 of the pyrrolo[1,2-a]azepine nucleus.\(^{36}\) The *croomine* type A contains four carbon atoms forming a lactone ring directly attached to C-9 in a spiro system. The *stichoneurine* B and *protostemonine* C type contain eight carbon atoms forming
a terminal lactone, but differ in their branching patterns. The genera *Croomia* and *Stichoneuron* produce only croomine and stichoneurine derivatives, respectively while the genus *Stemona* produces all three types of alkaloids.\(^{37}\)

\[\text{A} \quad \text{croomine-type}\]

\[\text{B} \quad \text{stichoneurine-type}\]

\[\text{C} \quad \text{protostemonine-type}\]

**Figure 1.12.** Classification of *Stemona* alkaloids.

**Figure 1.13.** Structures of stemocurtisine 44, stemocurtisinol 45 and oxyprotostemonine 46.

The *Stemona* alkaloids were first thought to be based upon a pyrrolo[1,2-\(a\)]azepine core. In 2003 Pyne\(^{38}\) isolated a new *Stemona* alkaloid stemocurtisine 44 which was based on a pyrrido[1,2-\(a\)]azepine core, a new structural type of *Stemona* alkaloid.
After one year the same group isolated two more alkaloids, stemocurtisinol 45 and oxyprotostemonine 46, from the roots of the same plant. Stemocurtisinol 45 is based upon a pyrrolo[1,2-α]azepine core, while oxyprotostemonine 46 is based upon a pyrrolo[1,2-α]azepine core (Figure 1.13). These alkaloids showed good larvicidal activity on malaria carrying mosquito larvae.39

1.8. Alkaloids having a Furo[3,2-b]pyrrole Nucleus

The furo[3,2-b]pyrrole nucleus is a common motif in a relatively small number of biologically active natural products for example lucilactene 47, 13α-lucilactaene, fusarin A 48 and D, UCS1025A 49 and B (Figure 1.14). Lucilactaene 47 was isolated from a strain of fungi from the genus Fusarium in 2001 by Osada.40 It was found to inhibit the cell-cycle in p53-transfected cancer cells. p53 is the tumour suppressor gene which controls cell cycle progression.41 It plays a critical role in apoptosis and in DNA repair. In many human tumours this gene is mutated and inactive.42 Fusarin A 48 and D were isolated from Fusarium moniliforme in 1992.43 The alkaloids UCS1025A 49 and B were discovered in the fermentation broth of the fungus Acremonium species. UCS1025A exhibited antimicrobial activity and antiproliferative activity against human tumour cell lines.44

Figure 1.14. Structures of lucilactaene 47, fusarin A 48 and UCS1025A 49.
Aims of the Project

The synthesis of pyrrolizidine, indolizidine and *Stemona* alkaloids are very desirable for structure-activity relationship studies since many of them are biologically active compounds. In this project we aimed to develop a common synthetic method to obtain the bicyclic heterocyclic core structures of the pyrrolizidine, indolizidine and *Stemona* alkaloids. In our synthetic approach (Scheme 1.1) these bicyclic cores (53) would be obtained from the ring closing metathesis (RCM) reactions of the \(N\)-alkenyl-5-styrylpyrrolidinones 52. The 4-benzyloxy or 4-hydroxy-5-alkenylpyrrolidines 52 would be obtained from the borono-Mannich reaction of 4-benzyloxy or 4-hydroxy-5-hydroxypyrrolidinone 50 and styrenylboronic acid.

Scheme 1.1. Proposed synthesis of pyrrolidine based alkaloids.

We also aimed to synthesize the furo[3,2-\(b\)]pyrroles 57 using a similar initial strategy. This heterocyclic core structure could be obtained from the metal catalysed cycloisomerization reactions of 2-alkynyl-3-hydroxypyrrolidines 56. The 2-alkynyl-3-hydroxypyrrolidines 56 could be obtained from the borono-Mannich reaction of 2,3-dihydroxypyrrolidine 54 and an alkynylboronic acids (Scheme 1.2). These borono-Mannich reactions would be expected to proceed through the \(N\)-acyliminium ion intermediates 51 and 55, respectively. As part of this PhD project two comprehensive review articles on the intermolecular reactions of \(N\)-acyliminium ions were written and published in *Synthesis* in 2009.\textsuperscript{45,46} These review articles are included as Appendices 1 and 2 of this thesis.

The results and discussion section of this thesis is divided into four chapters, Chapters 2-5. In Chapter 2 the reactions of in situ generated N-acyliminium ions 59 with organoboron compounds (borono-Mannich reaction) are reported in terms of product yields and diastereoselectivities. The RCM reaction of a N-alkenyl 5-styrylpyrrolidine was also examined. In Chapter 3, the reactions of N-acyliminium ions with nitriles (Ritter reaction) are documented along with the hydrolysis reactions of the adducts 61 to give novel 4-hydroxy-5-acylaminopyrrolidonones 62 (Scheme 1.3).

Scheme 1.3. General Scheme for Chapters 2 and 3.
In Chapter 4, the metal-catalyzed cycloisomerization reactions and copper-mediated cyclization-cyanation and cyclization-halogenation reactions of the 4-hydroxy-5-alkynylpyrrolidines 63 are reported (Scheme 1.4).

Scheme 1.4. General Scheme for Chapter 4.

In Chapter 5 the results of the copper mediated cyclization-cyanation reactions of 2-alkynylanilines 66 are described (Scheme 1.5).

Scheme 1.5. General Scheme for Chapter 5.
2. DIASTEREOSELECTIVE BORONO MANNICH REACTIONS OF PYRROLIDINONES

In this Chapter we report our efforts to develop a general method for preparing 4-hydroxy-5-substituted pyrrolidin-2-ones 71 from the reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones 69 with boronic acids (Scheme 2.1). For the specific synthesis of our target molecules we required these reactions to be highly diastereoselective in favour of either the 4,5-\textit{cis} or 4,5-\textit{trans} adducts. In the case of \textit{Stemona} alkaloid synthesis we specifically required a synthesis of the 4,5-\textit{cis} isomer 72 (n = 3).

\[ \text{R}_{1}^{O} \text{N} \text{R}_{2}^{O} \text{R} \text{O} \]

\[ \text{R}^{3} \text{B(OH)}_{2} \]

\[ \text{BF}_{3} \text{Et}_{2}O \]

\[ \text{Ph} \]

\[ \text{RCM} \]

\[ \text{O} \]

\[ \text{Ph} \]

\[ \text{B(OH)}_{2} \]

\[ \text{R}_{3}^{O} \text{N} \text{R}_{2}^{O} \text{R} \text{O} \]

\[ \text{70} \]

\[ \text{71} \]

\[ \text{73} \]

\[ \text{72} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]

\[ \text{77} \]

\[ \text{72} \]

\[ \text{73} \]

\[ \text{74} \]

\[ \text{76} \]
products \((cis : trans = 73 : 27\) and \(66 : 34\), respectively) while the pyrrolidinone 75 gave the 4,5-\(trans\) product with a \(trans : cis\) ratio of \(61 : 39\). Treatment of the \(N\)-substituted-5-acetoxypyrrolidin-2-ones 78 with silicon based nucleophiles under the catalysis of TIPSOTf, HNTf₂, or NbCl₅ yielded the 4,5-\(trans\) pyrrolidinones 79 with high diastereselectivities (Scheme 2.3).⁴⁸⁻⁵⁳ Interestingly, treatment of the \(N\)-unsubstituted 4-OTBS-5-methoxypyrrolidinone 80 with organosilyl compounds afforded the 4,5-\(cis\) adducts 81 in yields of 26-89% (Scheme 2.4).⁵⁰

Scheme 2.2. Reactions of pyrrolidinones 74-76 with TMSCN.

Scheme 2.3. Reactions of pyrrolidinones 78 with organosilyl compounds.

Scheme 2.4. Synthesis of 4,5-\(cis\) pyrrolidinones 81.
Reactions of the pyrrolidinones 82 and 84 with electron-rich aromatics such as indoles and 2-naphthol also gave the 4,5-trans pyrrolidinone products. Treatment of pyrrolidinone 82 with indoles furnished the 4,5-trans adducts 83a and 83b in respective yields of 90% and 75%, with diastereomeric ratios of 86 : 14 and 94 : 16, respectively (Scheme 2.5).49 The reaction of pyrrolidinone 84 with 2-naphthol gave the 4,5-trans product 85 exclusively in 76% yield (Scheme 2.6).54

Scheme 2.5. Reactions of 82 with indoles.

Scheme 2.6. Reaction of 84 with 2-naphthol.

Treatment of the pyrrolidinone 74 with tributylstannane cyanide furnished the 4,5-cis adduct 86 as the major product (Scheme 2.7).47 While, treatment of N-allyl-4,5-diacetoxypyrrolidinone 87 with allyltributylstannane in the presence of magnesium bromide gave a 67 : 33 diastereomeric mixture of cis and trans products 88. Its 4-OTBS analogue gave a mixture of cis and trans allylated products in a ratio of 69 : 31, respectively (Scheme 2.8).55,56
Scheme 2.7. Reaction of pyrrolidinone 74 with tributylstannane cyanide.

Scheme 2.8. Reactions of pyrrolidinones 87 with allyltributyltin.

The 4,5-\textit{trans} pyrrolidinones have also been synthesized \textit{via} the reaction of 5-acetoxy and 5-phenylsulfonyl pyrrolidinones with Grignard reagents. Treatment of 4,5-diacetoxy-\textit{N}-isopropylpyrrolidin-2-one 89 with vinylmagnesium bromide and ZnCl$_2$ yielded a 80 : 20 mixture of the \textit{trans} and \textit{cis} isomers of the 4-acetoxy-5-vinylpyrrolidinone 90 in 65% yield (Scheme 2.9).$^{57}$ The zinc chloride-diethyl ether complex promoted reaction of 4-benzyloxy-5-phenylsulfonylpyrrolidinone 91 with Grignard reagents led to the formation of the 4,5-\textit{trans} products 92 in yields of 50-89% (Scheme 2.10).$^{58}$

Scheme 2.9. Reaction of 89 with vinylmagnesium bromide.
Scheme 2.10. Reactions of 91 with Grignard reagents.

Although many methods have been developed for the synthesis of 4,5-disubstituted pyrrolidinones, most of them provided mixtures of 4,5-trans and 4,5-cis pyrrolidinones with variable diastereoselectivities. Thus the diastereoslective synthesis of 4,5-cis and 4,5-trans pyrrolidinones still remains an important topic to study. As mentioned earlier in this Chapter the 4,5-cis isomer of 72 (Scheme 2.1) was required for our Stermona alkaloids synthesis.

2.1. The Borono-Mannich Reaction

In 1998, Petasis\textsuperscript{59} reported a Mannich-type condensation reaction involving boronic acids (93), primary or secondary amines (94) and α-hydroxy aldehydes (95). These reactions were quite remarkable in terms of their high anti-diastereoselectivity and enantioselectivity. Using boronic acids was important since they do not react with aldehydes, but effectively trap the more reactive iminium intermediates formed in these reactions and have good air and water stability.\textsuperscript{60} Reactions of several organoboron compounds were examined and they all worked well (Table 2.1). In particular, reactions of phenylvinylboronic acid, p-methoxyphenylboronic acid and N-Boc-1H-pyrrol-2-yl-boronic acid afforded the corresponding Mannich adducts 96a-c in 84%, 63% and 86% yields, respectively. All products were obtained with very high diastereoselectivity (>99% de) and enantiopurities.

The mechanism of borono-Mannich reaction is not fully understood. The proposed mechanism involves formation of iminium ion intermediate 97, formation of boronate complex 98, and then intramolecular delivery of the nucleophile (R\textsuperscript{1}) to form the product 96 (Scheme 2.11).\textsuperscript{61}
Table 2.1. Selected results from Petasis’s paper.\(^{59}\)

\[
\begin{array}{cccc}
\text{Boronic acid} & \text{Amine} & \text{Aldehyde} & \text{Product} \\
\text{Ph} & \text{OH} & \text{Ph} & \text{N} \\
\text{Me} & \text{OH} & \text{C}_{5}\text{H}_{11} & \text{N} \\
\text{MeO} & \text{OH} & \text{Me} & \text{Ph} \\
\text{Boc} & \text{OH} & \text{OH} & \text{NBoc} \\
\text{Ph} & \text{OH} & \text{Me} & \text{Ph} \\
\text{R}^2 & \text{N} & \text{R}^3 & \text{OH} \\
\text{R}^4 & \text{OH} & \text{R}^2 & \text{R}^3 \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Boronic acid</th>
<th>Amine</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Yield% (de)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhOH</td>
<td>PhNMeH</td>
<td>C(<em>{5})H(</em>{11})OH</td>
<td>96a</td>
<td>84 (&gt;99%)</td>
</tr>
<tr>
<td>MeOPhOH</td>
<td>PhNPhMe</td>
<td>MeOH</td>
<td>96b</td>
<td>63 (&gt;99%)</td>
</tr>
<tr>
<td>N-BocPhOH</td>
<td>H(_2)NPh</td>
<td>OH</td>
<td>96c</td>
<td>86 (&gt;99%)</td>
</tr>
</tbody>
</table>

Scheme 2.11. Proposed mechanism of the borono-Mannich reaction.

For the Petasis reaction with formaldehyde an alternative mechanism was proposed.\(^{62}\) Three possible intermediates, the iminium salt 101, the aminal 102 and the semiaminal 103, can be formed from the mixing of the amine and formaldehyde (Scheme 2.12). It has been suggested that the reaction proceeds through semiaminal
103, where the hydroxyl group forms a boronate complex 104 with boronic acid 93. Subsequent intermolecular transfer of the nucleophile (R$_1^+$) provides the product 105 (Scheme 2.12).

Scheme 2.12. Alternative proposed mechanism of the borono-Mannich reaction.

The borono-Mannich reaction has been widely used in the total synthesis of natural products and related biologically active compounds. The total synthesis of (-)-cytoxazone 111, which is a novel cytokine modulator, was accomplished by Sugiyama in 2004 (Scheme 2.13).63 The precursor 3-amino-1,2-propanediols 109 and 110 were synthesised by a borono-Mannich reaction of DL-glyceraldehyde 106, (R)-1-(1-naphthyl)ethylamine 107 and 4-methoxyphenylboronic 108. The diols 109 and 110 were obtained as a 1 : 1 mixture in 50% yield.

Scheme 2.13. Synthesis of (-)-cytoxazone.
Pyne$^{64}$ reported the total synthesis of castanospermine 37, which is a potent inhibitor of several glycosidases and has potential for the treatment of viral infections and cancer, using the borono-Mannich reaction (Scheme 2.14). The precursor 115 was synthesised from the borono-Mannich reaction of (E)-styrene boronic acid 112, L-xylose 113 and allylamine 114. The amino-tetraol 115 was obtained in 53% yield. The same group reported the total synthesis of uniflorine A from the diastereomer of 115 which was obtained from the borono-Mannich reaction of D-xylose, allylamine and (E)-styrene boronic acid.$^{65}$


Batey$^{66}$ expanded the Petasis reaction to cyclic $N$-acyliminium ions. Racemic 2,3-dihydroxypyrrolidine 116 was treated with alkenyl- and arylboronic acids and esters 117 in the presence of BF$_3$.Et$_2$O to give the racemic cis-2,3-substituted pyrrolidines 118 (Table 2.2).

Table 2.2. Selected results from Batey’s paper.$^{66}$
Although these reactions were highly diastereoselective they did not extend these studies to enantiomerically enriched cyclic hemi-aminals having an endo-cyclic $N$-acyl group that were of interest to this project.

2.2. Borono-Mannich Reaction of Pyrrolidinones

2.2.1. Borono-Mannich Reaction of (4S)-1-Benzyl-4,5-dihydroxypryrrolidin-2-one

$O$-Protected-4-hydroxy-5-hydroxypryrrolidinones 119 can be obtained from a regioselective reduction of the corresponding succinimide 120 with NaBH$_4$. Succinimide 120 can be constructed by a condensation reaction of commercially available L-malic acid 121 and benzylamine 122 (Scheme 2.15).

Scheme 2.15. Retrosynthetic analysis for 119.

4,5-Dihydroxypryrrolidin-2-one 124 and the 4-benzyloxypryrrolidin-2-one 126 were chosen as precursors to study the borono-Mannich reaction (Scheme 2.16). Compound 124 was easily prepared in two steps from L-malic acid 121 and benzylamine 122. A mixture of L-malic 121 and benzylamine 122 (1.2 eq.) were heated at reflux temperature in xylene for 2 h to give the known succinimide 123 in 80% yield. The succinimide was treated with NaBH$_4$ (5.0 eq.) in CH$_2$Cl$_2$/EtOH (1 : 1) at -40 °C for 30 min to afford the 4,5-dihydroxypryrrolidinone 124 in 72% yield as a 92 : 8 mixture of diastereomers. This compound has not been reported in the literature. The $^1$H NMR spectrum of the major diastereomer showed a very small $J_{4,5}$ coupling constant, $J_{4,5} = 1.0$ Hz, which was consistent with the 4,5-trans-stereochemistry. However obtaining the $J_{4,5}$ coupling constant for the minor isomer proved difficult because of overlapping signals. Similarly, pyrrolidinone 126 was prepared in two steps from 123. Succinimide 123 was reacted with BnBr (3.0 eq.) in the presence of Ag$_2$O (3.0 eq.) in Et$_2$O at rt for 2 d to yield the known
benzylated succinimide 125 in 78% yield. Succinimide 125 was reduced to the corresponding known hemi-aminal 126 in 70% yield using the same reduction conditions that were used for the synthesis of 124. Compound 126 was obtained as a single cis isomer ($J_{4,5} = 6.5$ Hz).

Scheme 2.16. Synthesis of 124 and 126.

We first examined the borono-Mannich reactions of the 4-hydroxypyrrolidinone 124. Treatment of 124 with (E)-2-styrylboronic acid 112 (1.4 eq.) and BF$_3$·Et$_2$O (4.0 eq.) in CH$_2$Cl$_2$ at -78°C to 0°C according to Batey’s reaction conditions resulted in the recovery of only unreacted starting material 124. Increasing the temperature from 0°C to rt did not give the desired 5-hydroxy-4-styrylpyrrolidinone 127, instead it gave the cyclic boronate ester 128 (Scheme 2.17). The $^1$H NMR spectrum of 128 showed two vinyl proton resonances at 7.42 and 6.14 ppm, both as a doublet, with a $J$ value of 18.5 Hz. The pyrrolidine ring protons resonated at 5.59 (1H, d, $J = 6.0$ Hz, H5), 4.93 (1H, dd, $J = 6.0$, 7.0 Hz, H4), 2.83 (1H, dd, $J = 7.0$, 18.0 Hz, H3) and 2.71 (1H, d, $J = 18.0$ Hz, H3) ppm which was consistent with the structure of 128. The vinyl carbon signals appeared at 129.4 (C2’) and 127.2 (C1’) ppm in the $^{13}$C NMR spectrum. The pyrrolidine ring carbons resonated at 171.2 (C2), 89.4 (C5), 73.1 (C4) and 38.1 (C3) ppm. The low resolution (EI) mass spectrum of 128 showed a molecular ion peak at 319 amu while a high resolution (HREIMS) mass spectrometric analysis confirmed the molecular formula to be C$_{10}$H$_{18}$BNO$_3$. 

Reagents and conditions: a) PhCH$_2$NH$_2$ (1.1 eq.), xylene, reflux, 2 h; 80% b) BnBr (3.0 eq.), Ag$_2$O (3.0 eq.), Et$_2$O, 2 d; 78% c) NaBH$_4$ (5.0 eq.) CH$_2$Cl$_2$/EtOH : 1 : 1, -40°C, 30 min. 72% d) NaBH$_4$ (5.0 eq.) CH$_2$Cl$_2$/EtOH : 1 : 1, -40°C, 30 min. 70%.
Repeating this reaction with 5.0 equivalents of \((E)-2\text{-styrylboronic acid} \) 112 and 4.0 equivalents of BF₃.Et₂O in CH₂Cl₂ at 0 °C to rt again gave the boronate ester 128 in 78% yield. Using EtOAc, THF, CHCl₃, DMF or DCE as a solvent in the reaction of 124 with \((E)-2\text{-styrylboronic (1.4 eq.) acid and BF₃.Et₂O (5.0 eq.) resulted in only the formation of boronate complex 128. However, performing this reaction in CH₃CN yielded two products which were the boronate ester 128 (52%) and the novel Ritter reaction product 129 (21%) (Table 2.3, Entry 1). The Ritter product is a result of the reaction of the cyclic \(N\)-acyliminium ion intermediate with CH₃CN. The Ritter reactions of the \(N\)-acyl iminium ion intermediates formed from 124 and 126 will be the subject of Chapter 3 of this thesis. The use of potassium \((E)\)-styryltrifluoroborate (1.4 eq.) in this reaction resulted in the formation of 128 and 129 in 62% and 23% yields (Table 2.3, Entry 2), respectively. Treatment of 124 with \((E)-2\text{-styryl-1,3,2-dioxoborolane under the same experimental conditions also afforded the products 128 (58%) and 129 (20%) (Table 2.3, Entry 3).
We then attempted to synthesize the desired 5-hydroxy-4-styrylpyrrolidinone 127 from the boronate complex 128. Treatment of 128 with (Bu₄)NF (1.0 eq.) in CH₃CN or MeOH, with or without BF₃·Et₂O (1.0 eq.), with BF₃·Et₂O (1.0 eq.) and K₂CO₃ (1.0 eq.) at rt for 2 d were unsuccessful (Scheme 2.18). In all attempts only the boronate complex 128 was recovered. It was found to be a very stable molecule.

**Scheme 2.18.** Attempts to synthesize 5-styrylpyrrolidine 128 from boronate complex.

It was anticipated that the intermediate 130 could be formed in the above reactions which would give the N-acyliminium ion intermediate 131 which could lead the desired product 127. (Scheme 2.19).

**Scheme 2.19.** Proposed mechanism for the synthesis of 127 from 128.

The Mannich reaction was then performed in CH₃NO₂, since 124 is only slightly soluble in CH₂Cl₂, EtOAc, THF, CH₃Cl, DMF, DCE and forms the Ritter product 129 in CH₃CN. The pyrrolidinone 124 was unreactive when reacted with (E)-2-
styrylboronic acid 112 (1.4 eq.) or (1.4 eq. or 4.0 eq.) in CH₃NO₂ at rt. Treatment of 124 with 112 (1.4 eq.) and BF₃·Et₂O (4.0 eq.) in CH₃NO₂ at reflux temperature gave a compound that was tentatively assigned as the epoxide 132 and the desired addition product the 5-hydroxy-4-styrylpyrrolidinone 127 in a ratio of 70 : 30 respectively, from ¹H NMR spectroscopic analysis of the crude reaction mixture. Purification of the crude reaction mixture by column chromatography gave 127 in 20% yield with a high diastereoselectivity (dr = 91 : 9) (Scheme 2.20). The diastereomeric ratio was measured from the integrals for the CH₂Ph signals (4.93 ppm for major isomer, 5.05 ppm for minor isomer) of both isomers. The epoxide 132 could not be isolated by column chromatography suggesting that it was a relatively unstable molecule. Repeating the same reaction with (E)-2-styryl-1,3,2-dioxaborolane gave similar results. The stereochemistry of 127 and related products will be discussed in a later section of this Chapter.

![Scheme 2.20. Synthesis of 127 and 132.](image)

In the ¹H NMR spectrum of 127 signals for the vinylic protons H1` and H2` were observed at 6.51 (1H, d, J = 16.5 Hz) and 6.15 (1H, dd, J = 8.5, 16.5 Hz) ppm, respectively (Figure 2.1). The H4 and H5 protons of the pyrrolidine ring resonated at 4.43 (1H, ddd, J = 3.5, 6.0, 7.0 Hz) and 4.10 (1H, dd, J = 6.0, 8.5 Hz) ppm, respectively. The peaks at 2.73 (1H, dd, J = 7.0, 17.5 Hz) and 2.54 (1H, dd, J = 3.5, 17.5 Hz) ppm were assigned to H3α and H3β, respectively based upon the magnitude of their coupling constants to H4α. The ¹³C NMR spectrum also confirmed the structure. It showed a resonance at 172.9 ppm corresponding to the C2 carbonyl group. The signals for the vinylic carbons C2` and C1` were observed at 136.3 and 123.3 ppm, respectively. The pyrrolidine ring carbons C3, C4 and C5 showed resonances at 39.9, 67.5 and 65.2 ppm, respectively. The IR spectrum was also in good agreement with the structure showing a broad peak at 3334 cm⁻¹ for the O-H stretch and a sharp peak at 1669 cm⁻¹ for the C=O stretch. The LREIMS and
HREIMS analysis of 127 confirmed its molecular weight at 293 amu and the molecular formula as C_{19}H_{19}NO_{2}, respectively.

![Figure 2.1. 1H NMR spectrum (500 MHz, CDCl_3) of 127.](image)

The epoxide 132 was unstable on silica gel. After a number of failed attempts to purify it by column chromatography, it was decided to synthesise it by the treatment of 124 with BF_3.Et_2O (4.0 eq.) in CH_3NO_2 at reflux temperature (Scheme 2.21). TLC analysis of the reaction showed complete consumption of starting material after 5 h. The 1H NMR spectrum (Figure 2.2) of the crude product showed a relatively pure compound had been formed. The structure of 132 was assigned from its NMR, IR and HREIMS analysis. Its 1H NMR spectrum showed the typical splitting pattern of the diastereotopic H3 protons at 2.85 (1H, dd, J = 8.0, 18.5 Hz) and 2.68 (1H, d, J = 18.5 Hz) ppm. The methine protons H5 and H4 resonated at 5.41 (1H, d, J = 7.0 Hz) and 4.89 (1H, dd, J = 7.0, 8.0 Hz) ppm, respectively. The LREIMS spectrum of 132 showed a molecular ion peak at 189 amu and its molecular formula was found to be C_{11}H_{11}NO_{2} from HREIMS analysis.

![Scheme 2.21. Synthesis of epoxide 132.](image)
However, the $^1$H and $^{13}$C NMR spectra of the epoxide 132 were similar to that of pyrrolidine 124. Their molecular weights are not same but there was an 18 amu difference which could be the result of loss of a water molecule in the EI mass spectrum. In order to make sure that epoxide 132 was not the C-5 epimer of 124, compound 124 was epimerized by treating it with 10% HCl/THF at rt for 16 h to give a 80 : 20 mixture of the C-5 epimers that could not be separated by TLC (Scheme 2.22). $^1$H and $^{13}$C NMR spectra of 132 and the minor epimer of 124 were different (Table 2.4). The H4 proton signal appeared in the $^1$H NMR spectrum of 132 at 4.89 ppm while that of the epimer of 124 appeared at 4.24 ppm. The H3$\alpha$ and H3$\beta$ proton signals of the epoxide 132 appeared at 2.85 (dd, $J = 8.0$, 18.5 Hz) and 2.68 (1H, d, $J = 18.5$) ppm, respectively while those of the of epimer of 124 appeared at 2.62 (dd, $J = 6.5$, 17.5 Hz) and 2.42 (dd, $J = 2.5$, 17.7 Hz) ppm, respectively. The IR spectrum of 132 did not show any peak around 3300 cm$^{-1}$ that would corresponds to a O-H stretch. It was clear that the product 132 was not the C-5 epimer of 124.

Scheme 2.22. Epimerization of 124.
Table 2.4. Comparison of selected $^1$H NMR chemical shifts of 132 and 133.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^1$H NMR chemical shifts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H4</td>
</tr>
<tr>
<td>132</td>
<td>4.89 (t, $J = 7.0$ Hz)</td>
</tr>
<tr>
<td>133</td>
<td>4.24 (app q, $J = 6.0$ Hz)</td>
</tr>
</tbody>
</table>

Another possible product from the reaction of 124 with BF$_3$.Et$_2$O (Scheme 2.21) was the dimer 134 of the pyrrolidinone 124 (Scheme 2.23). However the mass spectrum of 132 did not show any peak at 378 amu for this possible dimer. Further, the N-PMB analogue of 134 was synthesized by one of the Pyne group members and was purified by column chromatography. This compound showed a clear molecular ion for the dimer structure in the ESI mass spectrum.

Scheme 2.23. Formation of the dimer 134.

The N-phenethyl analogue of 132, the compound 135 was prepared by Hwang. The C4 and C5 carbon resonances of 135 were observed at 66.4 and 84.3 ppm, respectively. The $^{13}$C NMR spectrum of 132 showed the C4 carbon signal much further downfield at 75.0 ppm, (Scheme 2.24). The $^{13}$C NMR chemical shift for C4 in 132 was thus not consistent with an epoxide structure and therefore the structure of 132 is not certain.

Scheme 2.24. Comparison of the C4 and C5 $^{13}$C NMR chemical shifts of 132 and 135.
Further, treatment of 132 with \((E)-2\text{-styrylboronic acid} (3.0 \text{ eq.})\) and \(\text{BF}_3\text{Et}_2\text{O} (4.0 \text{ eq.})\) in \(\text{CH}_3\text{NO}_2\) or potassium \((E)-\text{styryltrifluoroborate} (3.0 \text{ eq.})\) and \(\text{BF}_3\text{Et}_2\text{O} (4.0 \text{ eq.})\) in \(\text{CH}_3\text{NO}_2\) at 80 °C for 16 h did not give a reaction product (Scheme 2.25). These results also lead us to doubt the proposed epoxide structure of 132.

![Scheme 2.25. Reactions of epoxide 132.](image)

We also examined the borono-Mannich reaction of the pyrrolidinone 124 with aryl boronic acids. Six boronic acids were chosen and the reactions of these boronic acids with pyrrolidinone 124 which were performed under the optimized conditions using \(\text{MeNO}_2\) as a solvent with heating at reflux. The electron-rich aromatic boronic acids; 2-furylboronic acid, 2-benzofurylboronic acid and 3,4-dimethoxyphenylboronic acids gave addition products 136, 137 and 138, respectively (Scheme 2.26). Phenyl boronic acid, 4-methoxyphenylboronic acid, and 2-thienylboronic acids did not give any of the desired products. We found that 2-benzofurylboronic acid afford the 4,5-\text{cis} adduct 137 in 56% yield with a 92 : 8 diastereomeric ratio. 2-Furyl and 3,4-dimethoxyphenylboronic acids however gave the 4,5-\text{trans} adducts 136 and 138 in 65% and 44% yields, respectively with diastereomeric ratios of 77 : 23 and 72 : 28, respectively (Scheme 2.26). The stereochemistry of the adducts 127, 136, 137, and 138 will be discussed in a later section of this Chapter.

Although the exact mechanism of the borono-Mannich reaction is not known, the proposed mechanism in the literature\(^{62,72,73}\) for reactions involving acyclic \(N\)-acyliminium ions suggested the possible involvement of the boronate complex 144 in the above reactions of 124. Formation of the 4,5-\text{cis} pyrrolidinones 127 and 137 can be rationalized as arising from the boronate intermediate 144 followed by the intramolecular delivery of the carbon nucleophile to the same face of the iminium ion. While the stereochemical outcomes of products 136 and 138 suggests direct
addition of the boronic acid to the cyclic iminium ion had occurred, *anti* to the C-4 substituent. While the boronate intermediate 146, analogous to 128, may have formed in these reactions, its formation may be reversible under these reaction conditions (Scheme 2.27).

![Diagram](image)

**Scheme 2.26.** Results of Borono-Mannich reactions of 124.

![Diagram](image)

**Scheme 2.27.** Formation of *cis* and *trans* pyrrolidinones and boronate complex.
The stereochemistry assigned to the adducts 127 and 136-138 was based on the magnitude of $J_{4,5}$. In the literature, $J_{4,5}$ for 4,5-cis pyrrolidines 147 is typically between 5.5-7.5 Hz and that for 4,5-trans pyrrolidines 148 is typically between 0-2 Hz (Table 2.5).68-70

Table 2.5. Selected $J_{4,5}$ values for cis and trans pyrrolidines from the literature.68-70

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>$J_{4,5}$ Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>147</td>
<td>O</td>
<td>PMB</td>
<td>TBDMS</td>
<td>CN</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>H₂</td>
<td>CO₂Me</td>
<td>H</td>
<td>Allyl</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>H</td>
<td>TBDMS</td>
<td>Allyl</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>H</td>
<td>TBDMS</td>
<td>CH₃C(CH₂)₃Cl</td>
<td>5.8</td>
</tr>
<tr>
<td>148</td>
<td>O</td>
<td>PMB</td>
<td>TBDMS</td>
<td>CN</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>H₂</td>
<td>CO₂Me</td>
<td>H</td>
<td>Allyl</td>
<td>2.0</td>
</tr>
</tbody>
</table>

We found that $J_{4,5}$ for the major diastereomer of adducts 127 (Scheme 2.20) and 137 (Scheme 2.25) was 6.0 Hz and 7.0 Hz, respectively which is consistent with the 4,5-cis stereochemistry, while that of adducts 136 and 138 (Scheme 2.26) was 2.0 Hz and 2.5 Hz, respectively which suggested the 4,5-trans stereochemistry. The $J_{4,5}$ values of the minor cis isomers of adducts 136 and 138 were 7.0 Hz and 5.5 Hz, respectively and that of 127 and 137 were both 2.5 Hz which was also consistent with their proposed stereochemistries (Table 2.6).

Table 2.6. $J_{4,5}$ values of pyrrolidinones.

<table>
<thead>
<tr>
<th>Compound no</th>
<th>$J_{4,5}$ (Hz) of major isomer</th>
<th>$J_{4,5}$ (Hz) of minor isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>127</td>
<td>6.0</td>
<td>2.5</td>
</tr>
<tr>
<td>136</td>
<td>2.0</td>
<td>7.0</td>
</tr>
<tr>
<td>137</td>
<td>7.0</td>
<td>2.5</td>
</tr>
<tr>
<td>138</td>
<td>2.5</td>
<td>5.5</td>
</tr>
</tbody>
</table>
2.2.2. Borono-Mannich Reaction of (4S)-1-Benzyl-4-benzyloxy-5-hydroxypyrrolidin-2-one

The borono-Mannich reaction of the 4-O-benzyl pyrrolidinone 126 with (E)-2-styrylboronic acid was then investigated. When 126 was treated with 1.4 equivalents of (E)-2-styrylboronic acid 112 and BF₃·Et₂O (4.0 eq.) in CH₂Cl₂ at -78 °C to 0 °C, under Batey’s conditions, no reaction was observed (Table 2.8, Entry 1). However increasing the temperature to 0 °C afforded the 4,5-trans pyrrolidinone adduct 149 in 12% yield and good diastereoselectivity (dr = 90 : 10) (Table 2.8, Entry 2). Performing this reaction at 0 °C to rt gave the adduct 149 in 34% yield (Table 2.8, Entry 3). Increasing the molar equivalents of 112 to 3.0 resulted in formation of the addition product 149 in 47% yield (Table 2.8, Entry 4). The pyrrolidinone 126 was treated with 1.4 equivalents of the more nucleophilic potassium (E)-styryltrifluoroborate in CH₂Cl₂ at 0 °C to rt to afford the product 149 in 30% yield (Table 2.8, entry 5). Increasing the amount of potassium (E)-styryltrifluoroborate to 3.0 equivalents gave the adduct 149 in 58% yield (Table 2.8, Entry 6). (E)-2-styryl-1,3,2-dioxoborolane was also used as a nucleophilic partner but it gave lower yields of 149 than potassium (E)-styryltrifluoroborate. Treatment of 126 with 1.4 equivalents of (E)-2-styryl-1,3,2-dioxoborolane and BF₃·Et₂O (4.0 eq.) yielded the adduct 149 in 32% yield. The product 149 was obtained in 39% yield from the reaction of 126 with 3.0 equivalents of (E)-2-styryl-1,3,2-dioxoborolane and BF₃·Et₂O (4.0 eq.) (Table 2.8, Entries 7 and 8).

The 4,5-stereochemistry assigned to 149 was again based on the magnitude of $J_{4,5}$. In the $¹H$ NMR spectrum of 149, the signal of the H5 proton was a doublet with a $J$ value of 8.0 Hz which is the coupling constant between H5 and the adjacent vinyl proton H1'. The H4 proton appeared as a doublet with a $J$ value of 7.2 Hz which is the coupling constant between H4 and H3α. The coupling constant between the protons 4 and 5 was therefore 0 Hz which indicated the 4,5-trans stereochemistry. For further examination of its stereochemistry, 149 was subjected to a debenzylation reaction (Scheme 2.28). Compound 149 was reacted with BBr₃ (4.0 eq.) in CH₂Cl₂ at 0 °C for 10 min. to give the corresponding debenzylated product 150 in 90% yield. The $¹H$ and $¹³C$ NMR spectra of 150 were identical to the minor isomer that was formed from the reaction of 124 and (E)-2-styrylboronic acid 112 (Scheme 2.20).
The $J_{4,5}$ value of the debenzylated product 150 was 2.5 Hz, consistent with its assigned trans stereochemistry.

**Table 2.7. Optimization of borono-Mannich reaction of 126.**

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Eq. of Organoboron Compounds</th>
<th>Temperature</th>
<th>Yield%</th>
<th>dr$^a$ trans : cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B(OH)$_2$</td>
<td>1.4</td>
<td>-78 °C to 0 °C</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>B(OH)$_2$</td>
<td>1.4</td>
<td>0 °C</td>
<td>12</td>
<td>90 : 10</td>
</tr>
<tr>
<td>3</td>
<td>B(OH)$_2$</td>
<td>1.4</td>
<td>0 °C to rt</td>
<td>34</td>
<td>94 : 6</td>
</tr>
<tr>
<td>4</td>
<td>B(OH)$_2$</td>
<td>3.0</td>
<td>0 °C to rt</td>
<td>47</td>
<td>91 : 9</td>
</tr>
<tr>
<td>5</td>
<td>BF$_3$K</td>
<td>1.4</td>
<td>0 °C to rt</td>
<td>30</td>
<td>95 : 5</td>
</tr>
<tr>
<td>6</td>
<td>BF$_3$K</td>
<td>3.0</td>
<td>0 °C to rt</td>
<td>58</td>
<td>92 : 8</td>
</tr>
<tr>
<td>7</td>
<td>B(OCH$_2$)$_2$</td>
<td>1.4</td>
<td>0 °C to rt</td>
<td>32</td>
<td>98 : 2</td>
</tr>
<tr>
<td>8</td>
<td>B(OCH$_2$)$_2$</td>
<td>3.0</td>
<td>0 °C to rt</td>
<td>39</td>
<td>96 : 4</td>
</tr>
</tbody>
</table>

$^a$ Ratios were obtained from the $^1$H NMR analysis of the crude reaction mixture.

**Scheme 2.28.** Debenzylation of 149.

Formation of the 4,5-trans isomer 149 indicated the direct addition of the organoboron compound to the cyclic $N$-acyliminium ion intermediate (Scheme 2.29). Since there is large benzyl protecting group on the $\beta$ face of the $N$-acyliminium ion intermediate, the nucleophile prefers to attack from the $\alpha$ face of the molecule which resulted in the formation of 4,5-trans product.
Scheme 2.29. Mechanism of formation of trans product.

In order to generalize the borono-Mannich reaction, 126 was treated with six different aryl boronic acids (Scheme 2.30). Compound 126 was treated with 3.0 equivalents of boronic acid and 4.0 equivalents of BF$_3$.Et$_2$O in CH$_2$Cl$_2$ at 0 °C to rt for 16 h (Table 2.8). The electron-rich aromatic boronic acids; 2-furyl and 2-benzofurylboronic acid gave the corresponding addition products 151 and 152 in yields of 79% and 55%, respectively, with good trans distereoselectivities, while 2-thienylboronic acid afforded the unexpected 4,5-cis product 153 in 72% yield with a distereomeric ratio of cis : trans = 62 : 38. In contrast, phenylboronic acid did not react with 126, while its more electron-rich analogues, 4-methoxyphenylboronic acid and 3,4-dimethoxyphenyl boronic acid afforded the corresponding adducts 155 and 156 with respective yields of 48% and 74%, and good 4,5-trans diastereoselectivities (Table 2.8). The stereochemical outcomes of these reactions were based on the magnitude of $J_{4,5}$ which was typically 1.5-2.5 Hz for the trans isomers and 6.0-7.5 Hz for the corresponding cis isomers, consistent with the literature examples (Table 2.8).

Table 2.8. $J_{4,5}$ values of products of Borono-Mannich reaction of 126.

<table>
<thead>
<tr>
<th>Compound no</th>
<th>$J_{4,5}$ (Hz) of major isomer</th>
<th>$J_{4,5}$ (Hz) of minor isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>151</td>
<td>1.5</td>
<td>7.5</td>
</tr>
<tr>
<td>152</td>
<td>2.0</td>
<td>7.5</td>
</tr>
<tr>
<td>153</td>
<td>7.0</td>
<td>2.0</td>
</tr>
<tr>
<td>155</td>
<td>2.5</td>
<td>6.5</td>
</tr>
<tr>
<td>156</td>
<td>2.5</td>
<td>7.0</td>
</tr>
</tbody>
</table>
Scheme 2.30. Borono-Mannich adducts of 126.

The adduct 151 was also prepared from the reaction of 126 with furan (3.0 eq.) in the presence of BF$_3$.Et$_2$O (4.0 eq.) in CH$_2$Cl$_2$ at 0 °C to rt for 2 h in 40% yield (Scheme 2.31). The yield and diastereoselectivity of this reaction were lower than those of the reaction of 126 with 2-furylboronic acid.

Scheme 2.31. Alternative synthesis of 151.
2.2.3. **Borono-Mannich Reaction of (4S)-4,5-Dihydroxy-1-(pent-4-enyl)pyrrolidin-2-one**

As part of this project we planned to make 5-styrylpyrrolidinones of the type general 52 which could serve as valuable precursors for the total synthesis of pyrrolizidine, indolizidine and *Stemona* alkaloids, through the RCM reaction (Scheme 2.32).

![Scheme 2.32. RCM reaction of 52.](image)

After studying the borono-Mannich reactions of pyrrolidinone 124 and 126, we focused on the reaction of the *N*-pentenyl analogue of pyrrolidinone 124 with the aim of constructing the common pyrrolo[1,2-α]azepine core of *Stemona* alkaloids. Pyrrolidinone 157 could be obtained from the succinimide 159 in three steps (Scheme 2.33). The succinimide 159 could be synthesised in two different ways. The first way was the deprotection of the *N*-PMB derivative of succinimide 161 which could be obtained from the condensation reaction of L-malic acid and *p*-methoxybenzylamine. The second way for obtaining 159 was directly from the condensation of L-malic acid 121 and ammonia gas 160.

The first method was used for the synthesis of succinimide 159, to avoid the toxicity and handling problems of ammonia gas. The condensation reaction of *p*-methoxybenzylamine and L-malic acid was performed in xylene at reflux temperature for 2 h to give the succinimide 163 in 84% yield (Scheme 2.34). Before the deprotection of the PMB group the hydroxyl of 163 was protected to avoid formation of a very polar molecule. The succinimide 163 was treated with TBSCI (1.5 eq.), imidazole (1.2 eq.) and DMAP (0.1 eq.) in THF at 0 °C to rt for 16 h to give the protected product 164 in 90% yield (Scheme 2.34).
**Scheme 2.33.** Retrosynthetic analysis for N-pentenyl derivative 157.

Reagents and conditions: a) xylene, reflux, 2 h, 84%; b) TBSCI (1.5 eq.), imidazole (1.2 eq.), DMAP (0.1 eq.), THF, 0 °C to rt, 16 h, 90%.

**Scheme 2.34.** Synthesis of 164.

The reaction of 164 with cerium ammonium nitrate (CAN) (5.0 eq.) in CH$_3$CN/H$_2$O (1 : 1) at rt for 1 h afforded the product 165 in only 15% yield (**Scheme 2.35**). Both the PMB and the TBS groups had been cleaved under the oxidative reaction conditions. After 1 h of reaction TLC analysis showed a number of new product spots. Repeating this reaction at 0 °C gave the product 165 in an increased yield of 28%. As the TBS group was unstable in the deprotection reaction with CAN, DDQ was used as a deprotection agent. Treatment of succinimide 164 with DDQ (1.2 eq.) in CH$_2$Cl$_2$/H$_2$O (20 : 1) at rt for 16 h did not give any product and only unreacted starting material was recovered.
Scheme 2.35. Deprotection reaction of 164.

We then decided to protect the hydroxyl group with the more stable TBDPS protecting group. The succinimide 163 was treated with TBDPSCI (1.5 eq.), imidazole (1.2 eq.) and DMAP (0.1 eq.) in THF at 0 °C to rt for 16 h to give the silylated product 166 in 92% yield. Treatment of 166 with CAN (5.0 eq.) in CH₃CN/H₂O (1 : 1) at rt for 1 h afforded the desired product 167 in 40% yield (Scheme 2.36).

Scheme 2.36. Synthesis of 167.

Although we obtained the desired product 167, the overall yield for its synthesis was not satisfactory. The purification of the product 167 was very difficult due to an impurity that had nearly the same R_f value as that of 167, so that the column chromatography of the reaction mixture had to be done very carefully. Because of these problems we decided to synthesize the succinimide 159 directly from the condensation reaction of L-malic acid and ammonia. A suspension of L-malic acid in acetyl chloride was heated at reflux for 1.5 h, after removal of all volatiles the residue was treated with gaseous ammonia for 30 min and then the residue was treated with acetyl chloride at reflux temperature to afford the succinimide 159 in 56% yield (Scheme 2.37). The succinimide 159 reacted under Mitsunobu reaction conditions with 4-penten-1-ol (1.0 eq.), PPh₃ (1.0 eq.), DIAD (1.0 eq.) in THF at 0 °C to rt for 1 h to give N-pentenyl succinimide 168 in 81% yield. The N-pentenyl succinimide was treated with NaBH₄ (5.0 eq.) in MeOH/CH₂Cl₂ (1 : 1) at 0 °C for

![Scheme 2.35](image-url)
1.5 h to give the hemi- aminal 170 in 62% yield and as single isomer. $J_{4,5}$ was 6.5 Hz, indicative of the 4,5-cis stereochemistry. Deacetylation of 170 with K$_2$CO$_3$ in MeOH at rt for 2 h afforded the diol 157 in 67% yield (Scheme 2.37).

We next examined the borono-Mannich reaction of 157 with (E)-2-styrylboronic acid. Since 157 was soluble in CH$_2$Cl$_2$, unlike 124, these reactions were performed in CH$_2$Cl$_2$. The reaction of 157 with (E)-2-styrylboronic acid (3.0 eq.) and BF$_3$·Et$_2$O (4.0 eq.) in CH$_2$Cl$_2$ at 0 °C to rt yielded the desired addition product 171 in only 15% yield (Table 2.9, Entry 1). After 2 h of reaction, TLC analysis shows consumption of starting material and a new less polar spot which was the adduct 171. Increasing the polarity of the TLC solvent system to CH$_2$Cl$_2$/MeOH (1:1) did not raise any new spots from the baseline. An analysis of the $^1$H NMR spectrum of the crude reaction mixture showed mainly the desired product and did not provide a reason for the low yield. Treatment of 157 with potassium (E)-styryltrifluoroborate under the same experimental conditions afforded adduct 171 in an slightly increased yield of 21% (Table 2.9, Entry 2). Product 171 was obtained in 33% yield from the reaction of 157 with (E)-2-styrylboronic acid (3.0 eq.) and BF$_3$·Et$_2$O (4.0 eq.) in CH$_3$CN (Table 2.9, Entry 3). The $^1$H NMR spectrum of the crude reaction mixture showed methyl protons of the corresponding Ritter product at 2.01 ppm as a singlet. The ratio of 171 to the Ritter product was about 90:10.

Reagents and conditions: a) i.Acetyl chloride, ii. NH$_3$, iii. Acetyl chloride, 56%; b) 4-penten-1-ol, PPh$_3$, DIAD, THF, 0 °C to rt, 81%; c) NaBH$_4$ (5.0 eq.), MeOH/CH$_2$Cl$_2$ (1:1), 0 °C, 62%; d) K$_2$CO$_3$ (0.5 eq.), MeOH, rt, 67%.

Table 2.9. Results of borono-Mannich reaction of 157.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Solvent</th>
<th>Yield%</th>
<th>dr&lt;sup&gt;a&lt;/sup&gt; cis : trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B(OH)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>15</td>
<td>90 : 10</td>
</tr>
<tr>
<td>2</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;K</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>21</td>
<td>92 : 8</td>
</tr>
<tr>
<td>3</td>
<td>B(OH)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
<td>33</td>
<td>90 : 10</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratios were obtained from the <sup>1</sup>H NMR analysis of the crude reaction mixture.

With the adduct 171 in hand we decided to perform the ring closing metathesis reaction to obtain the corresponding pyrrolo[1,2-<i>a</i>]azepine 172. Adduct 171 was treated with Grubbs’ second generation catalyst (13% mol) in CH<sub>2</sub>Cl<sub>2</sub> at rt for 1 h to give the pyrrolo[1,2-<i>a</i>]azepine 172 in 72% yield. This bicyclic structure is common to the <i>Stemona</i> alkaloids.

Scheme 2.38. RCM reaction of 171.

The <sup>1</sup>H NMR spectrum of 172 showed signals for the H8, H9, H9a and H1 methine protons at 6.04-6.02 (1H, m), 5.64 (1H, d, <i>J</i> = 10.5 Hz), 4.40 (1H, br. s) and 4.38 (1H, br. s) ppm, respectively. The coupling constant <i>J</i><sub>8,9</sub> of 10.5 Hz was consistent with the expected <i>cis</i> alkene geometry in 172. The diastereotopic pairs of methylene protons resonated at 4.12 (1H, dt, <i>J</i> = 5.6, 13.8 Hz) and 2.95 (1H, dt, <i>J</i> = 6.6, 13.8 Hz) ppm for H5, at 2.61 (1H, ddd, <i>J</i> = 5.4, 16.5 Hz) and 2.45 (1H, dd, <i>J</i> = 3.3, 16.5 Hz) ppm for H2, at 2.39-2.36 (1H, m) and 2.24-2.16 (1H, m) ppm for H7, while those of H6 resonated at 1.84 (2H, m) ppm. The <sup>13</sup>C NMR spectrum was also consistent with the structure of 172. It showed methine resonances at 172.3 (C3), 134.3 (C8), 123.9 (C9) and 67.0 ppm (C9a). The four methylene carbons C2, C5, C6
and C7 were observed at 39.9, 41.2, 26.9 and 26.0 ppm, respectively. The IR spectrum was also in good agreement with the structure showing an O-H stretch at 3359 cm\(^{-1}\) and a C=O stretch at 1662 cm\(^{-1}\). The HREIMS analysis showed its molecular formula to be C\(_{17}\)H\(_{21}\)NO\(_2\), which is consistent with the structure of 172.

### 2.3. Grignard Reaction of Succinimide 125

Since 5-styrylpyrrolidinone type compounds were important for our synthetic projects (Scheme 2.32), we decided to try a different method to prepare this type of compound in higher yield and diastereoselectivities. These compounds can in principle be synthesized from the corresponding succinimide in two ways (Scheme 2.39). The first way is reduction of the succinimides to the hemi-aminals 174 and then the addition of nucleophiles as we have discussed earlier in this Chapter. The second way is the addition of the nucleophiles to succinimides first and then reduction. We thus studied the potential of this second method.

![Scheme 2.39](image)

**Scheme 2.39.** Two ways for the reparation of 5-substituted pyrrolidines.

Succinimide 125 was found to be unreactive when it was treated with organoboron compounds (Table 2.10). The reactions of 125 (E)-2-styrylboronic acid and potassium (E)-styryltrifluoroborate were tried under different reaction conditions and none of them provided the addition product and only the starting material was recovered. Treatment of 125 with (E)-2-styrylboronic acid (3.0 eq.) and BF\(_3\).Et\(_2\)O (4.0 eq.) in CH\(_2\)Cl\(_2\) at rt gave only succinimide 125 (Table 2.10, Entry 1). Repeating this reaction at 40 °C only afford the starting material (Table 2.10, Entry 2). Attempts to get the addition product from the reaction of 125 and more nucleophilic, potassium (E)-styryltrifluoroborate (3.0 eq.), in the presence of BF\(_3\).Et\(_2\)O (4.0 eq.) in
CH$_2$Cl$_2$ failed, and only the starting material was recovered (Table 2.10, Entry 3). Increasing the temperature of the reaction of 125 with potassium (E)-styryltrifluoroborate (3.0 eq.) in the presence of BF$_3$.Et$_2$O (4.0 eq.) to 40 °C did not give any of the desired product either (Table 2.10, Entry 4). Performing the reaction of 125 with potassium (E)-styryltrifluoroborate (3.0 eq.) and BF$_3$.Et$_2$O (4.0 eq.) in CH$_3$CN at 60 °C did not give any product (Table 2.10, Entry 5).

We then decided to try the reaction of the corresponding Grignard reagent with the succinimide 125 (Scheme 2.40). Since phenylvinylmagnesium bromide 177 is not commercially available, it was synthesized from the reaction of phenylvinyl bromide and magnesium turmings in THF at 40 °C for 1 h.$^{74}$ Freshly prepared phenylvinylmagnesium bromide was treated with succinimide 125 in THF at -78 °C to -10 °C for 4 h to afford a diastereomeric mixture of the tertiary carbinols 178 and 179 in 45% yield with a diastereomeric ratio of 58 : 42 (not necessarily respectively). This isomeric mixture could not be separated by column chromatography. Reduction of this mixture with Et$_3$SiH (5.0 eq.) and BF$_3$.Et$_2$O (4.0 eq.) in CH$_2$Cl$_2$ at -78 °C to rt for 16 h provided the trans-5-(2-phenylethyl)-2-pyrrolidinone 180 and not the desired 5-styrylpyrrolidinone product 149 (Scheme 2.40).

**Table 2.10.** Results of treatment of 125 with organoboron compounds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B(OH)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>B(OH)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>40 °C</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>BF$_3$K</td>
<td>CH$_2$Cl$_2$</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>BF$_3$K</td>
<td>CH$_2$Cl$_2$</td>
<td>40 °C</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>BF$_3$K</td>
<td>CH$_3$CN</td>
<td>60 °C</td>
<td>0</td>
</tr>
</tbody>
</table>
Scheme 2.40. Result of reaction of 125 with phenylvinylmagnesium bromide.

The observed product 180 suggested that after formation of the N-acyliminium ion intermediate 181 that 1,4-addition of hydride takes place to give the N-acyl enamine 182. Protonolysis of this intermediate 182 then gives iminium ion 183 and further reduction of this intermediate yielded the 4,5-\textit{trans} product 180 (Scheme 2.41). The proton source may have arisen from adventitious water in the reaction mixture after reaction with BF₃·Et₂O.

Scheme 2.41. Proposed mechanism for the formation of 180.

In the \textsuperscript{1}H NMR spectrum of 180, the signal of the H₄ proton appeared at 3.93 ppm as a doublet with $J_{3,4} = 6.5$ Hz and the signal of the H₅ proton appeared at 3.52 ppm as
a broad doublet with a $J$ value of 8.5 Hz which is the coupling constant between H5 and adjacent CH$_2$ protons. The coupling constant between the H4 and H5 protons was therefore calculated as 0 Hz which indicated the 4,5-$trans$ stereochemistry. In order to further prove the stereochemistry of 180, it was subjected to a debenzylation reaction. Product 180 reacted with PdCl$_2$ (0.8 eq.) in MeOH under a H$_2$ atmosphere for 1 h at rt to afford the debenzylated product 184 in 76% yield (Scheme 2.42). The product 149, from the reaction of 126 and (E)-2-styrylboronic acid (Table 2.7), was also subjected to the same debenzylation reaction conditions to afford the product 184 in 67% yield. The $^1$H and $^{13}$C NMR spectra of these two products were identical which confirmed that the stereochemistry of product 180 was 4,5-$trans$.

Reagents and conditions: a) PdCl$_2$ (0.8 eq.), H$_2$, MeOH, 1 h.

**Scheme 2.42.** Debenzylation of 180 and 149.

In conclusion, the 4,5-disubstituted pyrrolidinones were synthesized in a diastereoselective manner from the borono-Mannich reaction of 4-hydroxy and 4-benzyloxy-5-hydroxypyrrolidin-2-ones. The 4,5-dihydroxypyrrolidin-2-one gave the 4,5-$cis$ adducts 127 and 137 with very high $cis$ selectivity but in relatively low yields, while the 4-benzyloxy-5-hydroxypyrrolidin-2-one gave the 4,5-$trans$ adducts with good $trans$ selectivity and in moderate to good yields. Unfortunately the desired dienyl 4,5-$cis$ adduct 171, required for the synthesis of the *Stemona* alkaloids could only be obtained in a low yield of 33%. A RCM reaction of 171 gave the desired pyrrolo[1,2-$a$]azepine 172 in 72% yield.
3. DIASTEREOSELECTIVE RITTER REACTIONS OF PYRROLIDINONES

In Chapter 2 we reported the formation of the novel Ritter product 129 as an unwanted side product in the reaction of 124 with (E)-2-styrylboronic acid 122 when acetonitrile was used as a solvent. We decided to examine the scope and utility of this interesting reaction. In principle the Ritter product 129 could be hydrolysed to give the 2-acylaminopyrrolidinones 185 (Scheme 3.1). 2-Acylaminopyrrolidines are common motifs of the natural products odorine 186 and odorinol 187 (Figure 3.1).

**Scheme 3.1.** Synthetic pathway to 185.

**Figure 3.1.** Structures of odorine 186 and odorinol 187.

The first and unique synthesis of the odorine 186 and odorinol 187 was reported by Babidge\(^7\) in 1980. Their synthesis started with the acylation of L-proline 188 with 3-phenylpropanoyl chloride 189 to give amide 190. Then compound 190 was treated with ethyl chloroformate 191, followed by triethylamine and sodium azide to afford the corresponding acyl azide 192 which rearranged to form the isocyanate 193 on heating in THF. Addition of 2-(S)-butylmagnesium bromide 194 to 193 yielded odorine 186 in 72% yield (Scheme 3.2). From the optical rotations of natural and synthetic samples of odorine 186, it was discovered that they were enantiomers. This indicated the absolute configuration of 186 was as shown in Figure 3.1. A similar strategy was used in the synthesis of the enantiomer of odorinol 187.
Scheme 3.2. Synthesis of odorine 186.

3.1. The Ritter Reaction

In 1948, Ritter\textsuperscript{76,77} reported that the reaction of nitriles with alkenes 195 or tertiary alcohols 197 under acidic conditions gave amides 196 and 198 (Scheme 3.3). The use of hydrogen cyanide as a nitrile component resulted in the formation of \textit{N-tert}-alkyl formamides. In general, the Ritter reaction is the reaction of nitriles and carbocations to form \textit{N}-alkyl carboxamides. The carbocations can be generated from tertiary, secondary or benzylic alcohols, alkenes or alkyl halides. The nitrile substituent (R) can be a primary, secondary or tertiary alkyl, alkenyl, alkynyl, aryl or heteroaryl substituent.

Scheme 3.3. Ritter reactions of alkenes 195 and alcohols 197.

Treatment of 2-methylpent-2-ene 195a with acetonitrile, H\textsubscript{2}SO\textsubscript{4} and H\textsubscript{2}O gave the corresponding acetamide 196a in 75% yield (Table 3.1, Entry 1).\textsuperscript{76} Reaction of 2-methylbut-2-ene 195b with acrylonitrile and 2-(3-nitrophenyl)acetonitrile afforded
their respective amide adducts 196b and 196c in yields of 75% and 89%, respectively (Table 3.1, Entries 2 and 3). Treatment of 2-phenylpropan-2-ol with sodium cyanide, H\textsubscript{2}SO\textsubscript{4} and H\textsubscript{2}O yielded the formamide 198a in 61% yield (Table 3.1, Entry 4).

**Table 3.1. Results of the Ritter reaction of alkenes 195 and alcohols 197.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene or Alcohol</th>
<th>Nitrile</th>
<th>Product</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(H\textsubscript{3}C)\textsubscript{2}C\textsubscript{=CH}C\textsubscript{2}H\textsubscript{5} 195a</td>
<td>CH\textsubscript{3}CN</td>
<td>C\textsubscript{3}H\textsubscript{7}(H\textsubscript{3}C)\textsubscript{2}C\textsubscript{\textit{N}}\textsubscript{CH\textsubscript{3}}</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>C\textsubscript{2}H\textsubscript{5}(H\textsubscript{3}C)C\textsubscript{=CH}2 195b</td>
<td>H\textsubscript{2}C\textsubscript{=}CHCN</td>
<td>C\textsubscript{2}H\textsubscript{5}(H\textsubscript{3}C)\textsubscript{2}C\textsubscript{\textit{N}}\textsubscript{CH\textsubscript{2}CH\textsubscript{2}}</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>C\textsubscript{2}H\textsubscript{5}(H\textsubscript{3}C)C\textsubscript{=CH}2 195c</td>
<td>p\textsubscript{-}NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}CH\textsubscript{2}CN</td>
<td>C\textsubscript{2}H\textsubscript{5}(H\textsubscript{3}C)\textsubscript{2}C\textsubscript{\textit{N}}\textsubscript{CH\textsubscript{2}C\textsubscript{6}H\textsubscript{4}NO\textsubscript{2}}</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>PhC(CH\textsubscript{3})\textsubscript{2}OH 197a</td>
<td>NaCN</td>
<td>PhC(CH\textsubscript{3})\textsubscript{2}N\textsubscript{CH\textsubscript{2}CO\textsubscript{2}}</td>
<td>61</td>
</tr>
</tbody>
</table>

**Scheme 3.4.** Mechanism of the Ritter reaction.

In the mechanism of the Ritter reaction (Scheme 3.4) the hydroxyl group of the alcohol 197 is first protonated and then cleavage of the C-O bond of the cationic intermediate 199 generates the carbocation 200. The nitrile attacks the cation 200 to form a resonance stabilized nitrilium ion 201. The nitrilium ion 201 reacts with the
conjugate base of the acid to form an imidate 203. Finally, hydrolysis of the imidate intermediate yields the observed N-alkyl carboxamide 198.77

Since its discovery the Ritter reaction has been widely used in the total synthesis of natural products and alkaloids. In 1993, Heathcock78 reported the Ritter reaction of 3-indoleacetonitrile 205 and (1S)-(-)-β-pinen 206 in the synthesis of (+)-aristotelone 208 (Scheme 3.5). The Ritter reaction of 205 with 206 in the presence of Hg(NO₃)₂ in CH₂Cl₂ at -40 °C to rt for 2 h gave an imine intermediate which was reduced to the corresponding amine product 207 by NaBH₄.

Scheme 3.5. Ritter reaction of 205 and 206.

Concellon79 reported the preparation of enantiopure tetrasubstituted imidazoles 210 through the Ritter reaction of enantiopure 2-(1-aminoalkyl)aziridines 209 with nitriles (Table 3.2). These reactions were highly regio- and enantio-selective.

Table 3.2. Synthesis of imidazoles.

<table>
<thead>
<tr>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>Yield% of 210</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Bn</td>
<td>iBu</td>
<td>45</td>
</tr>
<tr>
<td>iPr</td>
<td>Bn</td>
<td>Bn</td>
<td>61</td>
</tr>
<tr>
<td>Ph</td>
<td>Bn</td>
<td>BnOCH₂</td>
<td>55</td>
</tr>
<tr>
<td>MeOCH₂</td>
<td>Allyl</td>
<td>iBu</td>
<td>58</td>
</tr>
</tbody>
</table>

The suggested mechanism (Scheme 3.6) involves selective coordination of the Lewis acid to the aziridine ring nitrogen, then intramolecular nucleophilic attack of the dibenzylamino group at C-2 of the ring to form the aziridinium ion 213. Ring opening of intermediate 213 takes place with inversion of configuration by an attack
of the nitrile molecule. \( N \)-cyclization of the resulting intermediate 214 afforded the cyclic \( N \)-acyliminium ion intermediate 215. Debenzylation of 215 and hydrolysis gave the observed imidazole 210.

Scheme 3.6. Proposed mechanism for the formation of imidazoles 210.

2-Oxazolines were prepared from the Ritter reaction of cyclic sulfites by Batoux\(^8\)\(^0\) in 2009. The reaction of 1,2-cyclic sulfites 216 with nitriles in the presence of Lewis acids in xylene at reflux temperature furnished the corresponding 2-oxazoles 217 in moderate yields (Scheme 3.7). While the reaction of \( o \)- and \( p \)-hydroxybenzonitriles provided the Ritter adducts in 57\% and 78\% yield, respectively, \( m \)-hydroxybenzonitrile did not give any product. 2-Cyanothiophene and propionitrile furnished the corresponding oxazoles in respective yields of 34\% and 50\%.

Scheme 3.7. Synthesis of 2-oxazoles 217.

In 1991, Danishefsky\(^8\)\(^1\) reported Ritter-like reactions of 1,2-anhydropyranose derivatives 218. Treatment of 1,2-anhydropyranose compounds 218 with CH\(_3\)CN and ZnCl\(_2\) afforded the corresponding oxazolines 219 in yields of 23-53\% (Scheme 3.8).
They suggested that a S\textsubscript{N}1 type opening of the epoxide ring resulted in the equatorial anomeric intermediate 221. Inversion of this intermediate to the axial anomeric intermediate 222 followed by intramolecular attack of oxygen gave the oxazolines 219 (Scheme 3.9).

**Scheme 3.8.** Synthesis of oxazolines 219.

**Scheme 3.9.** Proposed mechanism for the formation of oxazolines 219.

**Scheme 3.10.** The Holy reaction of arabinose 223 with cyanamide.
Jenkinson\textsuperscript{82} demonstrated the Holý reaction of 2-C-methyl arabinose \(223\) to form the oxazoline \(224\) in 62\% yield by treatment with cyanamide and ammonium hydroxide at 80 °C (Scheme 3.10).

### 3.1.1. Ritter Reactions of (4S)-1-Benzyl-4,5-dihydroxy-3-pyrrolidin-2-one

With the aim of preparing the pyrrolo[2,3-\(d\)]oxazole \(129\) in good yield, the pyrrolidinone \(124\) was first treated with 2.0 mol equivalents of BF\(_3\).Et\(_2\)O in CH\(_3\)CN at 0 °C to rt for 16 h. This reaction provided the pyrrolo[2,3-\(d\)]oxazole \(129\) in 88\% yield (Table 3.3, Entry 1). The use of 3.0 or 4.0 mol. equivalents of BF\(_3\).Et\(_2\)O under the same experimental conditions afforded the oxazole \(129\) in slightly enhanced yields of 93\% and 91\%, respectively (Table 3.3, Entries 2 and 3). Increasing the amount of BF\(_3\).Et\(_2\)O above 3.0 mol equivalents did not cause much of a difference in the yield of the reaction, thus we decided to use 3.0 mol. equivalents of BF\(_3\).Et\(_2\)O in future reactions. The effects of the concentration of \(124\) on the yield of \(129\) was also investigated. Repeating the reaction at 0.05 M and 0.2 M concentrations gave the desired product \(129\) in 90\% and 91\% yields, respectively (Table 3.3, Entries 4 and 5). The molar equivalents of BF\(_3\).Et\(_2\)O and the concentration of \(129\) did not have much of an affect on the yield of this reaction.

**Table 3.3. Results of reaction of \(124\) with CH\(_3\)CN.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. of BF(_3).Et(_2)O</th>
<th>Concentration of (124)</th>
<th>Yield% of (129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>0.1M</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>0.1M</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>4.0</td>
<td>0.1M</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>0.05M</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>0.2M</td>
<td>91</td>
</tr>
</tbody>
</table>

The structure of \(129\) was confirmed from NMR spectroscopic analysis. In the \(^1\)H NMR spectrum of \(129\) (Figure 3.2) the diastereotopic H6 protons resonated at 2.85
(1H, dd, $J = 7.5, 18.5$ Hz) and 2.69 (1H, d, $J = 18.5$ Hz) ppm. The coupling constants for $J_{6a,6b}$ was 18.5 Hz, $J_{6b,6a}$ was 7.5 Hz and $J_{6a,6a}$ was 0 Hz. H6a resonated at 4.90 (1H, t, $J = 7.5$ Hz) ppm, while H3a resonated more downfield at 5.38 (1H, d, $J = 7.5$ Hz) ppm. $J_{3a,6a}$ was 7.5 Hz. The dihedral angles calculated from molecular modelling studies using Spartan 04 (AMI) of 129 were consistent with the observed $J$ values. The dihedral angles ($\phi$) calculated for H6$\alpha$ and H6a was 96.6 °, indicative of a very small coupling constant (Figure 3.4), consistent with the observed 0 Hz coupling. The dihedral angle calculated for H6$\beta$ and H6a was -28.6 °, indicative of a relatively large coupling constant consistent with that observed (7.5 Hz). The methyl protons were observed at 2.03 ppm as a singlet. The $13^C$ NMR spectrum of 129 (Figure 3.3) was also consistent with the structure. The carbonyl carbon resonated at 170.7 ppm, while the quaternary carbon C2 resonated at 168.8 ppm. The DEPT spectrum of 129 showed two methine carbon resonances at 83.2 and 74.4 ppm corresponding to the C3a and C6a carbons, respectively and two methylene carbon signals at 44.2 and 37.5 ppm corresponding to C1' and C6, respectively. The methyl carbon resonance was observed at 14.1 ppm in the $13^C$ NMR spectrum. The LREIMS spectrum of 129 showed a molecular ion peak at 230 amu. Its molecular formula was found to be C$_{13}$H$_{14}$N$_{2}$O$_{2}$ from HREIMS analysis which was consistent with the structure of 129. The C=O bond stretch was observed at 1680 cm$^{-1}$ in its IR spectrum.

**Figure 3.2.** $^1$H NMR (500 MHz, CDCl$_3$) spectrum of 129.
The reaction of \( \text{124} \) with \( \text{CH}_3\text{CN} \) was remarkable for providing the Ritter adduct \( \text{129} \) in high yield and total diastereoselectivity. The \( ^1\text{H} \) NMR spectrum of \( \text{129} \) showed only one diastereoisomer. This result was unexpected since \( N \)-acyliminium ions can be attacked by nucleophiles from either face which results in the formation of both diastereomers. To explain the high yield and diastereoselectivity of the reaction, we suggested that the attack of nitriles to the \( N \)-acyliminium ion was reversible\(^{81-83} \) and gave a mixture of 4,5-\textit{trans} pyrrolidinone \( \text{226} \) and 4,5-\textit{cis} pyrrolidinone \( \text{227} \) isomers. The 4,5-\textit{cis} pyrrolidinone \( \text{227} \) cyclises to the oxazolidine cationic intermediate \( \text{228} \) more rapidly resulting in the formation of only the \textit{cis} isomer. Deprotonation of the intermediate \( \text{228} \) gives the observed oxazolidine \( \text{129} \) (Scheme 3.11). Consistent with this hypothesis were the calculated heats of formation of the \textit{cis} and \textit{trans} isomers of \( \text{129} \) using Spartan 04 (AMI). The heat of formation of the \textit{cis} isomer was -14.4 kcal/mol, while that of the \textit{trans} isomer was 24.3 kcal/mol. The \textit{cis} isomer, whose
heat of formation was 38.7 kcal/mol less than \textit{trans} isomer, was predicted to be thermodynamically much more stable.

Scheme 3.11. Proposed mechanism for the formation of 129.

A 2D NOESY experiment on 129 also confirmed its \textit{cis} stereochemistry. The protons H3a and H6a showed a cross peak which indicates a \textit{cis} relation between these two protons (Figure 3.5). There were also cross peaks observed between the protons H6a and H6β and the protons H6β and H6α.

Figure 3.5. The observed NOE correlations of 129.

Next the pyrrolidinone 124 was treated with isopropyl nitrile under the same reaction conditions to give the corresponding pyrrolo[2,3-\textit{d}]oxazole 229a in 90% yield as one isomer (Table 3.4, Entry 1). Aromatic nitriles were also tried in this reaction and they also worked well. The reaction of 124 with benzonitrile provided the desired Ritter product 229b in 86% yield, while that of 3,4-dimethoxybenzonitrile furnished the desired adduct 229c in 91% yield (Table 3.4, Entries 2 and 3). All reactions
worked well without the formation of any detectible side products. Their TLC analysis showed only one spot which was the product. Their $^1$H and $^{13}$C NMR spectra were consistent with their structures. LREIMS analysis confirmed the structures of compounds 229a-c possessing molecular ions consistent with their structures at, 258, 292 and 352 amu, respectively.

**Table 3.4.** Ritter reactions of 124.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound no</th>
<th>R</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>229a</td>
<td>(CH$_3$)$_3$CH</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>229b</td>
<td>Ph</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>229c</td>
<td>3,4-MeOC$_6$H$_4$</td>
<td>91</td>
</tr>
</tbody>
</table>

After having very high yields and diastereoselectivities from the Ritter reactions of 124, we decided to investigate the Ritter reactions of pyrrolidinone 126. The pyrrolidinone 126 was first treated with CH$_3$CN in the presence of BF$_3$.Et$_2$O (3.0 eq.) to afford the Ritter product 129 in 80% yield as one isomer and the known compound N-benzylacetamide 230 in 72% yield (Scheme 3.12). The $^1$H and $^{13}$C NMR spectra of the Ritter product 129 was identical to that of the product that was obtained from the reaction of diol 124 with CH$_3$CN (Table 3.3). Amide 230 was identified from a comparison of its NMR spectra with that reported in the literature.\textsuperscript{84}

**Scheme 3.12.** Reaction of 126 with CH$_3$CN.

The proposed mechanism (Scheme 3.13) for the Ritter reaction of 126 is similar to that proposed for the reaction of 124 with CH$_3$CN (Scheme 3.11) except for the
deprotonation step. In this case, instead of deprotonation of cation intermediate 233, debenzylation occurred and the benzyl cation underwent a Ritter reaction with CH₃CN to yield N-benzylacetamide 230 after an aqueous work up.

![Chemical structure](image)

**Scheme 3.13.** Proposed mechanism for the Ritter reaction of 129 and formation of 230.

The reaction of 126 with isopropyl nitrile and benzonitrile under the same experimental conditions yielded the corresponding oxazoles 229a and 229b in 87% and 80% yields, respectively and the known amide products N-benzylisobutylamide 234a and N-benzylbenzamide 234b in 77% and 63% yield, respectively (Table 3.5, Entries 1 and 2). The ¹H and ¹³C NMR spectra of 229a and 229b were identical to those of the products that were obtained from the reactions of 124 with isopropyl nitrile and benzonitrile, respectively.

**Table 3.5.** Results of Ritter reaction of 126.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield% of 229</th>
<th>Yield% of 234</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH₃)₂CH</td>
<td>87</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>80</td>
<td>63</td>
</tr>
</tbody>
</table>
We attempted to oxidize products 229a and 229b with MnO₂ (10 or 20 eq.) in toluene with heating at 100 °C for 24 h (Scheme 3.14). These oxidation reactions did not give the desired oxazole products 235a,b and only unreacted starting material was recovered.


3.2. Hydrolysis of Pyrrolo[2,3-d]oxazoles

Next the pyrrolo[2,3-d]oxazoles 129 and 229a were converted to the 2-acylaminopyrrolidinones through acidic hydrolysis. The Ritter product 129 was treated with 6N HCl in MeOH at rt for 25 min to give the corresponding 2-acylaminopyrrolidinone 185 in 42% yield (Scheme 3.15).

Scheme 3.15. Acidic hydrolysis of 129.

The product 185 was identified from analysis of its ¹H and ¹³C NMR spectra. The ¹H NMR spectrum showed a signal at 5.55 (1H, d, J = 6.5 Hz) ppm, corresponding to the H5 proton, and at 4.39 (1H, app. br. q, J = 6.5 Hz) ppm corresponding to the H4 proton. The J₄,₅ value of 6.5 Hz indicated the cis 4,5-stereochemistry. The signals for the diastereotopic hydrogens H3 appeared at 2.68 (1H, dd, J = 6.5, 17.5 Hz) and 2.46 (1H, dd, J = 4.5, 17.5 Hz) ppm. The methyl protons resonated at 1.88 ppm as a singlet. However the signals of the NH and OH protons could not be observed in the ¹H NMR spectrum of 185 (Figure 3.6) due to rapid exchange with the NMR solvent CD₃OD. However, a broad peak at 3318 cm⁻¹ in its IR spectrum clearly indicated the
existence of these groups. The $^{13}$C NMR spectrum was also consistent with the structure of 185 and showed resonances at 174.9 and 173.9 ppm for the two carbonyl carbons.

**Figure 3.6.** $^1$H NMR (500 MHz, CD$_3$OD) spectrum of 185.

When the oxazole 229a was subjected to the same acid hydrolysis reaction conditions the corresponding 2-acylaminopyrrolidinone 236 was obtained in 70% yield (Scheme 3.16).

**Scheme 3.16.** Acidic hydrolysis of 229a.

In this case, the product was soluble in CDCl$_3$ and the NH and OH proton signals of 238 were observed at 6.40 (1H, d, $J = 9.0$ Hz) and 3.87 (1H, d, $J = 4.5$ Hz) ppm, respectively in the $^1$H NMR spectrum (Figure 3.7). The methine protons H5 and H4 resonated at 5.58 (1H, dd, $J = 5.5$, 9.0 Hz) and 4.36 (1H, br. t, $J = 5.5$ Hz) ppm, respectively. $J_{4,5}$ was 5.5 Hz, indicative of a cis relation between H4 and H5. The $^{13}$C NMR spectrum was also consistent with the structure of 236 and it showed signals at 177.9 and 172.3 ppm corresponding to two carbonyl carbons. The DEPT spectrum showed three methine carbon signals at 66.2, 65.1 and 35.5 ppm corresponding to
C5, C4 and C2’, respectively and two methylene carbon resonances at 44.2 and 39.1 ppm corresponding to CH2Ph and C3, respectively. The signals for the diastereotopic methyl carbons were observed at 19.2 and 19.1 ppm. The IR spectrum of 236 also confirmed the structure showing a broad peak at 3291 cm⁻¹ for the N-H and O-H stretches and two sharp peaks at 1663 and 1649 cm⁻¹ for the two C=O stretches.

In conclusion, a high yielding and diastereoselective method has been developed to prepare chiral pyrrol[3,2-\(d\)]oxazoles using the Ritter reaction of 5-hydroxy or 5-benzyloxy-4-hydroxypyrrolidin-2-one with nitriles in the presence of BF₃.Et₂O. When the 4-benzyloxy-5-hydroxypyrrolidin-2-one substrate was used the corresponding N-benzyl amides were isolated from the Ritter reactions of benzyl cation and the nitrile. The isolation of these compounds were consistent with our proposed reaction mechanism. Two of the pyrrol[3,2-\(d\)]oxazoles compounds were hydrolyzed to the novel 5-acylaminopyrrolidinones, 185 and 236.
4. METAL CATALYZED CYCLOISOMERIZATION REACTIONS AND COPPER MEDIATED CYCLIZATION-HALOGENATION AND CYCLIZATION-CYANATION REACTIONS OF 2-ALKYNYL-3-HYDROXY PYRROLIDINES

In Chapter 2 we reported the borono-Mannich reactions of pyrrolidines, having an \textit{endo}-cyclic \(N\)-acyl group, with alkenyl and aryl boronic acids and borates. In this Chapter we focused on the borono-Mannich reaction of pyrrolidines 54, having an \textit{exo}-cyclic \(N\)-acyl group, with alkynyl boronates 55 and the metal-catalyzed cycloisomerization reactions of the borono-Mannich adducts 56 (Scheme 4.1). These adducts 56 can in principle be cyclised to novel furo[3,2-\(b\)]pyrroles 57 which is the common heterocyclic nucleus of the biologically active alkaloids, lucilactaene,\textsuperscript{40} 13\(\alpha\)-lucilactaene\textsuperscript{87} 47, UCS1025A 49 and fusarin A 48 which were discussed in Chapter 1, Section 1.8.

![Scheme 4.1. Proposed synthesis of furo[3,2-\(b\)]pyrroles 57.](image)

Metal-catalysed cycloisomerization of alkynes is a well known method for the construction of heterocyclic systems. Pd(II), Pt(II), Ag(I), Ru(CO)\textsubscript{12}, Au(I), Au(III), Cu(I) and Zn(II) salts have been used as catalyst in the cyclization reactions of alkynes.\textsuperscript{88-97} These transformations involve the fast and reversible complexation of the alkyne by the metal salt [M]. The resulting electrophilic alkyne complex 238 is reactive towards nucleophiles. Intramolecular nucleophilic attack on the alkyne complex results in the formation of the heterocyclic intermediate 239. Protonolysis of 239 gives the cycloisomerization product 240 and releases the metal catalyst [M] (Scheme 4.2).
Scheme 4.2. Mechanism of metal-catalyzed cycloisomerization reactions of alkynes 237.

The metal-catalyzed cyclization of alkynes bearing an oxygen nucleophile is a powerful method for the construction of various oxygen-containing heterocycles. Utimoto\(^9\) first reported the Pd(II)-catalyzed cyclization of 2-methoxy-3-alkyn-1-ols 241 to 2,3,5-trisubstituted furans 242 in good yields (Scheme 4.3). Treatment of alkynediols 243 with Pd(II) under the same experimental conditions gave spirocyclic acetals 244 through intramolecular addition of two hydroxyl groups to the internal alkyne (Scheme 4.4).

Scheme 4.3. Utimoto’s synthesis of furans 242.

Scheme 4.4. Synthesis of 244.

The furopyridines 246a,b were obtained from the cyclization reactions of 4-acetylenic pyridines 245a,b in the presence of CuI (Scheme 4.5).\(^9\) The TMS group did not survive under the reaction conditions. Cyclization of 245a produced the
corresponding furopyridine \(246a\) in 80% yield, while \(245b\) afforded the furopyridine \(246b\) in 86% yield.

![Scheme 4.5. Synthesis of furopyridines 246a and 246b.](image)

Carreira\textsuperscript{100} used ZnI\(_2\) as a catalyst in the cyclization of \(N\)-hydroxylamines \(247\) to 2,3-dihydroisoxazoles \(248\) (Scheme 4.6). Treatment of \(N\)-hydroxylamines with ZnI\(_2\) (0.1 eq.) and DMAP (0.1 eq.) in CH\(_2\)Cl\(_2\) furnished the cyclic products in yields of 82-97%. However, using other Lewis acids (BF\(_3\).Et\(_2\)O, AlCl\(_3\), Cu(OTf)\(_2\), Mg(OTf)\(_2\) and Sn(OTf)\(_2\)) together with DMAP in the same reaction did not provide the desired 2,3-dihydroisoxazoles.

![Scheme 4.6. Synthesis of 2,3-dihydroisoxazoles 248.](image)

Genet\textsuperscript{101} reported the cyclization of \textit{bis}-homopropargylic diols \(249\) under gold catalysis. The reactions of homopropargylic diols \(249\) with AuCl or AuCl\(_3\) provided easy access to the strained bicyclic ketals \(250\) under mild conditions (Scheme 4.7). The reaction did not give any of the bicyclic ketal product in the absence of the metal. In most cases the reaction had completed in 30 min, the longest reaction time was 50 min.
Scheme 4.7. Preparation of bicyclic ketal 250.

In a plausible mechanism for this reaction the Au catalyst forms the complex 251 with the triple bond (Scheme 4.8). The coordination to triple bond enhances the electrophilicity of the alkyne, which allows the addition of one alcohol to the triple bond. Protonolysis of the enol vinylgold intermediate 252 leads to an enol ether, which then undergoes a second intramolecular addition of the alcohol group to provide the product 250.

Scheme 4.8. Proposed mechanism for the formation of bicyclic ketal 250.

Silver has also found to be effective catalyst in the cycloisomerization of alkynols. 2-Methylene–oxolanes were prepared from the reaction of acetylenic alcohols 243a-e with Ag$_2$CO$_3$. A catalytic amount of Ag$_2$CO$_3$ was enough for cyclic substrates 253a,b, in which the two reacting parts of the molecule were close together (Table 4.1, Entries 1 and 2), while other substrates 253c-e needed stoichiometric amounts of Ag$_2$CO$_3$ (Table 4.1, Entries 3, 4 and 5).
Table 4.1. Synthesis of 2-methylene-oxolanes 254a-e.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkynol 253</th>
<th>Amount of Ag₂CO₃</th>
<th>Product 254</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>253a</td>
<td>10 mol %ₐ</td>
<td>254a</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>253b</td>
<td>10 mol%ₐ</td>
<td>254b</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>253c</td>
<td>100 mol%ₐ</td>
<td>254c</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>253d</td>
<td>100 mol%ₐ</td>
<td>254d</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>253e</td>
<td>100 mol%ₐ</td>
<td>254e</td>
<td>95</td>
</tr>
</tbody>
</table>

ₐ) Reactions were performed in benzene at 80 °C for 1 h, b) Reactions were performed in C₆D₆ at 80 °C for 6 h. c) Reaction was performed in C₆D₆ at 20 °C for 2 h.

Fürstner¹⁰³ showed PtCl₂ was an effective catalyst in the cycloisomerization reactions of ortho-alkynylphenols 255. Treatment of ortho-alkynylphenols 255 with PtCl₂ in toluene at 80 °C furnished the 2-substituted benzofurans 256 in yields of 88-98% (Scheme 4.9).

![Scheme 4.9. Synthesis of 2-substituted benzofurans 256.](image-url)
4.1. Borono-Mannich Reactions of Benzyl 2,3-Dihydroxyprololidine-1-carboxylate

The two components of the borono-Mannich reaction were not commercially available. The N-acyliminium ion precursor, benzyl 2,3-dihydroxyprololidine-1-carboxylate, was prepared in three steps from prololidine following a known procedure (Scheme 4.10). The first step was the silver(I)-catalyzed oxidation of prololidine to the 1-prololidine trimer with Na$_2$S$_2$O$_8$ in water. The second step was the N-acylation of trimer with CbzCl in THF to give. The third step was the dihydroxylation of double bond with K$_2$OsO$_4$.2H$_2$O to give. Although the first step looked simple we had many problems in making the trimer. A suspension of prololidine, NaOH, AgNO$_3$ in water was treated with aqueous solution of Na$_2$S$_2$O$_8$ below 10 °C as indicated in the literature. Since the temperature of the reaction after adding the Na$_2$S$_2$O$_8$ was not mentioned, the reaction mixture was first stirred at rt which did not give the desired oxidation product. The reaction was also performed at 10 °C or 0 °C but none of these reactions gave the desired trimer. However the use of a fresh bottle of Na$_2$S$_2$O$_8$ and stirring the reaction mixture at rt furnished the trimer in 50% yield. The freshness of the Na$_2$S$_2$O$_8$ was found to be crucial in this reaction. The freshly prepared trimer was subjected to a N-acylation reaction with CbzCl in the presence of Et$_3$N. A 0.1 M THF solution of the trimer was distilled into a flask precooled to -78 °C and then was treated with Et$_3$N and CbzCl to afford the desired N-Cbz prololidine in 60% yield. The dihydroxylation of the double bond of 260 worked smoothly to give the desired diol 116 in 85% yield as a single isomer.

![Scheme 4.10. Synthesis of diol 116.](image-url)
It should be noted that compound 116 is racemic and therefore all chiral derivatives or products arising from this compound are also racemic. In many cases these chiral derivatives or products are drawn as a single enantiomer, this is to show the relative configuration of the molecule.

The other component of the borono-Mannich reaction, potassium phenylethynyltrifluorobororate 262, was synthesized from the reaction of phenylacetylene 261 with nBuLi followed by treatment of the corresponding lithium acetylide with trimethylborate. Treatment of the resulting boronate ester with KHF$_2$ provided the potassium phenylethynyltrifluoroborate 262 in 60% yield (Scheme 4.11).$^{107,108}$

**Scheme 4.11.** Synthesis of 262.

Having both components of the reaction in hand, the borono-Mannich reaction of 116 and 262 was performed in CH$_2$Cl$_2$ with 3.0 mol equivalents of 262 and 4.0 mol equivalents of BF$_3$.Et$_2$O at 0 °C to rt for 16 h. The desired product was obtained in 46% yield with a diastereomeric ratio of 64 : 36 (Table 4.2, Entry 1). These isomers could be separated by column chromatography. Although we obtained the desired addition product the yield of the reaction was not satisfactory. The amounts of the trifluoroborate component and the Lewis acid component in the borono-Mannich reaction were increased to 5 mol equivalents which furnished the desired product in 50% yield (Table 4.2, Entry 2). In order to increase the yield of the desired product the reaction was repeated in MeNO$_2$ and CHCl$_3$ which provided the desired adduct in respective yields of 39% and 52% (Table 4.2, Entries 3 and 4). The use of CH$_3$CN as a solvent in the reaction was expected to give low yields, since it can react with the N-acyliminium ion intermediate to give the Ritter product. However, the borono-Mannich adduct 263 was obtained in a very high yield of 89% as a 73 : 27 diastereomeric mixture (Table 4.2, Entry 5). The $^1$H NMR spectrum of the crude reaction mixture did not show any signals that could be related to the possible Ritter product. The isomers of 263 could be separated by column chromatography. The $^1$H
and $^{13}$C NMR spectra of the individual isomers were in good agreement with their structures. In the $^1$H NMR spectrum of the major product, the H3 proton resonated at 4.85 (1H, br. s) ppm, while the H2 proton resonated at 4.41-4.32 (1H, m) ppm. The same methine protons, H3 and H2 of the minor isomer resonated at 4.66 (1H, s) and 4.50 (1H, br. s) ppm, respectively. The alkyne carbons of the minor isomer showed signals at 86.3 and 84.2 ppm, while those of the major isomer appeared at 87.2 and 84.0 ppm in $^{13}$C NMR spectra. The IR spectrum of the major isomer showed a broad peak at 3421 cm$^{-1}$ corresponding to the O-H stretch, a sharp band at 2245 cm$^{-1}$ corresponding to the C≡C stretch and a sharp peak at 1685 cm$^{-1}$ corresponding to the C=O stretch. Similarly, the IR spectrum of the minor isomer showed bands at 3477, 2287 and 1680 cm$^{-1}$ corresponding to the O-H, C≡C and C=O stretches, respectively.

Table 4.2. Optimization of borono-Mannich reaction of 116 and 262.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of 262</th>
<th>Equivalents of BF$_3$.Et$_2$O</th>
<th>Solvent</th>
<th>Yield% of 263</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>4</td>
<td>CH$_2$Cl$_2$</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>5</td>
<td>CH$_2$Cl$_2$</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>4</td>
<td>CH$_3$NO$_2$</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>4</td>
<td>CHCl$_3$</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>4</td>
<td>CH$_3$CN</td>
<td>89</td>
</tr>
</tbody>
</table>

Obtaining 263 as a diastereomeric mixture was unexpected since 2,3-cis pyrrolidines was obtained exclusively from the borono-Mannich reaction of 116 with alkenyl or aryl boronates in the literature. Although these isomers of 263 could be separated by column chromatography the signals in the $^1$H NMR spectrum were broad due to rotamers making the measurement of $J_{2,3}$ difficult. The stereochemistry of these isomers was not clear from NMR spectroscopic analysis. To help determine the stereochemistry, the diacetate derivative of 116 was synthesized and subjected to a borono-Mannich reaction with the same organotrifluoroboronate 262. The diol 116 was treated with Ac$_2$O and DMAP in pyridine at rt to give the 2,3-diacetate pyrrolidine 264 in 94% yield. The diacetate 264 was reacted with 262 under the optimized conditions to give the 2,3-trans adduct 265 exclusively in 77% yield.
(Scheme 4.12). For this compound $J_{2,3}$ was found to be 0 Hz from its $^1$H NMR spectrum which was consistent with the 2,3-\textit{trans} stereochemistry. The methine protons H2 and H3 of the pyrrolidine ring of 265 resonated at 4.74 (1H, s) and 5.20 (1H, s) ppm, respectively. The methyl protons resonated at 2.06 (3H, s) ppm. The carbonyl carbon of the acetate group resonated at 170.2 ppm, while that of the Cbz group was at 154.4 ppm. The methyl carbon signal was observed at 21.0 ppm in the $^{13}$C NMR spectrum. The adduct 265 was then subjected to a deacetylation reaction by treatment with K$_2$CO$_3$ in MeOH at rt to provide the 2,3-\textit{trans} adduct \textit{trans}-263 in 72\% yield (Scheme 4.12). The $^1$H and $^{13}$C NMR spectra of \textit{trans}-263 was identical to that of minor isomer of 263. It was thus concluded that the major isomer from the reaction of 116 and 262 was the 2,3-\textit{cis} pyrrolidine and the minor isomer was the 2,3-\textit{trans} pyrrolidine.

\begin{center}
\textbf{Scheme 4.12.} Synthesis of racemic \textit{trans}-263.
\end{center}

The high \textit{trans} selectivity of acetate derivatives can be explained by neighbouring-group participation of the acetate group to give a bridged bicyclic cationic intermediate 267 and then S$_N$2-like attack of the nucleophile on this intermediate would provide the \textit{trans} adduct 268 (Scheme 4.13).\textsuperscript{46}
4.2. Metal-Catalyzed Cycloisomerization Reactions of the 2,3-\textit{cis} Pyrroldine

As mentioned previously the cycloisomerization of alkynols have been performed under the catalysis of a range of metal salts. Salts of the metal cations Ag(I), Pd(II)/Cu(I) and Au(I) were chosen as a catalyst in this project. The 2,3-\textit{cis} pyrroldine \textit{cis}-263 was treated with 30 mol\% of AgNO\textsubscript{3} in methanol at rt for 2 h\textsuperscript{109}. The reaction afforded the 2,5-disubstituted furan 270 in a yield of 83\% but not the expected furo[3,2-\textit{b}]pyrrole structure 269 (Scheme 4.14). It was suggested that the desired bicyclic structure 269 was formed in the reaction first and then underwent a ring opening reaction to form furan 270. The structure of 270 was clearly identified by the presence of resonances in the \textsuperscript{13}C NMR spectrum (Figure 4.2) corresponding to the C3 and C4 carbons which appeared at 108.7 and 105.7 ppm, respectively. These chemical shifts are typical for the C3 and C4 carbons of furans\textsuperscript{110}. The chemical shifts of the C3a and C6a carbons in the desired bicyclic structure 269 were expected to appear between 70-80 ppm. The resonance at 4.92 (1H, br. s) ppm in the \textsuperscript{1}H NMR spectrum of 270 (Figure 4.1) corresponding to NH proton and was also consistent with the structure of 270. The H3 and H4 protons resonated at 6.13 (1H, d, \(J = 3.5\) Hz) and 6.54 (1H, d, \(J = 3.5\) Hz) ppm, respectively with a vicinal coupling constant of 3.5 Hz, typical values for \(J_{3,4}\) of furans\textsuperscript{110}. Furthermore the methylene protons H1’ and H2’ appeared as a triplet and broad quartet, respectively, consistent with a ring-opened structure. The existence of the N-H and C=O bonds were supported by two bands at 3246 and 1695cm\textsuperscript{-1}, respectively in the IR spectrum. LRESIMS analysis of the compound confirmed the molecular weight of 270 possessing a molecular ion consistent with the structure at 322 amu. The molecular formula of the compound was found to be C\textsubscript{20}H\textsubscript{19}NO\textsubscript{3} from HRESIMS analysis.

Figure 4.1. $^1$H NMR (500 MHz, CDCl$_3$) spectrum of 270.

Figure 4.2. $^{13}$C NMR (125 MHz, CDCl$_3$) spectrum of 270.

Performing the cycloisomerisation reaction of cis-263 under the catalysis of AgNO$_3$ in DMF at rt for 5 h produced the 270 in 63% yield (Table 4.3, Entry 2). When 10 mol % of AgNO$_3$ and MeOH was used, 270 was isolated in 75% yield after 10 h at rt (Table 4.3, Entry 3). However while the reaction worked well with the lower load of
catalyst, it needed a longer reaction time for completion. The use of 30 mol % of AgF or Ag₂O as catalyst afforded 270 in 71% and 75% yields, respectively (Table 4.3, Entries 4 and 5). Although AgF and Ag₂O were effective catalysts for this transformation, they needed longer reaction times than AgNO₃.

Table 4.3. Cycloisomerization of cis-263 with Ag(I).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield % of 270</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgNO₃ (30)</td>
<td>MeOH</td>
<td>2 h</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>AgNO₃ (30)</td>
<td>DMF</td>
<td>5 h</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>AgNO₃ (10)</td>
<td>MeOH</td>
<td>10 h</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>AgF (30)</td>
<td>MeOH</td>
<td>7 h</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>Ag₂O (30)</td>
<td>MeOH</td>
<td>8 h</td>
<td>75</td>
</tr>
</tbody>
</table>

We then tried Au(Ph₃P)Cl catalysed reactions of cis-263. At first the reaction was performed with 30 mol % of Au(Ph₃P)Cl in MeOH at rt for 8 h. Furan 270 was obtained in 87% yield (Table 4.4, Entry 1). Although this reaction was slower than that catalyzed by AgNO₃, it provided the product in a higher yield than Ag(I).

Encouraged by this result and aiming to get a similar yield with a lower load of catalyst, the reaction was repeated with 10 mol % and 5 mol % of Au(Ph₃P)Cl which furnished 270 in 74% and 60% yields, respectively (Table 4.4, Entries 2 and 3). The yields of these reactions were good, even with 10 mol% and 5 mol % of catalyst, but the reaction times were 21 h and 3 d, respectively. When 1 mol % of catalyst was used the reaction had not gone to completion even after 5 d. Column chromatography of the reaction mixture yielded 270 in only 22% yield and starting material was isolated in 49% yield. Performing the reaction in DMF with 30 mol % of Au(Ph₃P)Cl at rt for 24 h gave 270 in 70% yield (Table 4.4, Entry 4). The use of PdCl₂(PPh₃) (4 mol%) and CuI (5 mol%) as a catalyst system in MeOH at rt for 8 h afforded 270 in 69% yield (Table 4.4, Entry 5). Performing this reaction in DMF lowered the yield to 43% (Table 4.4, Entry 6). The order of catalyst reactivity in these transformation was found to be Ag(I) > Au(I) > Pd(II)/Cu(I).
Table 4.4. Cycloisomerization of cis-263 with Au(I) or Pd(II)/Cu(I) catalysts.

![Cycloisomerization of cis-263 with Au(I) or Pd(II)/Cu(I) catalysts.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield % of 270</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Au(Ph₃P)Cl (30)</td>
<td>MeOH</td>
<td>8 h</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Au(Ph₃P)Cl (10)</td>
<td>MeOH</td>
<td>21 h</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>Au(Ph₃P)Cl (5)</td>
<td>MeOH</td>
<td>3 d</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Au(Ph₃P)Cl (30)</td>
<td>DMF</td>
<td>10 h</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>PdCl₂(PPh₃) (4)/CuI (5)</td>
<td>MeOH</td>
<td>8 h</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>PdCl₂(PPh₃) (4)/CuI (5)</td>
<td>DMF</td>
<td>12 h</td>
<td>43</td>
</tr>
</tbody>
</table>

The cycloisomerization of trans-263 was also investigated. In an initial attempt trans-263 was treated with 30 mol % of AgNO₃ in MeOH at rt for 16 h which resulted in only the recovery of unreacted trans-263 quantitatively (Scheme 4.15). The use of Au(Ph₃P)Cl (30 mol%) did not give any product, trans-263 was isolated quantitatively. Performing the reaction in DMF with 30 mol % of AgNO₃ at 80 ºC yielded only the starting material.

![Scheme 4.15. Results of the treatment of trans-263 with Ag(I) or Au(I).](image)

4.3. Copper Mediated Cyclization-Halogenation and Cyclization-Cyanation Reactions of 2,3-cis Pyrrolidine

It is known that cyclization-iodination reactions of alkynols can be achieved by using the electrophilic iodinating agents, I₂, NIS, I(coll)₂PF₆ and ICl with or without a base. For example Larock¹¹¹ reported the synthesis of iodo benzofurans and iodo indoles from the electrophilic cyclizations of 2-alkynyl phenols and anilines with I₂ (Scheme 4.16).

Knight\textsuperscript{112} reported the cyclization of alk-3-yn-1,2-diols 273 with I\textsubscript{2} in the presence of NaHCO\textsubscript{3} to furnish \(\beta\)-iodofurans 274 in good yields (Scheme 4.17).

Scheme 4.17. Synthesis of iodofurans 274.

Okitsu\textsuperscript{113} showed the synthesis of 3-iodobenzofurans 276 via cyclization of 2-alkynyl-1-(1-ethoxyethoxy)benzenes 275 in the presence of I\textsubscript{(coll)}\textsubscript{2}PF\textsubscript{6}. They found that using BF\textsubscript{3}.Et\textsubscript{2}O as an additive in the reaction enhanced the reactions rate to give 276 in quantitative yield within 10 min. The iodocyclization reaction worked well with the different substrates to give the 3-iodo-2-substitutedbenzofurans in 70-100\% yields (Scheme 4.18).


Cyclization-chlorination and cyclization-bromination reactions of 2-alkynyl phenols were reported by Li.\textsuperscript{114} The 2-alkynyl phenols 277 were treated with PdX\textsubscript{2}/CuX\textsubscript{2} in
the presence of HEt₃NX in DCE at rt to afford a mixture of 3-halo-2-substituted benzofurans 278 and 2-substituted benzofurans 279 (Scheme 4.19). In the presence of PdX₂, 2-substituted benzofurans 279 were obtained in good yields whereas in the presence of PdX₂/CuX₂ and HEt₃NI, 2-substituted-3-halobenzofurans 278 were obtained as the major products.

\[
\begin{align*}
\text{Scheme 4.19. Synthesis of 3-halo-2-substituted benzofurans.}
\end{align*}
\]

We then tested the Cu(I) salts as a catalyst in the cycloisomerization reaction of 263. The reaction of cis-263 with 30 mol % of CuI in MeOH at rt did not proceed, cis-263 was recovered quantitatively. However, performing the reaction at 80 °C in DMF with with 1 mol equivalent of CuI under a nitrogen atmosphere furnished products 270 and 280 in 55% and 20% yields, respectively (Table 4.5, Entry 1). The product 280 was an important compound since it could potentially be a useful intermediate in many palladium-catalyzed processes, like the Sonogashira, Suzuki, and Heck coupling reactions. The structure of 280 was identified from its ¹H and ¹³C NMR spectra. The ¹³C NMR spectrum showed a resonance at 83.3 ppm, corresponding to C3a, at 71.7 ppm corresponding to C6a, and at 56.6 ppm corresponding to C3 which was consistent with the structure 280. The ¹H NMR spectrum (Figure 4.3) showed peak broadening due to carbamate rotamers. It showed a resonances at 5.46 (1H, br. s) and 5.33 (1H, s) ppm, corresponding to H3a and H6a, respectively. The IR analysis showed a C=O stretch at 1701 cm⁻¹, but did not show any peak corresponding to a NH stretch which was consistent with the bicyclic structure. LREIMS analysis confirmed the identity of the compound, possessing molecular ions consistent with the structure at 447 amu. With the aim of getting only the iodocyclic product 280, the reaction was performed with 3.0 mol equivalents of CuI under the same experimental conditions. The products 270 and 280 were obtained again but in a ratio of 25 : 75 and in respective yields of 19% and 52% (Table 4.5, Entry 2). However, 280 was isolated as the only product in 65% yield, when 6 mol equivalents
of CuI were used (Table 4.5, Entry 3). An attempt to synthesize 280 from the reaction of cis-263 with a catalytic amount of CuI (10 mol %) and LiI (1.5 eq.) failed. The starting material was recovered quantitatively.

### Table 4.5. Synthesis of 270 and 280.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of CuI</th>
<th>270 : 280&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield% of 270</th>
<th>Yield% of 280</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>77 : 23</td>
<td>55</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>25 : 75</td>
<td>19</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0 : 100</td>
<td>0</td>
<td>65</td>
</tr>
</tbody>
</table>

<sup>a</sup> From <sup>1</sup>H NMR analysis of the crude reaction mixture.

The proposed mechanism for the formation of products 270 and 280 involves the coordination of copper to the triple bond to form intermediate 281 and then formation of the organometallic intermediate 282 by nucleophilic attack of oxygen. Protonation of this intermediate gives the bicyclic structure 269 which then underwent an elimination reaction to the 2,5-disubstituted furan 270. Oxidation of the Cu(I) intermediate 282 to the Cu(II) intermediate 283 by oxygen or by a disproportionation reaction of Cu(I) and then reductive elimination would account for the formation of the iodo cyclic product 280 (Scheme 4.20).

![Figure 4.3. <sup>1</sup>H NMR (500 MHz, CDCl₃) spectrum of 280.](image-url)
Scheme 4.20. The proposed mechanism for the formation of 270 and 280.

We also attempted to make the iodocyclic product 280 via a cyclization-iodination reaction of cis-263. Treatment of cis-263 with I₂ (3.0 eq.) and NaHCO₃ (3.0 eq.) gave the product 270 in a yield of only 18% (Scheme 4.21). The LREIMS analysis of the crude reaction mixture showed molecular ion peaks of the product 280 447 amu. It also showed a molecular ion peak at 575 amu which was the molecular weight of the diiodide product, that formed from the addition of the iodine to the triple bond. The reaction of cis-263 with NIS (3.0 eq.) and NaHCO₃ (3.0 eq.) however produced a complex mixture of products (Scheme 4.22).

Scheme 4.21. Reaction of cis-263 with I₂ and NaHCO₃.
Scheme 4.22. Reaction of cis-263 with NIS.

After investigating CuI as catalyst in this reaction we turned our focus on CuBr and CuCl with the aim of preparing the chloro and bromo substituted bicyclic structures. Thus cis-263 was treated with CuBr under the optimized conditions. The reaction did not give the desired bromobicyclic product instead it gave a 75 : 25 mixture of the 3-bromo furan 284 and the furan 270 in respective yields of 41% and 25% (Scheme 4.23). The structure of the bromo furan 284 was identified from its NMR spectroscopic analysis. The signal for the methine proton H3 was observed at 6.23 (1H, s) ppm, while that of the NH proton was observed at 4.91 (1H, br. s) ppm in the $^1$H NMR spectrum. The $^{13}$C NMR spectrum confirmed the structure of 284 and showed signals at 113.1 and 96.4 ppm, corresponding to the C3 and C4 carbons, respectively. The HMBC spectrum of 284 showed a cross peak between the methylene protons H1' and the methine carbon C3, which confirmed that the bromo was at the C4 position of the furan. LR EIMS spectrum showed two molecular ion peaks at 401 and 403 amu for the two bromine isotopes of $^{79}$Br and $^{81}$Br, respectively.

Scheme 4.23. Reaction of cis-263 with CuBr.
When cis-263 was allowed to react with CuCl under the same experimental conditions, furan 270 was obtained exclusively in a yield of 61% (Scheme 4.24). The reactions of cis-263 with CuBr and CuCl were repeated twice under the same experimental conditions and the results did not change. The use of CuBr resulted in the formation of a mixture of 270 and 284, while the use of CuCl resulted in the formation of 270. Thus CuI was found to be most effective catalyst in the cyclization-halogenation reactions of cis-263.

We next focused on the reaction of cis-263 with CuCN, with the aim of getting a 3-cyano substituted furo[3,2-b]pyrrole. Thus cis-263 was treated with CuCN in DMF to furnish a mixture of 270 and 285 in respective yields of 26% and 30% (Scheme 4.25). The result of this reaction was significant since cyclization-cyanation reactions are not known. However the yield of 285 needed to be increased if this reaction could be of synthetic utility. NMR spectroscopic analysis of 285 was in good agreement with the structure. In the $^{13}$C NMR spectrum of the 285 the CN carbon resonance appeared at 82.6 ppm and the methine carbons C3a and C6a appeared at 87.1 and 65.1 ppm, respectively. The IR spectrum of 285 showed the C≡N and C=O
bond stretches at 2202 and 1708 cm$^{-1}$, respectively. HREIMS analysis showed the molecular formula to be C$_{21}$H$_{19}$N$_2$O$_3$ consistent with the structure.

**Scheme 4.25.** Reaction of cis-263 with CuCN.

The halo and cyano substituted products were assumed to form via a reductive elimination pathway of a RCu(II)X intermediate 283 as mentioned in **Scheme 4.20**. Presumably if we could oxidize the Cu(I) intermediate to the Cu(II) intermediate in situ we can increase the yield of these products using less amounts of copper salts. For this reason we decided to performed these reactions under an oxygen atmosphere. We first examine the reaction of cis-263 with 1.1 mol equivalents of CuI in DMF at 80 °C for 16 h which yielded the iodofuran 286 in 74% yield and 270 in 5% yield (**Scheme 4.26**). The relative ratio of these compounds was 91 : 9 from $^1$H NMR analysis of the crude reaction mixture. The iodofuran 286 was identified by the presence of resonances, in its $^1$H NMR spectrum corresponding to a furan methine group and a NH, which appeared as a singlet resonance at 6.27 ppm and a broad singlet resonance at 4.90 ppm, respectively. The $^{13}$C NMR spectrum of 286 also confirmed the structure and showed a resonance at 117.6 ppm corresponding to the furan methine carbon, at 61.4 ppm corresponding to C4. The IR spectrum showed N-H and C=O stretches at 3367 and 1683 cm$^{-1}$, respectively. HREIMS analysis confirmed its molecular formula to be C$_{20}$H$_{18}$NO$_3$I, consistent with the structure.

**Scheme 4.26.** Reaction of cis-263 with CuI under an O$_2$ atmosphere.
In order to prove that the iodofuran 286 is formed from the ring opening reaction of iodo bicyclic structure 280, and not from the iodination reaction of 270, compound 286 was treated with CuI (1.1 eq.) in DMF under an O₂ atmosphere for 16 h. The iodofuran 286 was isolated in 90% yield (Scheme 4.27). However, treatment of 270 with CuI under the same experimental conditions resulted in recovery of 270. So it was clear that in the reaction the bicyclic structure 280 was formed first and then underwent a ring opening reaction to yield the iodofuran 286. We suspect that Cu(II)O is formed from the reaction between Cu(I) and O₂ which acts as a base to catalyse the ring-opening reaction of 280 to 286. Further evidence for the above mechanism in the formation of 286 came from the treatment of 270 with NIS in CH₃CN at -10 °C to rt for 16 h which provided a 1 : 1 mixture of the 3-iodofuran 286 and the 4-iodofuran 287 in 36% yield (Scheme 4.28). Separation of these isomers could not be achieved due to the same R_f values of these products. The ¹H NMR analysis of the crude reaction mixture showed the methine proton resonances of 286 and 287 at 6.27 (1H, s) and 6.23 (1H, s), and two NH proton signals at 4.90 (1H, br. s) and 4.40 (1H, br. s) ppm, respectively. The LREIMS spectrum of the crude mixture showed a molecular ion peak at 447 amu, consistent with the structures. Treatment of 270 with NBS in CH₃CN at 0 °C to 55 °C for 16 h gave a 1 : 1 mixture of 4-bromofuran 284 and 3-bromofurans 288 in overall 22% yield (Scheme 4.29).

Scheme 4.27. Reaction of 280 with CuI.

Scheme 4.28. Treatment of 270 with NIS.
Scheme 4.29. Treatment of 270 with NBS.

Under similar conditions the reaction of cis-263 with CuBr afforded the 3-bromofuran 284 and the non-brominated furan 270 in a ratio of 95 : 5 and in 68% and 5% yields, respectively (Table 4.6, Entry 1). When CuCl was used as a catalyst 3-chlorofuran 289 and 270 were isolated in respective yields of 78% and 5% (Table 4.6, Entry 2) and in a ratio of 90 : 10. The structure of furan 289 was clear from its NMR spectroscopic analysis. The $^1$H NMR spectrum showed a signal at 6.17 (1H, s) ppm corresponding to the furan methine proton and a signal at 4.92 (1H, br. s) ppm corresponding to the NH proton. The furan methine carbon resonance was observed at 111.0 ppm while that of C4 was observed at 124.7 ppm in the $^{13}$C NMR spectrum.

Table 4.6. Reactions of cis-263 with copper salts under O$_2$ atmosphere.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Yield% of 270</th>
<th>Yield% of 284 or 289</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>5</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>5</td>
<td>78</td>
</tr>
</tbody>
</table>

The reaction of cis-263 with CuCN afforded a 35 : 65 mixture of products which were separated by column chromatography to give 285 and 270 in yields of 35% and 40%, respectively (Scheme 4.30). Interestingly the use of CuX (X = I, Cl, Br) furnished the halofurans products which were formed from the ring opening of the corresponding bicyclic products, while the CuCN catalyzed reaction yielded the cyano substituted bicyclic product 287. Product 287 was stable under the reaction conditions and did not give a ring-opened (furan) product. As a result the cyclisation-halogenation and cyclization-cyanation reactions of pyrrolidine cis-263 provided the halo- and cyano- substituted products in higher yields when these reactions were
performed under an oxygen atmosphere, consistent with the proposed reductive elimination mechanism (Scheme 4.20).

Scheme 4.30. Reaction of cis-263 with CuCN under O₂ atmosphere.

The cyclization-iodination and cyclization-cyanation reactions of 2,3-trans pyrrolidine trans-263 were also tested. Compound trans-263 was treated with 1.1 mol equivalents of CuX (X = I, CN) in DMF at 80 °C for 16 h under an O₂ atmosphere. None of these attempts worked, in all cases trans-263 was recovered quantitatively (Scheme 4.31).

Scheme 4.31. Treatment of trans-263 with CuI and CuCN.

Since Cu(II) salts have been used in cyclization-halogenation reactions in the literature, cis-362 was treated with 6 mol equivalents of CuBr₂. The reaction gave two products 290 and 270 in respective yields of 30% and 25% (Scheme 4.32). The structure of the dibromo product 290 was confirmed from NMR spectroscopic analysis. The quarternary carbons C1′ and C2′ resonated at 111.6 and 115.0 ppm, respectively. The IR spectrum was confirmed the structure showing a broad peak at 3326 cm⁻¹ corresponding to the O-H stretch, and a sharp peak at 1710 cm⁻¹ corresponding to the C=O stretch. The mass spectrometric analysis showed three molecular ion peaks at 479, 481 and 483 amu for the bromine isotopic peaks which was consistent with the structure.
Scheme 4.32. Reaction of cis-263 with CuBr₂.

In order to investigate the synthetic potential of the metal-catalyzed cycloisomerizations of cis-263, the tandem palladium-catalyzed cycloisomerization-cross coupling reaction of cis-263 was studied. Treatment of cis-263 with PhI, Pd(dba)₂ and K₂CO₃ in CH₃CN at 50 °C for 12 h gave the arylated product 291 and 270 in yields of 38% and 19%, respectively (Scheme 4.33). Unlike the bromo and chloro substituted furo[3,2-b]pyrroles, but like the iodo derivative 280 and CN derivative 287, product 291 did not undergo a ring opening reaction to form a diphenyl substituted furan. Compound 291 was stable under the reaction conditions. The structure of 291 was established by its NMR spectroscopic studies. The signals for the methine protons H₃a and H₆a were observed at the respective chemical shifts of 5.24 (1H, br. s) and 5.67 (1H, br. d, J = 5.5 Hz) ppm. The methine carbons of 291, C₃a and C₆a, resonated at 82.4 and 69.6 ppm, respectively. The chemical shifts of these carbons were typical of a furo[3,2-b]pyrrole structure. The C=O stretch was observed at 1701 cm⁻¹ in its IR spectrum. The HREIMS analysis revealed the molecular formula C₂₆H₂₃NO₃ which was consistent with the structure. We assume that product 291 arises via a reductive elimination mechanism on an intermediate analogous to 283 in Scheme 4.20, in which the Cu(II)I species is replaced by a PhPd(II) species.

Scheme 4.33. Tandem cyclization-cross coupling reaction of cis-263.
In conclusion, methods for the synthesis of novel 3-halo-2,5-substituted furans and 3-cyano, 3-iodo and 3-phenyl substituted furo[3,2-\textit{b}]pyrroles have been developed.
5. COPPER MEDIATED CYCLIZATION-CYANATION REACTIONS OF ORTHO-ALKYNYLANILINES

In Chapter 4 we reported novel copper mediated cyclization-halogenation and cyclization-cyanation reactions of a 2-alkynyl-3-hydroxypyrrolidine. In this Chapter we applied this methodology to ortho-alkynylanilines with the aim of synthesizing 3-functionalized-2-substituted indoles. The indole ring is a key structural feature of a vast number of biologically active natural and unnatural compounds. Thus the synthesis and functionalization of the indole ring has been the object of many researchers. We aimed to synthesize 3-halo and 3-cyano indoles from the cyclization-halogenation and cyclization-cyanation reactions of ortho-alkynylanilines. The ortho-alkynylanilines could be obtained from the Sonagoshira coupling reaction of ortho-haloanilines and terminal alkynes (Scheme 5.1).

Scheme 5.1. Proposed synthesis of 3-halo and 3-cyano indoles.

5.1. Synthesis of Indoles

The Fisher indole synthesis, reductive cyclizations of aromatic nitro compounds and cyclization of ortho-alkynylanilines are the most common methods to construct the indole ring (Scheme 5.2). The Fisher indole synthesis is the construction of the indole ring by heating arylhydrazones of ketone or aldehydes in the presence of a protic acid or a Lewis acid. Reductive cyclization of aromatic nitro compounds has been accomplished by catalytic hydrogenation over Pd/C, Pt/C or a combination of Raney nickel and hydrazine. Precursors for the reductive cyclization reactions to indoles can be β-amino-ortho-styrenes, ortho-β-nitrostyrenes, ortho-nitrobenzylcarbonyls, ortho-nitrophenylacetonitriles or ortho-nitrostyrenes. In this Chapter we will focus on the cyclization of ortho-alkynylanilines to form the indole ring. The synthesis of indoles via cyclization
of ortho-alkynyl anilines usually involves two steps. The first step is the Sonogashira cross-coupling of ortho-halo-anilines or 2-carboxamidoaryl triflates with the terminal alkynes. The second step is the cyclization of ortho-alkynylanilines in the presence of metal alkoxides, Pd(II) salts or iodine. Although Pd(II) salts are the most common catalysts in this cyclization reactions platinum, molybdenum, iridium, rhodium, zinc, mercury and indium salts have also been used.

Wang reported the synthesis of 5,6-difluorooindole from the cyclization of the ortho-alkynylaniline (Scheme 5.3). The Sonogashira coupling of 303 with trimethylsilylacetylene in the presence of Pd(OAc)$_2$ and (o-tolyl)$_3$P in Et$_3$N afforded the alkyne 304 in 94% yield. Treatment of 304 with EtONa at 70 °C for 14 h yielded the 5,6-difluorooindole 305 in a yield of 82%.

Scheme 5.2. Three methods for the synthesis of indole ring.
Reagents and conditions: a) Pd(OAc)$_2$ (1.5 mol%), (α-tolyl)$_3$P (2 mol%), Et$_3$N, TMSacetylene, rt, 16 h, 94%; b) EtONa, EtOH, 70 °C, 14 h, 82%.

**Scheme 5.3.** Synthesis of 5,6-difluoroindole 305.

Indole derivatives containing oxygen-bearing substituents, such as hydroxyl, alkoxy, or acyloxy group, at the benzene moiety are present in a number of physiologically active substances. Sakamato$^{133}$ developed a strategy for synthesizing indoles with these substituents. The cyclization of *ortho*-alkynylanilines 306 in the presence of $^t$BuOK furnished indoles 307 in 70-79% yields (Scheme 5.4). The TMS and CO$_2$Me groups did not survive under the cyclization reaction conditions.

**Scheme 5.4.** Synthesis of oxygen-bearing substituted indoles 307.

2-Substituted indoles 309 have been synthesized from the PdCl$_2$ catalyzed cycloisomerization reaction of alkynylanilines 308. Treatment of 308 with PdCl$_2$ (5 mol%) in CH$_3$CN at 70 °C provided 2-arylindoles 309 in 55-95% yields (Scheme 5.5). The method is very useful for making the free NH-2-substituted indoles.$^{134}$

The proposed mechanism (Scheme 5.6) of the palladium-catalyzed cyclization of alkynylanilines involves the coordination of palladium(II) to the triple bond of 310 to form a π-alkyne-palladium complex 311. Intramolecular nucleophilic attack of the nitrogen to the activated triple bond forms the σ-indolylpalladium complex 312. Protonation of this intermediate at C-3 with loss of palladium(II) gives the indole product 313.$^{134}$
Scheme 5.5. Synthesis of 2-substituted-NH-indoles 309.

Scheme 5.6. The proposed mechanism of Pd(II)-catalyzed cyclization of 2-alkynylanilines.

The synthesis of indoles via cyclization of ortho-alkynylaniline derivatives usually requires two steps. However, a one-pot synthesis of indoles from ortho-idoanilines 314 and terminal alkynes 315 under Sonogashira reaction conditions was reported (Scheme 5.7). Yamanaka\textsuperscript{135} observed that treatment of terminal alkynes with ortho-iodo-N-mesylanilidines 314 in the presence of Pd(PPh)_3Cl_2 and CuI in Et_3N afforded directly indole products 317. In control experiments the indole product was observed when 2-trimethylsilylethylnyl-N-mesylanilidine was heated with Pd(PPh)_3Cl_2 and CuI, however no indole product was observed using only Et_3N and DMF.
Scheme 5.7. One-pot synthesis of indoles.

Another one-pot procedure for the synthesis of highly substituted indoles was reported by Larock.\textsuperscript{136,137} The palladium catalyzed reaction of ortho-iodoaniline derivatives 318 with internal alkynes 319 furnished the complex indoles 320 in a single step (Scheme 5.8). This is an important method for synthesizing complex indoles since both starting materials can possess considerable functionality. The reaction is regioselective and always provides 2,3-disubstituted indoles, where the more sterically hindered group of the alkyne occupies the 2 position of the indole.

Scheme 5.8. One-pot synthesis of 2,3-disubstituted indoles 320.

Utimoto\textsuperscript{138} described the reaction of ortho-alkynyl-N-methoxycarbonylanilidines 321 with allylic chlorides 322 in the presence of a palladium catalyst (Scheme 5.9). While the reaction occurred under mild conditions with N-methoxycarbonylanilides, the unprotected amino group or the acetamido derivative gave low yields. It was also found that the use of the proton scavenger, methyloxirane, was essential. In the mechanism of this palladium catalyzed cyclization (Scheme 5.6), a σ-indolylpalladium intermediate 312 forms and undergoes protonolysis to form 2-substituted indoles. Trapping of this intermediate by allylic chlorides afforded the 2-alkenyl-3-substituted indoles 323.
Scheme 5.9. Palladium catalyzed reactions of 321 with 322.

Ribecai\textsuperscript{139} recently reported the microwave assisted cyclization of ortho-alkynylanilines to form indoles in the absence of added catalyst, acids or bases (\textbf{Scheme 5.10}). They synthesized indole and 2-substituted indoles 325 by heating 2-alkynylanilines 324 in water using a microwave reactor. The use of organic solvents resulted in only 1-3\% yields of indole products while the use of a 75 : 25 mixture of organic solvent and water gave slightly increased yields of 3-10\%.

\begin{tikzpicture}[descr/.style={fill=white,inner sep=2pt,outer sep=0pt}] \node (A) at (0,0) {\textbf{Scheme 5.10.} Microwave-assisted synthesis of indoles.} \end{tikzpicture}

Wang\textsuperscript{140} demonstrated the direct synthesis of 3-halo-2-substituted indoles 328 from the treatment of \textit{N}-acetyl-2-alkynylanilines 326 with bromo or chloro salts of Pd(II)/Cu(II) in DCE at 40 °C for 5 h. The reaction of 326 with PdBr\textsubscript{2} or PdCl\textsubscript{2} (5 mol\%) and CuBr\textsubscript{2} or CuCl\textsubscript{2} (5 mol\%) afforded products 327 and 328 in moderate to good yields (\textbf{Scheme 5.11}). They found that \textit{N}-unprotected and \textit{N}-benzyl protected alkynylanilines did not give any of the desired products.
Scheme 5.11. Synthesis of 3-haloindoles.

Scheme 5.12. The proposed mechanism for the formation of 3-haloindoles 328.

The proposed mechanism\textsuperscript{140} (Scheme 5.12) starts with coordination of the palladium species to the triple bond of 326 to form intermediate 329 and then intramolecular nucleophilic attack of nitrogen results in the formation of indolylpalladium complex 330. Protonation of this intermediate gives the product 327. Reductive elimination of 330 gives the product 328 and Pd(0). The Pd(II) catalyst is regenerated from the redox reaction of the Pd(0) with CuX\textsubscript{2}. The 2-substituted indole 327 can also provide halogenated indoles 328 via halogenation with CuX\textsubscript{2}. In control experiments, 326 was treated with PdBr\textsubscript{2} (1.0 eq) in DCE at 40 °C to give a mixture of products 327.
and 328 in 21% and 75% yields, respectively. However treatment of 327 with CuBr₂ in DCE at 40 °C afforded the haloindole 328 in 58% yield.

5.2. Synthesis of 3-Cyanoindoles

3-Cyanoindoles have been synthesized from the solid phase Madelung indole synthesis. The ortho-substituted anilines were first attached to a resin using reductive amination and then the resin-bound aniline was acylated. Cyclization of 331 in the presence of tBuOK furnished the 3-cyano-2-substituted indoles 332 in 43-88% yields (Scheme 5.13). The products were quantitatively removed from the resin by treatment with TFA/Et₃SiH (95 : 5).

![Scheme 5.13. Solid phase synthesis of 3-cyano indoles.](image)

Zhao synthesized 3-cyano indoles via thermolysis of 2-aryl-2H-aziridines 334. Heating 334 in xylene at 140 °C for 4-12 h yielded 3-cyano 2-substituted indoles 335 in yields of 72-94%. They prepared 334 from the enamine derivatives 333 via oxidative cyclization using phenyliodine(III) diacetate (PIDA).

![Scheme 5.14. Synthesis of 3-cyanoindoles from 2-aryl-2H-aziridines.](image)

Zhao synthesized 3-cyanoindoles also from N-aryl enamines via PIDA-mediated oxidative C-C bond formation. Treatment of N-aryl enamines 336 with PIDA (1.3 eq.) in DCE at 60 °C gave 3-cyano-2-substituted indoles 337 in 33-91% yields.
The use of phenyliodine(III) bis(trifluoroacetate) (PIFA) resulted in the formation of indoles 337 in moderate yields (40-55%). The reaction has good functional group tolerance and allowed for the formation of 2-alkyl or 2-aryl indoles in good yields.

Reaction of arylhalides with CuCN to form arylecyanides is known as the Rosenmund-van Braun reaction. Although the reaction showed good tolerance to functional groups, it needs high temperatures (150-280 °C) which has limited its applications. Buchwald reported a modified version of the Rosenmund-van Braun reaction which worked under relatively mild conditions. They synthesized 5-cyanoindole 340 from the corresponding bromide 338 upon treatment with CuI, KI, NaCN and diamine ligand 339 at 110 °C for 24 h (Scheme 5.16).

The Sonogashira115 reaction is a cross coupling of terminal alkynes 342 with vinyl or aryl halides 341 (Scheme 5.17). A palladium complex and a halide salt of copper(I)
is used as a catalyst. An organic base usually serves as the solvent, however occasionally a co-solvent is used or an inorganic base. Palladium catalysts can be Pd(PPh₃)₂Cl₂ or Pd(PPh₃)₄, the copper(I) salt can be CuI or CuBr. The palladium complex activates the organic halides via oxidative addition to the carbon halogen bond. Copper(I) halides activates the terminal alkyne by forming a copper(I) acetylide in the presence of the base.¹⁴⁶

\[ R^1-X + H\equiv R^2 \xrightarrow{\text{Pd(0) or Pd(II)/ligand}} \text{Cu(I) salt / base / solvent} \xrightarrow{\text{amine base}} [\text{amine base}]H^+X^- \]

**Scheme 5.17.** The Sonogashira reaction.

The mechanism (Scheme 5.18) of the Sonogashira reaction involves oxidative addition of a Pd(0) species to the aryl or vinyl halides (R¹-X) to give R¹Pd(II)XLn 344 and then transmetallation by the copper(I) acetylide to give 345. Reductive elimination then affords the coupled product 343 and regenerates the Pd(0) catalyst.¹⁴⁶

**Scheme 5.18.** The mechanism of the Sonogashira coupling reaction.
5.3.2. Sonogashira Reactions of ortho-Iodoaniline Derivatives

The Sonogashira reaction of aniline derivatives is well established in the literature.\textsuperscript{146} In order to investigate the scope of cyclization-cyanation reaction we decided to synthesize ortho-alkynylanilines that have electron donating or electron withdrawing groups on the aniline component or on the alkyne component. We chose PdCl$_2$(PPh$_3$)$_2$ and CuI as a catalyst and Et$_3$N as a base and solvent. At first we decided to investigate the Sonogashira reactions of 2-iodoaniline with phenylacetylene and its derivatives having electron-donating or electron withdrawing substituents. 2-Iodoaniline $\text{347}$ was treated with phenylacetylene $\text{348a}$ in the presence of PdCl$_2$(PPh$_3$) (5 mol%) and CuI (5 mol%) in Et$_3$N at reflux temperature for 2 h. The reaction afforded the desired known\textsuperscript{129} alkynylaniline $\text{349}$ in a high yield of 90\% (Scheme 5.19). The NMR spectroscopic data of $\text{349}$ were identical to the published data.\textsuperscript{129} The LREIMS spectrum showed a molecular ion peak at 194 amu, consistent with the structure. The reaction of 2-iodoaniline with 4-ethynylanisole $\text{348b}$ under the same experimental conditions yielded the desired known\textsuperscript{147} alkynylaniline $\text{350}$ in 83\% yield (Scheme 5.19). The methoxy protons resonated at 3.80 (3H, s) ppm, while the NH proton appeared at 4.21 (2H, br. s) ppm in the $^1$H NMR spectrum of $\text{450}$. The alkyne carbons resonated at 94.5 ppm and 84.4 ppm, while the methoxy carbon resonated at 55.2 ppm in the $^{13}$C NMR spectrum of $\text{350}$. Treatment of 2-iodoaniline $\text{347}$ with 1-ethynyl-4-fluorobenzene $\text{348c}$ in the presence of PdCl$_2$(PPh$_3$)$_2$ and CuI in Et$_3$N furnished the desired adduct $\text{351}$ in 86\% yield (Scheme 5.19). The structure of $\text{351}$ was clear from its NMR, IR and MS analyses. The aromatic protons ortho to the F-substituent resonated at 7.48 (2H, dd, $J = 5.5$, 8.5 Hz) ppm and showed a $^1$H-$^{19}$F coupling constant of 5.5 Hz. While the meta protons resonated at 6.72-6.69 (2H, m) ppm. The $^{13}$C-$^{19}$F coupling constants of the aromatic ortho and meta methine carbons and the quarternary para carbon to F were 22.0 Hz, 8.5 Hz and 3.7 Hz, respectively and they resonated at 115.6, 133.3 and 119.3 ppm, respectively. The ipso carbon resonated at 162.4 (d, $J = 247$ Hz) ppm. The alkyne carbons appeared at 93.5 ppm and 85.5 ppm in the $^{13}$C NMR spectrum of $\text{351}$. The molecular formula was found to be $\text{C}_{14}\text{H}_{11}\text{NF}$ from the HREIMS analysis, consistent with the structure.
Scheme 5.19. Sonogashira reaction of ortho-idoaniline 347.

After investigating the Sonogashira reaction of ortho-idoaniline, we decided to study the Sonogashira reactions of aniline derivatives having an electron donating or electron withdrawing substituents, with phenylacetylene. Cyano and methoxy groups were chosen as substituents on the aniline ring. Since anilines with electron donating group substituents were not commercially available we decided to synthesize 2-iodo or 2-bromo-4-methoxyaniline from p-anisidine 352. The reaction of 352 with Br₂ in acetic acid resulted in the formation of a complex mixture. The desired 2-bromo-4-methoxyaniline 353 however was successfully synthesized from the reaction of 352 with nBu₄NBr₃ (Scheme 5.20). The reaction afforded the products 353 and 354 in respective yields of 42% and 20%. The starting material 352 was also recovered from this reaction in 20% yield.

Scheme 5.20. Synthesis of 2-bromo-4-methoxyaniline 353.
The 2-bromo-4-methoxyaniline 353 was subjected to a Sonogashira reaction under the optimised conditions. This reaction furnished the desired alkynyylaniline 356 in 83% yield (Scheme 5.21). The $^1$H and $^{13}$C NMR spectra of 356 confirmed the structure. The NH$_2$ protons resonated at 4.0 (2H, br. s) ppm, while the methoxy protons resonated at 3.75 (3H, s) ppm in the $^1$H NMR spectrum. In the $^{13}$C NMR spectrum alkyne carbon signals were observed at 94.6 and 85.9 ppm, while the methoxy carbon resonated at 55.8 ppm. The Sonogashira reaction of 4-cyano-2-iodoaniline 355 with phenylacetylene under the same experimental conditions gave the known$^{131}$ alkynyylaniline 357 in a high yield of 94% (Scheme 5.21). The NMR analysis confirmed the structure of 357. The $^1$H NMR spectrum showed a resonance for the NH$_2$ protons at 4.81 (2H, br. s) ppm. The $^{13}$C NMR spectrum showed signals at 96.1 and 83.3 ppm corresponding to the alkyne carbons and at 100.0 ppm corresponding to CN carbon. The IR spectrum was also consistent with the structure. It showed a broad band at 3467 cm$^{-1}$ corresponding to the NH stretch and a sharp peak at 2215 cm$^{-1}$ corresponding to the C≡N stretch. HREIMS analysis confirmed its molecular formula to be C$_{15}$H$_{10}$N$_2$.

Scheme 5.21. Sonogashira reactions of 353 and 355.

The Sonogashira reaction of 2-iodoaniline 347 with the aliphatic alkyne, 1-heptyne, was also studied. Compound 347 was treated with 1-heptyne under the optimised reaction conditions to afford the desired adduct 358 in 91% yield (Scheme 5.22). The structure of 358 was identified from its NMR spectroscopic analysis. The methylene protons were observed at 1.47-1.30 (4H, m), 1.65-1.57 (2H, m) and 2.45 (2H, m)
ppm, while the methyl protons were observed at 0.92 (3H, t, J = 7.0 Hz) ppm. The NH₂ protons resonated at 4.15 (2H, br. s) ppm. In the ¹³C NMR spectrum the methylene carbon signals were observed at 31.1, 28.6, 22.2 and 19.5 ppm while that of the methyl carbon was observed at 13.9 ppm. The alkyne carbon resonances appeared at 108.9 and 95.7 ppm. HREIMS analysis revealed its molecular formula to be C₁₃H₁₇N, consistent with the structure.

![Scheme 5.22](image)

**Scheme 5.22.** The Sonogashira reaction of 2-iodoaniline 347 and 1-heptyne.

5.4. **Protection Reactions of ortho-Alkynylanilines**

Metal-catalyzed cyclization reactions of ortho-alkynylanilines are usually performed with N-protected aniline derivatives since most of the methods cannot deal with the N-unprotected anilines. When ortho-alkynylaniline 349 was subjected to cyclization-cyanation reaction with CuCN (1.1 eq.) in DMF at 80 °C for 16 h, it produced a very polar complex mixture (Scheme 5.23). We decided to protect nitrogen of the 349 with Ts and TFA groups which have commonly been used in similar reactions.¹²⁰,¹²¹

![Scheme 5.23](image)

**Scheme 5.23.** Treatment of 349 with CuCN.

Compound 349 was treated with TsCl (1.2 eq) and pyridine (2.0 eq) in CH₂Cl₂ at 0 °C to rt for 16 h to give the desired sulfonamide 359 in a high yield of 95% (Scheme 5.24). The ¹H and ¹³C NMR spectra of 359 was in good agreement with the structure. The methyl protons resonated at 2.31 (3H, s) ppm while the methyl carbon resonated at 21.4 ppm. The alkyne carbon signals were observed at 96.0 and 83.6 ppm in the
$^{13}$C NMR spectrum. The N-H and C≡C bond stretches were observed at 3267 and 2366 cm$^{-1}$, respectively in the IR spectrum. Similarly the reaction of 349 with (CF$_3$CO)$_2$O (1.2 eq) and pyridine (2.0 eq) under the same experimental conditions provided the trifluoroacetamide 360 in 93% (Scheme 5.24). The $^1$H NMR spectrum of 360 was consistent with its desired structure and showed a resonance at 8.90 (1H, br. s) ppm corresponding to the NH proton. The carbonyl carbon was observed at 154.4 ppm as a quartet with a $^{13}$C-$^{19}$F coupling constant of 37.6 Hz, while the CF$_3$ was observed at 115.8 ppm as a quartet with a coupling constant of 287.6 Hz in the $^{13}$C NMR spectrum. The alkyne carbons resonated at 98.0 and 82.8 ppm. The N-H and C≡C bond stretches were observed at 3344 and 2366 cm$^{-1}$, respectively in the IR spectrum.

Scheme 5.24. The reaction of 349 with TsCl and (CF$_3$CO)$_2$O.

The ortho-alkynylaniline derivatives 350, 351, 356 and 357 were also subjected to $N$-protection reactions under the same experimental conditions. These protection reactions worked smoothly and yielded the desired products in high yields. When the alkynylanilines 350, 351, 356 and 357 were treated with (CF$_3$CO)$_2$O/pyridine the desired products 361-365 were obtained in yields of 96%, 96%, 90% and 91%, respectively (Table 5.1, Entries 1,2,3 and 4). Their structures were confirmed by NMR analysis. The carbonyl carbon resonances of products 361-365 were observed at 154.3 (q, $J = 37.3$ Hz), 154.6 (q, $J = 37.8$ Hz), 154.3 (q, $J = 36.6$ Hz) and 154.7 (q, $J = 37.7$ Hz) ppm, respectively in their $^{13}$C NMR spectra, while the CF$_3$ carbon resonated at 114.3 (q, $J = 287.5$ Hz), 115.9 (q, $J = 287.7$ Hz), 115.8 (q, $J = 287.5$ Hz) and 115.4 (q, $J = 287.5$ Hz) ppm, respectively. MS analysis of compounds 361-365.
revealed molecular ions 319, 307, 319 and 314 amu, respectively consistent with their structures. Although the \( N \)-protection reaction of 357 with \((\text{CF}_3\text{CO})_2\text{O}\) worked well and provided the product 364 in 91% yield, the tosylation reaction of 357 gave unsatisfactory results at rt for 16 h. However heating the reaction mixture at 40 °C for 6 h afforded the tosylated product 365 in 57% yield (Table 5.1, Entry 5) and unreacted aniline 357 in 25% yield. The structure of 365 was clearly identified by the presence of resonances, in both the \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra, corresponding to the tosyl methyl group, which were observed at 2.94 (3H, s) and 21.5 ppm. LREIMS analysis also confirmed the identity of the compound with a molecular ion consistent with the structure at 372 amu.

Table 5.1. Results of protection of ortho-alkynylanilines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound no</th>
<th>R</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>361</td>
<td>H</td>
<td>OMe</td>
<td>TFA</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>362</td>
<td>H</td>
<td>F</td>
<td>TFA</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>363</td>
<td>OMe</td>
<td>H</td>
<td>TFA</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>364</td>
<td>CN</td>
<td>H</td>
<td>TFA</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>365</td>
<td>CN</td>
<td>H</td>
<td>Ts</td>
<td>57(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Reaction was performed at 40 °C.

The \( N \)-Ts and \( N \)-TFA derivatives of 2-heptynylaniline 358 were also prepared. Treatment of 358 with TsCl and pyridine at 0 °C to rt for 18 h afforded the desired product 366 in a yield of 82% (Scheme 5.25). The structure of 366 was identified from its NMR and MS analysis. The \( N \)-TFA derivative of 367 was prepared upon treatment with \((\text{CF}_3\text{CO})_2\text{O}\) and pyridine in CH\(_2\)Cl\(_2\) at 0 °C to rt for 1 h (Scheme 5.25). The desired product 367 was isolated in a high yield of 89%.
Scheme 5.25. Reaction of 357 with TsCl and (CF₃CO)₂O.

5.5. Cyclization-Cyanation Reactions of ortho-Alkynylanilines

After preparing the precursors for the cyclization-cyanation reactions, the reaction of ortho-alkynylaniline 359 with CuCN was performed. Treatment of 359 with CuCN (1.1 eq) in DMF at 100 °C under an oxygen atmosphere gave a 58 : 42 mixture of the cyanated indole 368 and the 3-unsubstituted indole 369 in respective yields of 41% and 34% (Table 5.2, Entry 1). The indole 369 is a known compound and its NMR data were the same as those in the literature. The ¹H NMR spectrum (Figure 5.2) showed resonances at 6.54 (1H, s) ppm, corresponding to methine proton H3 and at 2.28 (3H, s) ppm, corresponding to the methyl protons. The 3-cyano indole 368 was identified from its NMR spectroscopic analysis. The ¹H and ¹³C NMR spectra were in good agreement with the structure. The signal for the methine proton at the C3 position was not observed in the ¹H NMR spectrum of 368, while the methyl protons resonated at 2.33 (3H, s) ppm (Figure 5.1). The CN carbon resonated at 96.7 ppm, and the methyl carbon resonated at 21.6 ppm in the ¹³C NMR spectrum. The presence of cyano group was also confirmed by the sharp band in the IR spectrum at 2230 cm⁻¹. HREIMS analysis confirmed its molecular formula to be C₂₂H₁₆N₂O₂S. The reaction was repeated with 2.2 mol equivalents of CuCN under the same reaction conditions with the aim of obtaining only 3-cyanoindole. The reaction afforded products 368 and 369 in 48% and 26% yields, respectively. ¹H NMR analysis of the crude mixture showed 368 and 369 in a ratio of 74 : 26, respectively (Table 5.2, Entry 2). The yield and ratio of 3-cyanoindole 368 over 369 was increased by increasing the amount of CuCN. The use of 3.0 mol equivalents of
CuCN in the same reaction resulted in the formation of a 97 : 3 mixture of products 368 and 369 which were isolated in 74% and 3% yield, respectively (Table 5.2, Entry 3). The ratios were determined by measuring the integrals of the methyl proton signals for both products in the $^1$H NMR spectrum of the crude reaction mixture.

Table 5.2. Optimization of cyclization-cyanation reaction of 359.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of CuCN</th>
<th>Yield% of 368</th>
<th>Yield% of 369</th>
<th>368 : 369$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>41</td>
<td>34</td>
<td>58 : 42</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>48</td>
<td>26</td>
<td>74 : 26</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>74</td>
<td>3</td>
<td>98 : 2</td>
</tr>
</tbody>
</table>

$^a$ Ratios were obtained from the $^1$H NMR spectrum of the crude reaction mixture.

Figure 5.1. $^1$H NMR (500 MHz, CDCl$_3$) spectrum of 368.

Figure 5.2. $^1$H NMR (500 MHz, CDCl$_3$) spectrum of 369.
Next, the TFA protected aniline derivative \textbf{360} was subjected to the same reaction under the optimized experimental conditions (3.0 eq. of CuCN). The reaction yielded the 3-cyanoindole \textbf{370} exclusively in a high yield of 80\% (Table \textbf{5.3}, Entry 1). The TFA group did not survive under the reaction conditions. The \textsuperscript{1}H NMR spectrum of \textbf{370} confirmed the structure by showing a resonance at 11.5 (1H, br. s) ppm corresponding to the NH proton. The \textsuperscript{13}C NMR spectrum was also confirmed the structure by showing a resonance at 83.7 ppm corresponding to the CN carbon. The DEPT experiment showed 5 quarternary aromatic carbons at 145.5, 136.6, 130.7, 129.7 and 117.1 ppm, and seven aromatic methine carbons at 130.6, 130.1, 127.8, 124.8, 122.9, 119.4 and 113.2 ppm. The IR spectrum possessed bands at 3221 and 2217 cm\textsuperscript{-1}, corresponding to the N-H and C≡N stretches. LRESIMS analysis showed a \([M + H]\)\textsuperscript{+} ion at 219 amu, consistent with the structure. The reaction was repeated with 1.1 and 2.2 mol equivalents of CuCN in order to find the optimum amount of CuCN. The use of 1.1 equivalents of CuCN resulted in formation of \textbf{370} exclusively in a yield of 69\% while the use of 2.2 equivalents of CuCN gave the product \textbf{370} in 55\% yield exclusively (Table \textbf{5.3}, Entries 2 and 3). The use of 3.0 equivalents of CuCN provided the best results for both tosyl and TFA derivatives.

\textbf{Table \textit{5.3}. Optimizaton of cyclization-cyanation reaction of \textbf{360}.}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of CuCN</th>
<th>Yield% of \textbf{370}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
<td>69</td>
</tr>
</tbody>
</table>

The cyclization-cyanation reactions of \textbf{361} and \textbf{362} using 3.0 equivalents of CuCN afforded the desired 3-cyanoindoles \textbf{371} and \textbf{372} in respective yields of 77\% and 65\% (Scheme \textbf{5.26}). The \textsuperscript{1}H NMR spectrum of \textbf{371} was consistent with the desired structure and showed the NH proton peak at 11.4 (1H, br. s) ppm and the methoxy protons at 3.89 (3H, s) ppm. The CN carbon resonated at 81.9 ppm in the \textsuperscript{13}C NMR spectrum. The N-H and C≡N bond stretches were observed in the IR spectrum of \textbf{371} at 3257 cm\textsuperscript{-1} and 2212 cm\textsuperscript{-1}, respectively. Further the HREIMS analysis revealed its
molecular formula as C_{16}H_{12}N_{2}O. The $^1$H NMR spectrum of 372 showed a resonance for the NH proton at 11.5 (1H, br. s) ppm. In the $^{13}$C NMR spectrum the CN carbon was observed at 83.7 ppm. The quarternary aromatic ipso carbon (CF) resonated at 164.2 (d, $J_{C,F} = 247.6$ Hz) ppm, while the aromatic methine carbons at the ortho and meta position to fluorine resonated at 130.2 (d, $J_{C,F} = 8.5$ Hz) and 116.9 (d, $J_{C,F} = 7.1$ Hz) ppm, respectively. The quarternary aromatic carbon para to the fluorine substituent was observed at 116.5 (d, $J_{C,F} = 3.1$ Hz) ppm. The IR spectrum confirmed the structure by showing bands at 3257 cm$^{-1}$, corresponding to N-H bond stretch, and 2213 cm$^{-1}$ corresponding to the C≡N bond stretch. Thus the cyanation-cyclization reactions tolerated well the electron donating and electron withdrawing substituents on the phenyl ring of the alkyne.

![Scheme 5.26. Cyclization-cyanation reactions of 361 and 362.](image)

After obtaining encouraging results from the cyclization–cyanation reaction of 361 and 362, the ortho-alkynylanilines 363 and 364 were subjected to the same reaction under the same experimental conditions. The desired 3-cyanoindoles 373 and 374 were obtained in 78% and 60% yield, respectively (Scheme 5.27). The $^1$H and $^{13}$C NMR spectroscopic and MS data were in good agreement with the structures. As a result the cyclization-cyanation reaction worked equally well with both electron donating or electron withdrawing substituents on both phenyl rings of the 2-alkynylanilines.
Scheme 5.27. Cyclization-cyanation reactions of 363 and 364.

Although the N-TFA derivative of 4-cyano-2-alkynylaniline 364 afforded the cyanoindole 374 exclusively, the N-Ts analogue of the same precursor gave a mixture of indole and 3-cyanoindole. Treatment of 365 with CuCN under the same experimental conditions furnished a 60 : 40 mixture of products 375 and 376 in 38% and 22% yields, respectively (Scheme 5.28). The H3 and methyl protons appeared at 6.56 (1H, s) and 2.31 (3H, s) ppm, respectively in the $^1$H NMR spectrum of 375. The cyano carbon and methyl carbon resonances appeared at 107.6 and 21.6 ppm, respectively in the $^{13}$C NMR spectrum. The IR spectrum of 375 showed the $\text{C} \equiv \text{N}$ bond stretch at 2223 cm$^{-1}$, while the HREIMS analysis revealed the molecular formula C$_{22}$H$_{17}$N$_2$O$_2$S, consistent with the proposed structure. The $^1$H and $^{13}$C NMR spectra of 376 was also in good agreement with the proposed structure. The methyl protons resonated at 2.36 (3H, s) ppm, while its carbon resonated at 21.6 ppm. The cyano carbon signals were observed at 109.1 and 96.0 ppm in the $^{13}$C NMR spectrum. The HRESIMS analysis confirmed molecular formula of 376 as C$_{23}$H$_{16}$N$_3$O$_2$S.

Scheme 5.28. Cyclization-cyanation reaction of 365.
The cyclization-cyanation reactions of ortho-heptylaniline derivatives were also studied. 3-Cyano-2-pentylindole 377 was synthesized from the reaction of 367 with CuCN (3.0 eq) under the optimized reaction conditions in 73% yield (Scheme 5.29). The $^1$H NMR spectrum of 377 showed resonances at 8.70 (1H, br. s) ppm corresponding to the NH, and at 2.94 (2H, t, $J = 7.0$ Hz), 1.80-1.78 (2H, m) and 1.38-1.35 (4H, m) ppm corresponding to methylene protons, and at 0.90 (3H, t, $J = 7.0$ Hz) ppm corresponding to methyl protons of the pentyl side chain. The $^{13}$C NMR spectrum showed a signal at 84.7 ppm corresponding to the CN carbon. The DEPT spectrum showed four methylene carbons at 31.1, 28.7, 27.5 and 22.2 ppm and a methyl carbon at 13.8 ppm, consistent with the structure of 377. The C≡N bond stretch was observed at 2208 cm$^{-1}$ in the IR spectrum. The HRESIMS analysis also confirmed the structure of 377 by revealing the molecular formula as C$_{14}$H$_{17}$N$_2$.

**Scheme 5.29.** Synthesis of 3-cyano-2-pentylindole 375.

While the cyclization-cyanation reaction of 367 provided the 3-cyano-2-pentylindole 377 exclusively, the N-Ts analogue 366 afforded two products. The reaction of 366 furnished a 70 : 30 mixture of products 378 and 379 that were separated by column chromatography in respective yields of 55% and 24% (Scheme 5.30). The structures of 378 and 379 were identified from their NMR spectroscopic analysis. For 378 the methylene protons resonated at 3.20 (2H, t, $J = 7.0$ Hz), 1.82-1.77 (2H, m) and 1.43 (4H, m) ppm while the methyl protons resonated at 2.37 (3H, s) and 0.91 (3H, t, $J = 7.0$ Hz) ppm in the $^1$H NMR spectrum. The $^{13}$C NMR spectrum showed the CN carbon signal at 94.5 ppm. The DEPT spectrum confirmed the structure of 378 by showing four methylene carbon resonances at 31.4, 30.4, 28.5 and 22.2 ppm, and two methyl carbon signals at 21.6 and 13.9 ppm. Further the IR spectrum showed a band at 2228 cm$^{-1}$ corresponding to the C≡N group. The $^1$H NMR spectrum of 379 confirmed the structure and showed the diagnostic H3 proton resonance at 6.37 (1H, s) ppm. It was concluded that the N-Ts derivatives of anilines provided mixtures of
indole and cyanoindole products while the N-TFA derivatives afforded the 3-cyanoindole products exclusively. The cyclization-cyanation was useful for making both 2-aryl or 2-alkyl-3-cyanoindoles.

**Scheme 5.30.** Reaction of 366 with CuCN.

An attempt to obtained the cyanoindole from the reaction of 359 with a catalytic amount of CuCN and a cheap cyanide source failed. The ortho-alkynylaniline 359 was treated with CuCN (10 mol%) and KCN (3.0 eq) and TMEDA (1.0 eq) in DMF at 100 °C under an oxygen atmosphere. After 16 h the TLC analysis showed only starting material (Scheme 5.31). The reaction temperature was increased to 130 °C and the reaction mixture was stirred at this temperature for 6 h which resulted in only recovery of unreacted starting material. It was thought that the poor solubility of KCN in DMF might be a problem and for this reason TMSCN was next used as a cyanide source. The use of TMSCN (1.0 eq.) under the same experimental conditions resulted in only quantitative recovery of the unreacted starting material (Scheme 5.31).

**Scheme 5.31.** Attempts to synthesize 3-cyanoindole by using 10 mol% of CuCN.

### 5.5.1. Attempts to Synthesise 3-Haloindoles

Unexpectedly the copper mediated cyclization-halogenation reactions of 2-alkynylanilines did not work. Treatment of 359 with CuI (3.0 eq) in DMF at 100 °C or 130 °C under an oxygen atmosphere did not give any of the desired 3-iodoindole,
the unreacted starting material was recovered (Scheme 5.32). The use of CuBr (3.0 eq) under the same experimental conditions did not change the result, only unreacted 359 was recovered.

Scheme 5.32. Attempts to make 3-haloindoles.

In conclusion, a novel method for the synthesis of 3-cyanoindoles have been developed. This method showed good tolerance to electron-donating and electron withdrawing substituents and allowed 3-cyanoindoles to be obtained in a single step. While the method of Wang (Scheme 5.11) provides 3-bromo and 3-chloro indoles in one step from ortho-alkynylanilines this method has not been extended to make 3-cyanoindoles. Future studies could involve the examination of Wang’s conditions using CuCN/O2 instead of CuBr2 or CuCl2 to prepare 3-cyanoindoles.
6. CONCLUSIONS

The development of new methods for the synthesis of functionalized pyrrolidines is of important since they are the common ring structure that forms the bicyclic, heterocyclic core structure of the pyrrolizidine, indolizidine and *Stemona* alkaloids. 

In Chapter 2 we reported our efforts to develop a general method for preparing 4-hydroxy-5-substituted pyrrolidin-2-ones [71] from the borono-Mannich reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones [69] with boronic acids. The 4,5-dihydroxypyrrolidin-2-one [124] gave the 4,5-*cis* adducts [127] and [137] with very high *cis* selectivity but in relatively low yields, while the 4-benzyloxy-5-hydroxypyrrolidin-2-one gave the 4,5-*trans* adducts with good *trans* selectivity and in good to moderate yields. Unfortunately the desired dienyl 4,5-*cis* adduct [171], required for the synthesis of the *Stemona* alkaloids, could only be obtained in the low yield of 33%. A RCM reaction of [171] gave the desired pyrrolo[1,2-*a*]azepine [172] in 72% yield.

In Chapter 2 we also reported the formation of the novel Ritter reaction product, a pyrrolo[3,2-*b*]oxazole [129], as an unwanted side product in the reaction of [124] with (*E*)-2-styrylboronic acid [122] when acetonitrile was used as a solvent.

In Chapter 3 we described an efficient synthesis of pyrrolo[3,2-*b*]oxazoles from the Ritter reactions of 4-hydroxy or 4-benzyloxy-5-hydroxypyrrolidin-2-ones with nitriles in the presence of BF$_3$.Et$_2$O. When 4-benzyloxy-5-hydroxypyrrolidin-2-one was used as the substrate the corresponding pyrrolo[3,2-*b*]oxazoles were formed along with the corresponding N-benzyl amides, which were formed from the Ritter reactions of benzyl cation and the nitrile. The isolation of these amide compounds were consistent with our proposed reaction mechanism. Two of the pyrrolo[3,2-*d*]oxazole compounds were hydrolyzed to the novel 5-acylaminopyrrolidinones [185] and [236].

In Chapter 4 we reported the metal-catalyzed cycloisomerization reactions of 3-hydroxy-2-alkynylpyrrolidine [263] which was obtained from the borono-Mannich reaction of 2,3-dihydroxypyrrolidine [116] and potassium phenylethynyltrifluoroborate [262]. The cycloisomerization reaction of the pyrrolidine *cis*-263 afforded the 2,5-disubstituted furan [270] when Ag(I), Au(I) or Pd(II)/Cu(I) were used as a catalyst. While 3-halo-2,5-disubstituted furans were synthesized from the CuCl or CuBr
mediated reactions of pyrrolidine 116. Novel 3-iodo, 3-phenyl and 3-cyano substituted furo[3,2-\textit{b}]pyrroles were synthesized from the reactions of 116 with CuI, CuCN and PhI/Pd(dba)$_2$, respectively.

In Chapter 5 a novel method for the synthesis of 3-cyanoindoles was developed. This method showed good tolerance to electron-donating and electron withdrawing substituents on the starting ortho-alkynylaniline and allowed 3-cyanoindoles to be obtained in a single step. While the method of Wang (Scheme 5.11) provides 3-bromo and 3-chloro indoles in one step from ortho-alkynylanilines this method has not been extended to make 3-cyanoindoles. Future studies could involve the examination of Wang’s conditions using CuCN/O$_2$ instead of CuBr$_2$ or CuCl$_2$ to prepare 3-cyanoindoles.
7. **EXPERIMENTAL**

7.1. **General Experimental**

7.1.1. **Reaction Conditions**

All reactions were performed in an oven dried glassware under an atmosphere of nitrogen, unless otherwise stated. Reactions were monitored by thin-layer chromatographic analysis.

Anhydrous CH$_2$Cl$_2$ and MeOH were obtained from Sigma-Aldrich Chemical Co. Anhydrous THF was obtained by distillation from sodium wire/benzophenone.

“Evaporation” refers to the removal of solvent under reduced pressure using a rotary evaporator and then the removal of the last traces of solvent under high vacuum.

“Dried” refers to the drying of organic extracts over MgSO$_4$ or Na$_2$SO$_4$. Commercial substances were used without further purification. Petrol refers to the hydrocarbon fraction of bp 45-55 °C.

7.1.2. **Nuclear Magnetic Resonance (NMR) Spectroscopy**

$^1$H and $^{13}$C NMR spectra were recorded on a Varian Inova NMR Spectrometer ($^1$H NMR at 500 MHz and $^{13}$C NMR at 125 MHz) or Varian Unity-300 ($^1$H NMR at 300 MHz, $^{13}$C NMR at 75 MHz) instruments. CDCl$_3$ (internal reference at $\delta$ 7.26 for $^1$H NMR and $\delta$ 77.00 for $^{13}$C NMR) was used as the NMR solvent unless otherwise stated. The following abbreviations were used; s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets, br = broad. NMR assignments were based on COSY, HSQC, HMBC and DEPT experiments.

7.1.3. **Chromatography**

TLC analyses were performed using aluminium backed Merck silica gel TLC plates. Compounds were detected under a 254 nm ultraviolet lamp if applicable, or by staining with an acidified aqueous solution of ammonium molybdate and cerium(IV) sulphate, followed by development with a 1400 W heat gun. Flash column chromatography was performed using Merck silica gel (40 – 63 μm) packed by the slurry method.
7.1.4. Melting Points

Melting points were obtained using a Gallenkamp MF-370 capillary tube melting point apparatus and are uncorrected.

7.1.5. Polarimetry

Optical rotations were measured using a 1 cm cell, in a Jasco DIP-370 digital polarimeter. Specific rotations were calculated by using the average value of 10 optical rotation measurements.

7.1.6. Mass Spectrometry

Low-resolution mass spectra were obtained on a Shimadzu GC mass spectrometer (EI) or Waters LCZ single quadropole (ESI). High-resolution mass spectra (exact masses) were obtained on a VG Autospec mass spectrometer (EI) or a Waters QTOF (ESI). HRMS were obtained in lieu of elemental analysis and $^1$H and $^{13}$C NMR spectroscopy were used as the criteria for purity.

7.1.7. Infrared Spectrometry

Infrared spectra were obtained as neat samples on a Smart Omni-Sampler Avator ESP Nicolet-Brand.

7.2. Experimental for Chapter 2

\((S)-1\text{-Benzyl-3-hydroxypyrrolidine-2,5-dione} \ (123)\)

\[
\begin{align*}
\text{HO} & \\
\text{O} & \\
\text{N} & \\
\text{Ph} & \\
\text{123} & 
\end{align*}
\]

To a suspension of L-malic acid (5.00 g, 37.2 mmol) in xylene (250 mL) in a Dean-Stark and condenser equipped round bottom flask was added benzylamine (3.99 g, 37.2 mmol) at rt. The resulting suspension was heated at reflux temperature for 2 h, then xylene was removed in vacuo. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title compound (6.10 g, 80%) as a white solid.

R$_f$ : 0.53 (1 : 1, EtOAc/petrol).

Mp 100-102 °C (Lit$^67$ Mp = 101-102 °C).

\(\left[\alpha\right]_{D}^{23} +16.8^\circ \ (c \ 0.23, \ \text{CHCl}_3) \) (Lit$^67$ \(\left[\alpha\right]_{D}^{25} +75.4^\circ \ (c \ 4.4, \ \text{CHCl}_3)\)).
\( ^1 \)H NMR \( \delta \) 7.33-7.22 (5H, m, ArH), 4.61 (2H, s, H1`), 4.58-4.54 (1H, m, H3), 4.38 (1H, br. s, OH), 3.01 (1H, dd, \( J = 8.0, 18.0 \) Hz, H4), 2.65 (1H, dd, \( J = 5.0, 18.0 \) Hz, H4).

\( ^13 \)C NMR \( \delta \) 173.8 (CO), 172.1 (CO), 135.2 (ArC), 128.7 (ArCH), 128.6 (ArCH), 128.0 (ArCH), 69.4 (C3), 42.3 (C1`), 37.2 (C4).

\( ^1 \)H and \( ^13 \)C NMR data matched the published data.

EIMS \( m/z \) 205 (M\(^+\), 70%).

(4S)-1-Benzyl-4,5-dihydroxypyrrolidin-2-one (124)

(S)-1-Benzyl-3-hydroxypyrrolidine-2,5-dione (1.00 g, 4.87 mmol) was dissolved in a mixture of EtOH and \( CH_2Cl_2 \) (40 mL, 1 : 1), and the solution was cooled to -20 °C. NaBH\(_4\) (0.92 g, 24.3 mmol) was added portionwise and the resulting suspension was stirred at -20 °C for 30 min. The mixture was poured into a saturated aqueous solution of NaHCO\(_3\) (30 mL) and was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (MgSO\(_4\)) and concentrated in vacuo. The crude product was purified by column chromatography (increasing polarity from 1 : 1, EtOAc/petrol to EtOAc) to give the title compound (0.725 g, 72%, \( dr = 92 : 8 \)) as a white solid.

\( R_f : 0.22 \) (1 : 1, EtOAc/petrol).

Mp 109-111 °C.

\([\alpha]_D^{23} +19.2^o \) (c 0.21, MeOH).

\( \nu_{\text{max/cm}^{-1}} \) 3477, 1644, 1449, 1332, 1178, 1081.

\( ^1 \)H NMR (CD\(_3\)OD) 7.32-7.24 (5H, m, ArH), 4.85 (1H, d, \( J = 15.5 \) Hz, H1`), 4.76 (1H, dd, \( J = 1.5 \) Hz, H5), 4.12 (1H, dd, \( J = 1.5, 6.5 \) Hz, H4), 4.08 (1H, d, \( J = 15.5 \) Hz, H1`), 2.86 (1H, dd, \( J = 6.5, 17.0 \) Hz, H3), 2.22 (1H, dd, \( J = 1.5, 17.0 \) Hz, H3).

\( ^13 \)C NMR (CD\(_3\)OD) 175.7 (C2), 137.6 (ArC), 129.6 (ArCH), 128.9 (ArCH), 128.4 (ArCH), 90.1 (C4), 72.3 (C5), 43.9 (C1`), 39.3 (C3).

EIMS \( m/z \) 207 (M\(^+\), 75%).

HREIMS calculated for C\(_{11}\)H\(_{13}\)NO\(_3\) (M\(^+\)), 207.0895, found 207.0902.
(S)-1-Benzyl-3-(benzyloxy)pyrrolidine-2,5-dione (125)

The alcohol 123 (2.00 g, 9.75 mmol) was dissolved in Et$_2$O (100 mL) and then BnBr (5.0 g, 29.2 mmol) and Ag$_2$O (6.76 g, 29.2 mmol) were added. The resulting suspension was stirred at rt for 2 d in the dark. The reaction mixture was filtered through a pad of Celite and concentrated 	extit{in vacuo}. The crude product was purified by column chromatography (1 : 2, EtOAc/petrol) to give the title product (2.24 g, 78%) as a pale yellow solid.

R$_f$: 0.46 (1 : 2, EtOAc/petrol).

Mp 74-76 °C (Lit.$^{67}$ Mp 76-77.5 °C).

$[^{13]}$\textalpha$ ^{23}$D $+23.6^\circ$ (c 0.18, CHCl$_3$) (Lit.$^{67}$ $[^{13]}$\textalpha$ ^{25}$ $+34.7^\circ$ (c 0.7, CHCl$_3$)).

$^1$H NMR $\delta$ 7.38-7.30 (10H, m, ArH), 4.98 (1H, d, $J$ = 11.5 Hz, H2`), 4.78 (1H, d, $J$ = 11.5 Hz, H2`), 4.67 (2H, s, H1`), 4.37-4.34 (1H, m, H3), 2.94 (1H, dd, $J$ = 8.0, 18.0 Hz, H4), 2.66 (1H, dd, $J$ = 4.5, 18.5 Hz, H4).

$^{13}$C NMR $\delta$ 175.8 (CO), 173.9 (CO), 136.8 (ArC), 135.6 (ArC), 129.0 (ArCH), 128.9 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 73.2 (C2`), 72.3 (C3), 42.4 (C1`), 36.5 (C4).

$^1$H and $^{13}$C NMR data matched the published data.

EIMS m/z 295 (M$^+$, 65%).

(4$S,5$S)-1-Benzyl-4-(benzyloxy)-5-hydroxypyrrolidin-2-one (126)

Prepared in a similar fashion to 124 above, from 125 (0.70 g, 2.5 mmol) and NaBH$_4$ (0.47 g, 12.6 mmol) in CH$_2$Cl$_2$/EtOH (30 mL, 1 : 1) with stirring at -20 °C for 30 min. The crude product was purified by column chromatography (1 : 2, EtOAc/petrol) to give the title product (0.51 g, 70%, dr = 100 : 0) as a white solid.

R$_f$: 0.37 (1 : 2, EtOAc/petrol).

Mp 130-132 °C (Lit.$^{58}$ Mp 130-130.5 °C).

$[^{13]}$\textalpha$ ^{23}$D $+37.1^\circ$ (c 0.17, CHCl$_3$) (Lit.$^{58}$ $[^{13]}$\textalpha$ ^{24}$ $+20.6^\circ$ (c 1.2, CHCl$_3$)).

$^1$H NMR $\delta$ 7.36-7.28 (10H, m, ArH), 4.98 (1H, dd, $J$ = 6.5, 7.5 Hz, H5), 4.90 (1H, d, $J$ = 14.5 Hz, H1`), 4.61 (1H, d, $J$ = 11.5 Hz, H2`), 4.56 (1H, d, $J$ = 11.5 Hz, H2`), 4.16 (1H, d, $J$ = 14.5 Hz, H1`), 4.10 (1H, dd, $J$ = 6.5, 7.0 Hz, H4), 3.50 (1H, br. s, OH), 2.59 (2H, d, $J$ = 7.0 Hz, H3).
\(^{13}\)C NMR δ 171.0 (C2), 136.5 (ArC), 136.3 (ArC), 128.6 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.3 (ArCH), 127.9 (ArCH), 127.5 (ArCH), 81.1 (C5), 72.1 (C2’), 71.7 (C4), 43.4 (C1’), 35.9 (C3).

\(^1\)H and \(^{13}\)C NMR data matched the published data.

EIMS m/z 297 (M\(^+\) 100%).

\((3aS, 6aS, E)-1\text{-Benzyl-5-styryl-hexahydroborolo[3,4-b]pyrrol-2(1}H\text{-one (128)}\)

To a solution of \textbf{124} (0.10 g, 0.482 mmol) and trans-styrylboronic acid (0.214 g, 1.45 mmol) in dry CH\(_2\)Cl\(_2\) (5.0 mL) at 0 °C under N\(_2\), was added dropwise BF\(_3\)·OEt\(_2\) (0.273 g, 1.927 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated NaHCO\(_3\) solution (15 mL) was added and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 15 mL). The combined extracts were dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo}. The title product was obtained without further purification (0.113 g, 78%).

R\(_f\) : 0.34 (1 : 1, EtOAc/petrol).

\([\alpha]_{D}^{25} +48.3^\circ\ (c 0.32, CHCl\(_3\)).\)

\(v_{\text{max/cm}^{-1}}\) 1685, 1449, 1367, 1065.

\(^1\)H NMR δ 7.42 (1H, d, \(J = 18.5\) Hz, H2’), 7.35-7.20 (10H, m, ArH), 6.14 (1H, d, \(J = 18.5\) Hz, H1’), 5.59 (1H, d, \(J = 6.0\) Hz, H5), 5.02 (1H, d, \(J = 14.5\) Hz, H3’), 4.93 (1H, dd, \(J = 6.0, 7.0\) Hz, H4), 4.15 (1H, d, \(J = 14.5\) Hz, H3’), 2.83 (1H, dd, \(J = 7.0, 18.0\) Hz, H3), 2.71 (1H, d, \(J = 18.0\) Hz, H3).

\(^{13}\)C NMR δ 171.2 (C2), 136.9 (ArC), 135.6 (ArC), 129.4 (C2’), 128.7 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 127.8 (ArCH), 127.2 (C1’), 89.4 (C5), 73.1 (C4), 43.9 (C3’), 38.1 (C3).

EIMS m/z 319 (M\(^+\), 100%).

HREIMS calculated for C\(_{19}\)H\(_{18}\)BNO\(_3\) (M\(^+\)) 319.1379, found 319.1376.

\((1S, 5S)-2\text{-Benzyl-6-oxa-2-aza-bicyclo[3.1.0]hexan-3-one (132)}\)

To a solution of \textbf{124} (0.10 g, 0.482 mmol) in nitromethane (5 mL), at 0 °C was added BF\(_3\)·OEt\(_2\) (0.273 g, 1.93 mmol). The mixture was stirred at 80 °C for 5 h. A saturated solution of NaHCO\(_3\) (5 mL) was added, and aqueous layer was extracted with dichloromethane (3 x 10 mL).
The combined extracts were dried (MgSO₄), and concentrated in vacuo. The title compound was unstable to silica gel and was obtained as an oil without further purification (0.071 g, 78%).

Rₛ : 0.31 (EtOAc).

[α]ᵦ₂₄<sup>+</sup> +53.7° (c 0.42, CHCl₃).

υ<sub>max</sub>/cm<sup>-1</sup> 1690, 1449, 1362, 1214, 1081, 1019.

¹H NMR δ 7.33-7.22 (5H, m, ArH), 5.41 (1H, d, J = 7.0 Hz, H5), 5.03 (1H, d, J = 14.5 Hz, H1’), 4.89 (1H, dd, J = 7.0, 8.0 Hz, H4), 4.07 (1H, d, J = 14.5 Hz, H1’), 2.85 (1H, dd, J = 8.0, 18.5 Hz, H3), 2.68 (1H, d, J = 18.5 Hz, H3).

¹³C NMR δ 171.1 (C2), 136.2 (ArC), 128.9 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 83.5 (C5), 75.0 (C4), 44.7 (C1’), 37.7 (C3).

EIMS m/z 189 (M⁺, 75%).

HREIMS calculated for C₁₁H₁₁NO₂ (M⁺) 189.0789, found 189.0783.

**General Procedure for Borono-Mannich Reaction of 124 and Preparation of (4S, 5S, E)-1-Benzyl-4-hydroxy-5-styrylpyrrolidin-2-one (127)**

To a solution of 124 (0.10 g, 0.482 mmol) in anhydrous MeNO₂ (5 mL), at 0 °C was added trans-styrylboronic acid (0.214 g, 1.4 mmol) and then BF₃·OEt₂ (0.273 g, 1.93 mmol). The mixture was stirred at 80 °C for 16 h. A saturated aqueous solution of NaHCO₃ (5 mL) was added, and aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined extracts were dried (MgSO₄), and concentrated in vacuo. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title compound (0.027 g, 20%, dr = 91 : 9) as a white solid,

Rₛ : 0.32 (1 : 1, EtOAc/petrol).

Mp 128-130 °C.

υ<sub>max</sub>/cm<sup>-1</sup> 3334, 1669, 1444, 1426, 1262, 1176, 1071.

¹H NMR δ (major cis isomer) 7.35-7.18 (10H, m, ArH), 6.51 (1H, d, J = 16.5 Hz, H2’), 6.15 (1H, dd, J = 8.5, 16.5 Hz, H1’), 4.93 (1H, d, J = 15.5 Hz, H3’), 4.43 (1H, ddd, J = 3.5, 6.0, 7.0 Hz, H4), 4.10 (1H, dd, J = 6.0, 8.5 Hz, H5), 3.96 (1H, d, J = 15.5 Hz, H3’), 2.73 (1H, dd, J = 7.0, 17.5 Hz, H3), 2.54 (1H, dd, J = 3.5, 17.5 Hz, H3), 2.45 (1H, br.s, OH).
\(^{13}\)C NMR \(\delta\) (major cis isomer) 172.9 (C2), 136.5 (ArC), 136.3 (C2’), 135.7 (ArC), 128.6 (ArCH), 128.6 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 127.4 (ArCH), 126.6 (ArCH), 123.3 (C1’), 67.5 (C4), 65.2 (C5), 44.3 (C3’), 39.9 (C3).

EIMS \(m/z\) 293 (M\(^+\), 100%).

HREIMS calculated for C\(_{10}\)H\(_{19}\)NO\(_2\) (M\(^+\)) 293.1417, found 293.1415.

\((4S, 5S)-1\)-Benzyl-5-(furan-2-yl)-4-hydroxypyrrolidin-2-one (136)

Prepared using the general method above, from 124 (0.150 g, 0.725 mmol), 2-furanboronic acid (0.243 g, 2.17 mmol), MeNO\(_2\) (5.0 mL) and BF\(_3\)·OEt\(_2\) (0.411 g, 2.90 mmol), except that the reaction mixture was warmed to rt and stirred for 16 h. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title compound (0.126 g, 65%, dr = 77 : 23) as an oil.

\(R_f\) : 0.53 (1:1, EtOAc/petrol).

\(\nu_{\text{max}}\) cm\(^{-1}\): 3365, 1669, 1447, 1253, 1149, 1070, 1012.

\(^1\)H NMR \(\delta\) (major trans isomer) 7.38 (1H, d, \(J = 1.5\) Hz, H5’), 7.30-7.17 (5H, m, ArH), 6.34 (1H, dd, \(J = 1.5, 3.0\) Hz, H4’), 6.21 (1H, d, \(J = 3.0\) Hz, H3’), 4.92 (1H, d, \(J = 15.5\) Hz, H6’), 4.42 (1H, ddd, \(J = 2.0, 2.5, 6.0\) Hz, H4), 4.31 (1H, d, \(J = 2.0\) Hz, H5), 3.58 (1H, d, \(J = 15.5\) Hz, H6’), 3.00 (1H, dd, \(J = 6.5, 17.0\) Hz, H3), 2.48 (1H, dd, \(J = 2.5, 17.0\) Hz, H3).

\(^{13}\)C NMR \(\delta\) (major trans isomer) 172.9 (C2), 150.1 (C2’), 143.5 (C5’), 135.8 (ArC), 128.7 (ArCH), 128.3 (ArCH), 128.0 (ArCH), 110.3 (C4’), 109.0 (C3’), 69.5 (C4), 63.9 (C5), 44.2 (C6’), 39.8 (C3).

\(^1\)H NMR \(\delta\) (minor cis isomer) 7.46 (1H, d, \(J = 1.5\) Hz, H5’), 7.30-7.17 (5H, m, ArH), 6.42 (1H, dd, \(J = 1.5, 3.0\) Hz, H4’), 6.17 (1H, d, \(J = 3.0\) Hz, H3’), 4.98 (1H, d, \(J = 15.0\) Hz, H6’), 4.57 (1H, d, \(J = 7.0\) Hz, H5), 4.53 (1H, ddd, \(J = 7.5, 7.0, 2.5\) Hz, H4), 3.60 (1H, d, \(J = 15.0\) Hz, H6’), 2.70 (1H, dd, \(J = 7.5, 17.0\) Hz, H3), 2.65 (1H, dd, \(J = 2.5, 17.0\) Hz, H3).

\(^{13}\)C NMR \(\delta\) (minor cis isomer) 172.5 (C2), 148.3 (C2’), 135.7 (ArC), 128.7 (ArCH), 128.5 (ArCH), 128.0 (ArCH), 127.6 (C5’), 111.1 (C4’), 110.5 (C3’), 66.9 (C4), 59.8 (C5), 44.6 (C6’), 39.1 (C3).

EIMS \(m/z\) 257 (M\(^+\), 100%).

HREIMS calculated for C\(_{15}\)H\(_{15}\)NO\(_3\) (M\(^+\)) 257.1049, found 257.1049.
(4S, 5R)-5-(Benzofuran-2-yl)-1-benzyl-4-hydroxypyrrolidin-2-one (137)  
Prepared using the general method above, from 124 (0.05 g, 0.241 mmol), 2-benzofuranboronic acid (0.117 g, 0.724 mmol), MeNO₂ (3.0 mL) and BF₃·OEt₂ (0.137 g, 0.966 mmol). The crude product was purified by column chromatography (Et₂O) to give the title compound (0.041 g, 56%, dr = 92 : 8) as an oil.  
Rf : 0.47 (Et₂O).  
υmax/cm⁻¹ 3308, 1670, 1454, 1417, 1355, 1306, 1255, 1167, 1108, 1086.  
¹H NMR δ (major cis isomer) 7.51 (1H, d, J = 8.0 Hz, ArH), 7.41 (1H, d, J = 8.0 Hz, ArH), 7.54-7.29 (6H, m, ArH), 7.08 (1H, d, J = 8.0 Hz, ArH), 6.64 (1H, s, H3’), 5.06 (1H, d, J = 15.0 Hz, H2’), 4.64 (1H, d, J = 7.0 Hz, H5), 4.57 (1H, app br. q, J ca 7 Hz, H4), 3.61 (1H, d, J = 15.0 Hz, H2’), 2.76-2.74 (2H, m, H3).  
¹³C NMR δ (major cis isomer) 172.5 (C2), 155.3 (ArC), 151.3 (ArC), 135.7 (ArC), 128.4 (ArCH), 128.2 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 124.8 (ArC), 123.1 (ArCH), 121.2 (ArCH), 111.5 (ArCH), 107.7 (C3’), 67.0 (C4), 60.2 (C5), 44.5 (C2’), 39.1 (C3).  
¹H NMR δ (minor trans isomer) 7.54 (1H, d, J = 8.0 Hz, ArH), 7.42 (1H, d, J = 8.0 Hz, ArH), 7.36-7.14 (7H, m, ArH), 6.58 (1H, s, H3’), 5.12 (1H, d, J = 15.0 Hz, H2’), 4.57 (1H, br. dd, J = 7.0, 2.5 Hz, H4), 4.48 (1H, s, H5), 3.71 (1H, d, J = 15.0 Hz, H2’), 3.07 (1H, dd, J = 7.0, 17.5 Hz, H3), 2.52 (1H, dd, J = 2.5, 17.5 Hz, H3).  
¹³C NMR δ (minor trans isomer) 172.8 (C2), 155.2 (ArC), 152.6 (ArC), 135.7 (ArC), 128.6 (ArCH), 128.1 (ArCH), 127.6 (ArCH), 125.5 (ArC), 124.8 (ArCH), 123.1 (ArCH), 121.1 (ArCH), 111.4 (ArCH), 105.9 (C3’), 69.6 (C4), 64.3 (C5), 44.4 (C2’), 39.9 (C3).  
EIMS m/z 307 (M⁺, 100%).  
HREIMS calculated for C₁₉H₁₇NO₃ (M⁺) 307.1208, found 307.1207.  

(4S, 5R)-1-Benzyl-5-(3,4-dimethoxyphenyl)-4-hydroxypyrrolidin-2-one (138)  
Prepared using the general method above, from 124 (0.05 g, 0.241 mmol), 3,4-dimethoxyphenylboronic acid (0.132 g, 0.724 mmol) and BF₃·OEt₂ (0.137 g, 0.966 mmol). The desired product (0.035 g, 44%, dr = 72 : 28) was obtained
as an oil after purification by column chromatography (EtOAc).

R_f : 0.23 (EtOAc).

υ_{max}/cm^{-1} 3352, 1699, 1505, 1463, 1272, 1257, 1149, 1016.

^1^H NMR δ (major trans isomer) 7.28-7.21 ( 5H, m, ArH), 7.02 (1H, s, ArH), 6.89 (1H, d, J = 8.0 Hz, ArH), 6.72 (1H, d, J = 8.0 Hz, ArH), 4.88 (1H, d, J = 2.5 Hz, H5), 4.82 (1H, d, J = 14.5 Hz, H1’), 4.23 (1H, br. dd, J = 2.5, 6.5 Hz, H4), 4.10 (1H, d, J = 14.5 Hz, H1’), 3.89 (3H, s, OMe), 3.80 (3H, s, OMe), 2.58 (1H, dd, J = 6.5, 17.0 Hz, H3), 2.46 (1H, d, J = 17.0 Hz, H3).

^1^C NMR δ (major trans isomer) 172.4 (C2), 149.3 (ArC), 147.9 (ArC), 136.0 (ArC), 128.6 (ArC), 128.5 (ArCH), 127.9 (ArCH), 127.6 (ArCH), 125.2 (ArCH), 121.0 (ArCH), 111.6 (ArCH), 81.8 (C4), 65.13 (C5), 55.8 (OMe), 43.2 (C1’), 38.3 (C3).

^1^H NMR δ (minor cis isomer) 7.28-7.21 (5H, m, ArH), 6.99 (1H, s, ArH), 6.86 (1H, d, J = 8.0 Hz, ArH), 6.70 (1H, d, J = 8.0 Hz, ArH), 5.06 (1H, d, J = 14.5 Hz, H1’), 4.47 (1H, d, J = 5.5 Hz, H5), 4.43-4.45 (1H, br.m H4), 3.87 (3H, s, OMe), 3.77 (3H, s, OMe), 3.63 (1H, d, J = 14.5 Hz, H1’), 2.70 (1H, dd, J = 6.5, 17.0 Hz, H3), 2.54 (1H, d, J = 17.0 Hz, H3).

^1^C NMR δ (minor cis isomer) 174.1 (C2), 149.2 (ArC), 147.8 (ArC), 135.7 (ArC), 128.6 (ArC), 128.4 (ArCH), 128.2 (ArCH), 127.5 (ArCH), 125.2 (ArCH), 121.0 (ArCH), 111.6 (ArCH), 66.7 (C5), 66.3 (C4), 55.9 (OMe), 44.6 (C1’), 39.5 (C3).

EIMS m/z 327 (M^+, 100%).

HREIMS calculated for C_{19}H_{21}NO_{4} (M^+) 327.1470, found 327.1468.

**General Procedure for Borono-Mannich Reaction of 126 and Preparation of (4S, 5R, E)-1-Benzyl-4-(benzyloxy)-5-styrylpyrrolidin-2-one (149)**

To a solution of 126 (0.150 g, 0.504 mmol) and potassium (E)-2-styryltrifluoroborate (0.315 g, 1.49 mmol) in dry CH_{2}Cl_{2} (5 mL) at 0 °C under N_{2}, was added dropwise BF_{3}·OEt_{2} (0.286 g, 2.06 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated NaHCO_{3} solution (5 mL) was added and the aqueous layer was extracted with CH_{2}Cl_{2} (3 x 10 mL). The combined extracts were dried (MgSO_{4}), filtered and concentrated in vacuo. The crude product was purified by column chromatography (1 : 4, EtOAc/petrol) to give the title compound (0.113 g, 58%, dr = 92 : 8) as an oil.

R_f : 0.32 (1 : 2, EtOAc/petrol).
$\nu_{\text{max}}/\text{cm}^{-1}$ 1692, 1495, 1451, 1261, 1096, 1071, 1028.

$^1$H NMR $\delta$ (major trans isomer) 7.58-7.15 (15H, m, ArH), 6.45 (1H, d, $J = 15.7$ Hz, H2'), 5.91 (1H, dd, $J = 15.7$, 8.0 Hz, H1'), 5.07 (1H, d, $J = 14.7$ Hz, H3'), 4.50 (2H, s, H4'), 4.10 (1H, d, $J = 7.2$ Hz, H4), 3.99 (1H, d, $J = 8.0$ Hz, H5), 3.91 (1H, d, $J = 14.7$ Hz, H3'), 2.82 (1H, dd, $J = 7.2$, 17.5 Hz, H3), 2.58 (1H, d, $J = 17.5$ Hz, H3).

$^{13}$C NMR $\delta$ (major trans isomer) 172.4 (C2), 137.3 (ArC), 136.2 (ArC), 135.7 (ArC), 133.9 (C2'), 128.7 (ArCH), 128.6 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.8, (ArCH) 127.6 (ArCH), 127.4 (ArCH), 126.5 (ArCH), 125.6 (C1'), 77.0 (C5), 71.2 (C4), 65.9 (C4'), 44.0 (C3'), 37.2 (C3).

EIMS $m/z$ 383 (M+, 80%).

HREIMS calculated for C$_{26}$H$_{25}$NO$_2$ (M+) 383.1881, found 383.1885.

(4$S$, 5$R$, E)-1-Benzyl-4-hydroxy-5-styrylpyrrolidin-2-one (150)

To a solution of 127 (0.080 g, 0.208 mmol) in CH$_2$Cl$_2$ (10 mL) at 0 °C under N$_2$, was added dropwise BBr$_3$ (0.209 g, 0.835 mmol). The mixture was stirred for 10 min, and then water (15 mL) and saturated aqueous NaHCO$_3$ solution (5mL) were added. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated in vacuo. The crude product was purified by column chromatography (increasing polarity from 1 : 1, EtOAc/petrol to EtOAc) to give the title compound (0.055 g, 90%) as an oil.

R$_f$ : 0.62 (EtOAc).

$\nu_{\text{max}}/\text{cm}^{-1}$ 3334, 1664, 1511, 1449, 1253, 1058.

$^1$H NMR $\delta$ 7.32-7.21 (10H, m, ArH), 6.47 (1H, d, $J = 15.5$ Hz, H2'), 5.90 (1H, dd, $J = 8.5$, 15.5 Hz, H1'), 4.90 (1H, d, $J = 15.0$ Hz, H3'), 4.23 (1H, br. dd, $J = 6.5$, 2.5 Hz, H4), 3.94 (1H, d, $J = 15.0$ Hz, H3'), 3.92 (1H, d, $J = 8.5$ Hz, H5), 2.84 (1H, dd, $J = 6.5$, 17.0 Hz, H3), 2.63 (1H, br. s., OH), 2.45 (1H, dd, $J = 2.5$, 17.0 Hz, H3).

$^{13}$C NMR $\delta$ 172.6 (C2), 136.2 (ArC), 135.6 (C2'), 134.2 (ArC), 128.7 (ArCH), 128.6 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.5 (ArCH), 126.5 (ArCH), 125.09 (C1'), 70.6 (C4), 68.9 (C5), 44.2 (C3'), 39.4 (C3).

EIMS $m/z$ 293 (M+, 100%).

HREIMS calculated for C$_{19}$H$_{19}$NO$_2$ (M+) 293.1415; found 293.1409.
Method A. Prepared using the general method above, from 126 (0.150 g, 0.504 mmol), 2-furanboronic acid (0.169 g, 1.51 mmol), BF$_3$·OEt$_2$ (0.286 g, 2.06 mmol) and CH$_2$Cl$_2$ (5 mL). The desired product (0.140 g, 79%, dr = 71 : 29) was obtained as an oil after purification by column chromatography (1 : 3, EtOAc/petrol). R$_f$: 0.44 (1 : 3, EtOAc/petrol).

Method B. To a solution of 126 (0.10 g, 0.336 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C under N$_2$ was added furan (0.068 g, 1.00 mmol) and then BF$_3$·OEt$_2$ (0.168 g, 1.34 mmol). The reaction mixture was stirred at rt for 2 h. Saturated aqueous NaHCO$_3$ solution (5 mL) was added and aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined extracts were dried (MgSO$_4$), filtered, and concentrated in vacuo. The desired product (0.045 g, 40%, dr = 55 : 45) was obtained as an oil after purification by column chromatography (1 : 3, EtOAc/petrol). R$_f$: 0.44 (1 : 3, EtOAc/petrol).

$\nu_{\text{max}}$/cm$^{-1}$ 1673, 1452, 1263, 1154, 1072, 1027.

$^1$H NMR $\delta$ (major trans isomer) 7.35 (1H, d, $J$ = 1.2 Hz, H5’), 7.29-7.05 (10H, m, ArH), 6.32 (1H, dd, $J$ = 1.2, 3.2 Hz, H4’), 6.16 (1H, d, $J$ = 3.2 Hz, H3’), 5.07 (1H, d, $J$ = 15.0 Hz, H6’), 4.51 (1H, d, $J$ = 1.5 Hz, H5), 4.45 (2H, s, H7’), 4.24-4.20 (1H, m, H4), 3.64 (1H, d, $J$ = 15.0 Hz, H6’), 2.93 (1H, dd, $J$ = 7.0, 17.5 Hz, H3), 2.59 (1H, dd, $J$ = 2.5, 17.5 Hz, H3).

$^{13}$C NMR $\delta$ (major trans isomer) 172.4 (C2), 150.3 (C2’), 143.0 (C5’), 137.1 (ArC), 135.7 (ArC), 128.4 (ArCH), 128.2 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.4 (ArC), 127.3 (ArCH), 110.2 (C3’), 108.6 (C4’), 76.1 (C4), 71.0 (C7’), 60.85 (C5), 44.0 (C6’), 37.3 (C3).

$^1$H NMR $\delta$ (minor cis isomer) 7.45 (1H, d, $J$ = 1.2 Hz, H5’), 7.29-7.05 (10H, m, ArH), 6.38 (1H, dd, $J$ = 1.2, 3.0 Hz, H4’), 6.29 (1H, d, $J$ = 3.0 Hz, H3’), 5.07 (1H, d, $J$ = 14.7 Hz, H6’), 4.67 (1H, d, $J$ = 7.5 Hz, H5), 4.32 (2H, s, H7’), 4.30-4.28 (1H, m, H4), 3.58 (1H, d, $J$ = 14.7 Hz, H6’), 2.84 (1H, dd, $J$ = 8.5, 16.5 Hz, H3), 2.71 (1H, dd, $J$ = 2.5, 16.5 Hz, H3).

$^{13}$C NMR $\delta$ (minor cis isomer) 171.8 (C2), 148.8 (C2’), 143.0 (C5’), 137.0 (ArC), 135.9 (ArC), 128.4 (ArCH), 128.2 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.5
(ArCH), 127.3 (ArCH), 110.3 (C3’), 110.2 (C4’), 73.2 (C4), 71.4 (C7’), 57.8 (C5),
44.3 (C6’), 36.6 (C3).
EIMS $m/z$ 347 (M+, 100%).
HREIMS calculated for C$_{22}$H$_{21}$NO$_3$ (M+) 347.4078, found 347.4079.

(4$S$, 5$R$)-5-(Benzofuran-2-yl)-1-benzyl-4-(benzyloxy)pyrrolidin-2-one (152)

Prepared using the general method above, from 126 (0.10 g, 0.336 mmol),
benzofuranboronic acid (0.163 g, 1.0 mmol),
BF$_3$·OEt$_2$ (0.190 g, 1.34 mmol) and CH$_2$Cl$_2$ (5 mL). The
desired product (0.110 g, 55%, dr = 89 : 11) was obtained as
an oil after purification by column chromatography (1 : 3,
EtOAc/petrol).

R$_f$ : 0.47 (1 : 2, EtOAc/petrol).

$\nu_{\text{max}}/\text{cm}^{-1}$ 1684, 1454, 1417, 1253, 1109, 1093.

$^1$H NMR $\delta$ (major trans isomer) 7.53 (1H, d, $J = 8.0$ Hz, ArH), 7.42 (1H, d, $J = 8.0$
Hz, ArH), 7.28-7.18 (12H, m, ArH), 6.55 (1H, s, H1’), 5.15 (1H, d, $J = 15.2$ Hz,
H2’), 4.63 (1H, d, $J = 2.0$ Hz, H5), 4.49 (2H, s, H3’), 4.30-4.28 (1H, m, H4), 3.71
(1H, d, $J = 15.2$ Hz, H2’), 3.01 (1H, dd, $J = 7.0$, 17.2 Hz, H3), 2.65 (1H, dd, $J = 2.5$,
17.2 Hz, H3).

$^{13}$C NMR $\delta$ (major trans isomer) 172.6 (C2), 155.1 (ArC), 137.0 (ArC), 135.6 (ArC),
128.5 (ArCH), 128.3 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.5 (ArCH), 127.4
(ArCH), 124.7 (ArC), 127.1 (ArCH), 123.0 (ArCH), 121.0 (ArCH), 111.3 (ArCH),
105.4 (C1’), 76.1 (C4), 71.2 (C3’), 61.3 (C5), 44.2 (C2’), 37.4 (C3).

$^1$H NMR $\delta$ (minor cis isomer) 7.56 (1H, d, $J = 8.0$ Hz, ArH), 7.48 (1H, d, $J = 8.0$ Hz,
ArH), 7.29-7.02 (12H, m, ArH), 6.67 (1H, s, H1’), 5.16 (1H, d, $J = 15.0$ Hz, H2’),
4.78 (1H, d, $J = 7.5$ Hz, H5), 4.49 (1H, d, $J = 12.0$ Hz, H3’), 4.43-4.39 (1H, m, H4),
4.39 (1H, d, $J = 12.0$ Hz, H3’), 3.65 (1H, d, $J = 15.0$ Hz, H2’), 2.93 (1H, dd, $J = 8.0$,
16.5 Hz, H3), 2.76 (1H, dd, $J = 8.0$, 16.5 Hz, H3).

$^{13}$C NMR $\delta$ (minor cis isomer) 172.0 (C2), 155.3 (ArC), 137.0 (ArC), 135.9 (ArC),
128.7 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.8 (ArCH), 127.7 (ArC), 127.5
(ArCH), 127.2 (ArCH), 127.0 (ArCH), 124.5 (ArC), 122.9 (ArCH), 120.9 (ArCH),
111.5 (ArCH), 107.1 (C1’), 73.4 (C4), 71.8 (C3’), 58.3 (C5), 44.5 (C2’), 36.6 (C3).
EIMS $m/z$: 397 (M+, 75%).
HREIMS calculated for C_{26}H_{23}NO_{3} (M^+) 397.1676, found 397.1677.

(4S, 5R)-1-Benzyl-4-(benzyloxy)-5-(2-thienyl)pyrrolidin-2-one (153)

Prepared using the general method above, from 126 (0.10 g, 0.336 mmol), 2-thiopheneboronic acid (0.127 g, 1.0 mmol), BF₃·OEt₂ (0.190 g, 1.34 mmol) and CH₂Cl₂ (5 mL). The desired product (0.088 g, 72%, dr = 62 : 38) was obtained as an oil after purification by column chromatography (1 : 4, EtOAc/petrol). Rᵣ : 0.33 (1 : 3, EtOAc/petrol).

υ_{max}/cm^{-1} 1685, 1451, 1434, 1269, 1111, 1072.

¹H NMR δ (major cis isomer) 7.29-7.22 (9H, m, ArH), 7.13 (1H, d, J = 7.0 Hz, ArH), 7.03 (2H, m, H5', H4'), 6.95 (1H, d, J = 3.5 Hz, H3'), 5.13 (1H, d, J = 15.0 Hz, H6'), 4.89 (1H, d, J = 7.0 Hz, H5), 4.33 (1H, d, J = 12.0 Hz, H7'), 4.33-4.29 (1H, m, H4), 4.28 (1H, d, J = 12.0 Hz, H7'), 3.58 (1H, d, J = 15.0 Hz, H6'), 2.79 (1H, dd, J = 7.5, 17.5 Hz, H3), 2.72 (1H, dd, J = 7.5, 17.5 Hz, H3).

¹H NMR δ (minor trans isomer) 7.39-7.12 (10H, m, ArH), 7.03 (1H, m, H5'), 6.98 (1H, dd, J = 3.2, 4.7 Hz, H4'), 6.84 (1H, d, J = 3.2 Hz, H3'), 5.17 (1H, d, J = 15.5 Hz, H6'), 4.72 (1H, d, J = 2.0 Hz, H5), 4.47 (2H, s, H7'), 4.11-4.07 (1H, m, H4), 3.65 (1H, dd, J = 15.5 Hz, H6'), 2.93 (1H, dd, J = 7.0, 17.5 Hz, H3), 2.59 (1H, dd, J = 2.5, 17.5 Hz, H3).

¹³C NMR δ (major cis isomer) 171.1 (C2), 140.5 (C2'), 137.7 (ArC), 136.0 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.4 (C5'), 126.8 (C4'), 126.4 (C3'), 73.3 (C4), 71.7 (C6'), 60.2 (C5), 44.1 (C7'), 36.8 (C3).

¹H NMR δ (minor trans isomer) 7.23 (C2), 141.6 (C2'), 137.1 (ArC), 135.7 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 127.8 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 127.1 (C5'), 125.9 (C4'), 125.7 (C3'), 79.5 (C4), 71.3 (C6'), 63.0 (C5), 44.0 (C7'), 37.0 (C3).

EIMS m/z 363 (M⁺, 100%).

HREIMS calculated for C_{22}H_{21}NO_{2}S (M⁺) 363.1296, found 363.1293.
(4S, 5R)-1-Benzyl-4-(benzylxoy)-5-(4-methoxyphenyl)pyrrolidin-2-one (155)

Prepared using the general method above, from 126 (0.10 g, 0.336 mmol), p-methoxyphenylboronic acid (0.214 g, 1.00 mmol), BF$_3$·OEt$_2$ (0.190 g, 1.34 mmol), and CH$_2$Cl$_2$ (5 mL). The desired product (0.063 g, 48%, dr = 72 : 28) was obtained as an oil after purification by column chromatography (1:3, EtOAc/petrol).

R$_f$ : 0.42 (1:3, EtOAc/petrol).

$\nu_{\text{max}}$/cm$^{-1}$ 1690, 1512, 1442, 1408, 1248, 1175, 1072.

$^1$H NMR $\delta$ (major trans isomer) 7.29-7.12 (10H, m, ArH), 7.00 (2H, d, $J = 8.0$ Hz, ArH), 6.89 (2H, d, $J = 8.0$ Hz, ArH), 5.10 (1H, d, $J = 15.0$ Hz, H1'), 4.37 (2H, s, H2'), 4.34 (1H, d, $J = 2.5$ Hz, H5), 3.90-3.87 (1H, m, H4), 3.74 (3H, s, OMe), 3.44 (1H, d, $J = 15.0$ Hz, H1'), 2.87 (1H, dd, $J = 6.5$, 17.0 Hz, H3), 2.60 (1H, dd, $J = 2.5$, 17.0 Hz, H3).

$^{13}$C NMR $\delta$ (major trans isomer) 172.9 (C2), 159.5 (ArC), 137.3 (ArC), 135.8 (ArC), 128.5 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.8 (ArCH), 127.5 (ArCH), 127.4 (ArC), 127.3 (ArCH), 127.1 (ArCH), 114.4 (ArCH), 79.4 (C4), 71.1 (C5), 67.0 (C2'), 55.2 (OMe), 43.9 (C1'), 37.2 (C3).

$^1$H NMR $\delta$ (minor cis isomer) 7.28-7.12 (14H, m, ArH), 7.10 (2H, d, $J = 8.5$ Hz, ArH), 6.93 (2H, d, $J = 8.5$ Hz, ArH), 5.15 (1H, d, $J = 14.5$ Hz, H1'), 4.53 (1H, d, $J = 6.5$ Hz, H5), 4.25-4.23 (1H, m, H4), 4.17 (1H, d, $J = 12.0$ Hz, H2'), 4.12 (1H, d, $J = 12.0$ Hz, H2'), 3.76 (3H, s, OMe), 3.48 (1H, d, $J = 14.5$ Hz, H1'), 2.73 (2H, m, H3).

$^{13}$C NMR $\delta$ (minor cis isomer) 172.6 (C2), 159.6 (ArC), 137.2 (ArC), 136.0 (ArC), 129.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.7 (ArC), 127.4 (ArCH), 127.1 (ArCH), 113.8 (ArCH), 73.5 (C4), 71.6 (C5), 64.4 (C2'), 55.2 (OMe), 44.1 (C1'), 37.6 (C3).

EIMS m/z 387 (M+, 100%).

HREIMS calculated for C$_{25}$H$_{25}$NO$_3$ (M+) 387.1833, found 387.1834.
(4S, 5R)-1-Benzyl-4-(benzylkoxy)-5-(3,4-dimethoxyphenyl)pyrrolidin-2-one (156)

Prepared using the general method above, from 126 (0.10 g, 0.336 mmol), 3,4-dimethoxyphenylboronic acid (0.182 g, 1.0 mmol), BF₃·OEt₂ (0.190 g, 1.34 mmol), and CH₂Cl₂ (5 mL). The desired product (0.103 g, 74%, dr = 74 : 26) was obtained as an oil after purification by column chromatography (1 : 2, EtOAc/petrol).

Rᶠ : 0.47 (1 : 3, EtOAc/petrol).

υmax/cm⁻¹ 1689, 1515, 1453, 1413, 1260, 1237, 1139, 1072, 1026.

¹H NMR δ (major trans isomer) 7.28-7.12 (10H, m, ArH), 6.85 (1H, d, J = 8.0 Hz, ArH), 6.66 (1H, dd, J = 2.0, 7.7 Hz, ArH), 6.48 (1H, d, J = 2.0 Hz, ArH), 5.14 (1H, d, J = 15.5 Hz, H1’), 4.45 (2H, s, H2’), 4.40 (1H, d, J = 2.5 Hz, H5), 4.00-3.97 (1H, m, H4), 3.88 (3H, s, OMe), 3.79 (3H, s, OMe), 3.58 (1H, d, J = 15.5 Hz, H1’), 2.88 (1H, dd, J = 7.0, 17.0 Hz, H3), 2.60 (1H, dd, J = 3.5, 17.0 Hz, H3).

¹³C NMR δ (major trans isomer) 172.7 (C2), 149.4 (ArC), 148.8 (ArC), 137.2 (ArC), 135.8 (ArC), 134.9 (ArC), 128.3 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 127.4 (ArCH), 127.4 (ArCH), 118.9 (ArCH), 111.3 (ArCH), 109.3 (ArCH), 79.1 (C4), 71.0 (C2’), 67.3 (C5), 55.7 (OMe), 43.9 (C1’), 37.0 (C3).

¹H NMR δ (minor cis isomer) 7.28-7.12 (10H, m, ArH), 6.85 (1H, d, J = 8.0 Hz, ArH), 6.72 (1H, d, J = 8.0 Hz, ArH), 6.71 (1H, s, ArH), 5.10 (1H, d, J = 15.0 Hz, H1’), 4.51 (1H, d, J = 7.0 Hz, H5), 4.22-4.20 (1H, m, H4), 4.19 (1H, d, J = 11.5 Hz, H2’), 4.08 (1H, d, J = 11.5 Hz, H2’), 3.91 (3H, s, OMe), 3.78 (1H, d, J = 15.0 Hz, H1’), 3.73 (3H, s, OMe), 2.73 (2H, m, H3).

¹³C NMR δ (minor cis isomer) 172.8 (C2), 149.5 (ArC), 148.9 (ArC), 137.3 (ArC), 136.0 (ArC), 128.3 (ArCH), 128.0 (ArCH), 127.6 (ArCH), 127.3 (ArCH), 127.2 (ArCH), 127.1 (ArCH), 126.6 (ArCH), 121.2 (ArCH), 111.9 (ArCH), 110.6 (ArCH), 73.6 (C4), 71.5 (C2’), 64.9 (C5), 55.6 (OMe), 44.1 (C1’), 37.7 (C3).

EIMS m/z 417 (M⁺, 80%).

HREIMS calculated for C₂₆H₂₇NO₄ (M⁺) 417.1941, found 417.1940.
(S)-3-Hydroxy-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (163)

Prepared in a similar fashion to 123 above, using L-malic acid (2.00 g, 15 mmol), p-methoxybenzylamine (2.04 g, 15 mmol) and xylene (150 mL) with stirring at reflux temperature for 2 h. The crude product was purified by column chromatography (2 : 1, EtOAc/petrol) to give the title compound as a light yellow solid (2.96 g, 84%).

Rf : 0.52 (2 : 1, EtOAc/petrol).

Mp 108-110 °C.

$[\alpha]_{D}^{24} +24.5^\circ$ (c 0.28, CHCl$_3$).

$\nu_{\text{max/cm}}^{-1}$ 3441, 1685, 1513, 1431, 1408, 1302, 1247, 1177, 1105, 1025, 928.

$^1$H NMR $\delta$ 7.30 (2H, d, $J = 8.0$ Hz, ArH), 6.82 (2H, d, $J = 8.0$ Hz, ArCH), 4.61-4.58 (3H, m, H3, H1`), 3.77 (3H, s, OMe), 3.03 (1H, dd, $J = 8.5, 18.5$ Hz, H4), 2.65 (1H, dd, $J = 2.5, 18.5$ Hz, H4).

$^{13}$C NMR $\delta$ 178.0 (CO), 173.8 (CO), 159.4 (ArC), 130.3 (ArCH), 127.4 (ArC), 114.0 (ArCH), 66.9 (C3), 55.2 (OMe), 41.9 (C1`), 37.1 (C4).

EIMS $m/z$ 235 (M$^+$, 100%).

HREIMS calculated for C$_{12}$H$_{13}$NO$_4$ (M$^+$) 235.0809, found 235.1204.

(S)-3-(tert-Butyldimethylsilyloxy)-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (164)

To a solution of 163 (2.0 g, 8.50 mmol), imidazole (0.69 g, 10.2 mmol) and DMAP (0.10 g, 0.85 mmol) in THF (100 mL) at 0 °C were added TBSCl (3.37 g, 12.76 mmol). The reaction mixture was allowed to warm to rt and was stirred at this temperature for 16 h. Saturated aqueous solution of NaHCO$_3$ (40 mL) was added and aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated in vacuo. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title product as a colorless oil (2.66 g, 90%).

Rf : 0.83 (1 : 2, EtOAc/petrol).

$[\alpha]_{D}^{23} +22.9^\circ$ (c 0.11, CHCl$_3$) (Lit. value not reported).
$^1$H NMR $\delta$ 7.31 (2H, d, $J = 8.5$ Hz, ArH), 6.81 (2H, d, $J = 8.5$ Hz, ArH), 4.57 (2H, s, C1’), 4.55-4.53 (1H, m, H3), 3.70 (3H, s, OMe), 2.96 (1H, dd, $J = 7.5$, 18.0 Hz, H4), 2.57 (1H, dd, $J = 4.5$, 18.0 Hz, H4), 0.89 (9H, s, (CH$_3$)$_3$C), 0.16 (6H, s, (CH$_3$)$_2$Si).

$^{13}$C NMR $\delta$ 176.3 (CO), 173.9 (CO), 159.3 (ArC), 130.4 (ArC), 127.9 (ArCH), 113.9 (ArCH), 67.9 (C3), 55.2 (OMe), 41.7 (C1’), 38.8 (C4), 25.6 (C(CH$_3$)$_3$), 18.2 (C(CH$_3$)$_3$), -4.7 (CH$_3$)$_2$Si), -5.3 (CH$_3$)$_2$Si).

$^1$H and $^{13}$C NMR data matched with the published data.

ESIMS $m/z$ 350 (M + H$^+$, 100%).

**{(S)-3-Hydroxypyrrolidine-2,5-dione (165)}**

To a solution of 165 (0.50 g, 1.43 mmol) in CH$_3$CN/H$_2$O (20 mL, 1 : 1) at 0 °C was added CAN (3.9 g, 7.15 mmol). The reaction mixture was stirred at 0 °C for 1 h. EtOAc (20 mL) and water (10 mL) were added and aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc) to give the title product as a white solid (0.046 g, 28%).

Mp 93-94 °C (Lit.$^{151}$ Mp 95 °C).

$[\alpha]_{D}^{23} +19.6$° (c 0.20, CHCl$_3$) (Lit. Value not reported).

R$_f$ : 0.33 (EtOAc).

$^1$H NMR $\delta$ (CD$_3$OD) 10.9 (1H, br. s, NH), 4.80 (1H, br. s, OH), 4.59-4.57 (1H, m, H3), 3.02 (1H, dd, $J = 6.0$, 17.5 Hz, H4), 2.52 (1H, dd, $J = 2.5$, 17.5 Hz, H4).

$^{13}$C NMR $\delta$ (CD$_3$OD) 180.1 (CO), 176.7 (CO), 68.0 (C3), 38.6 (C4).

$^1$H and $^{13}$C NMR data matched with the published data.

**{(S)-3-({tert-Butyldiphenylsilyloxy)-1-(4-methoxybenzyl)pyrrolidine-2,5-dione (166)}**

Prepared in a similar fashion to 164 above from 163 (1.0 g, 4.25 mmol), imidazole (0.347 g, 5.1 mmol), DMAP (0.05 g, 0.42 mmol) and TBDPSCl (1.75 g, 6.38 mmol) with stirring at rt for 16 h. The crude product was purified by column chromatography (1 : 6, EtOAc/petrol) to give the title product (2.21 g, 92%) as a colorless oil.
R$_f$ : 0.68 (1 : 6, EtOAc/petrol).

$[\alpha]_{D}^{23}$ +28.7$^\circ$ (c 0.15, CHCl$_3$).

$^1$H NMR $\delta$ 7.84 (2H, d, $J = 7.5$ Hz, ArH), 7.69 (2H, d, $J = 7.5$ Hz, ArH), 7.46-7.33 (8H, m, ArH), 6.83 (2H, d, $J = 8.5$ Hz, ArH), 4.58 (2H, s, C1'), 4.54-4.52 (1H, m, C3), 2.63 (1H, dd, $J = 8.0$, 18.0 Hz, H4), 2.57 (1H, dd, $J = 5.0$, 18.0 Hz, H4), 1.13 (9H, s, (CH$_3$)$_3$C).

$^1$H NMR $\delta$ 175.8 (CO), 173.5 (CO), 159.2 (ArC), 135.8 (ArCH), 135.6 (ArCH), 132.7 (ArC), 131.8 (ArC), 130.3 (ArCH), 130.1 (ArCH), 130.0 (ArC), 127.8 (ArCH), 127.7 (ArCH), 113.8 (ArCH), 68.3 (C3), 55.1 (OMe), 41.6 (C1'), 38.6 (C4), 26.6 (C(CH$_3$)$_3$), 19.1 (C(CH$_3$)$_3$).

ESIMS $m/z$ 474 (M + H$,^+$, 30%).

HRESIMS calculated for C$_{28}$H$_{32}$NO$_4$Si (M + H$^+$) 474.1582, found 474.1566.

(S)-3-(tert-Butyldiphenylsilyloxy)pyrrolidine-2,5-dione (167)

Prepared in a similar fashion to 165 above from 166 (0.69 g, 1.47 mmol), CAN (4.02 g, 7.34 mmol) and CH$_3$CN/H$_2$O (50 mL, 1 : 1) with stirring at rt for 1 h. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title product (0.20 g, 40%) as a colorless oil.

R$_f$ : 0.68 (1 : 6, EtOAc/petrol).

$[\alpha]_{D}^{23}$ +47.1$^\circ$ (c 0.25, CHCl$_3$).

$\nu$$_{\text{max}}$/cm$^{-1}$ 3242, 1716, 1475, 1429, 1337, 1183, 1112, 840.

$^1$H NMR $\delta$ 8.99 (1H, br. s, NH), 7.83 (2H, d, $J = 6.5$ Hz, ArH), 7.71 (2H, d, $J = 6.5$ Hz, ArH), 7.48-7.41 (6H, m, ArH), 4.60-4.57 (1H, m, H3), 2.69-2.64 (2H, m, H4), 1.14 (9H, (CH$_3$)$_3$C).

$^{13}$C NMR $\delta$ 176.8 (CO), 174.3 (CO), 135.9 (ArCH), 135.6 (ArCH), 132.6 (ArC), 131.7 (ArC), 130.1 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 69.2 (C3), 39.6 (C4), 26.6 (C(CH$_3$)$_3$), 19.0 (C(CH$_3$)$_3$).

ESIMS $m/z$ 353 (M + H$,^+$, 100%).

HRESIMS calculated for C$_{20}$H$_{24}$NO$_3$Si (M + H$^+$) 353.1579, found 353.1596.
(S)-2,5-Dioxopyrrolidin-3-yl acetate (168)

A suspension of L-malic acid (4.0 g, 29.8 mmol) in acetyl chloride (15 mL) was heated at reflux temperature for 1.5 h and then all volatiles were removed in vacuo. The resulting yellow oil was diluted with THF (25 mL) and treated with a stream of gaseous ammonia over 10 min. to give a white solid. Acetyl chloride (15 mL) was added to the white solid and the mixture was heated at reflux temperature for 2 h. The crude product was purified by column chromatography (2 : 1, EtOAc/petrol) to give the title compound as a light yellow solid (2.62 g, 56%).

Rf : 0.47 (2 : 1, EtOAc/petrol).

Mp 112-115 °C (Lit.Mp 112-114 °C).

\[ \alpha \]_{23}^{D} +31.3° (c 0.18, CHCl₃) (Lit. \[ \alpha \]_{25}^{D} +48.0 ° (c 2.2, MeOH)).

\(^1\)H NMR δ 8.88 (1H, br. s, NH), 5.47 (1H, dd, J = 5.0, 9.0 Hz, H3), 3.19 (1H, dd, J = 8.5, 18.5 Hz, H4), 2.74 (1H, dd, J = 5.5, 18.5 Hz, H4), 2.17 (CH₃).

\(^13\)C NMR δ 173.6 (CO), 173.1 (CO), 170.0 (CO), 68.6 (C3), 37.0 (C4), 20.6 (CH₃).

\(^1\)H and \(^13\)C NMR data matched with the published data.

EIMS m/z 157 (M⁺, 100%).

(R)-2,5-Dioxo-1-(pent-4-enyl)pyrrolidin-3-yl acetate (169)

A solution of 168 (0.500 g, 3.18 mmol), 4-penten-1-ol (0.275 g, 3.18 mmol) and PPh₃ (0.835 g, 3.18 mmol) at 0 °C was treated with DIAD (0.640 g, 3.18 mmol) over 5 min. The resulting reaction mixture was warmed to rt and stirred for 1 h. The solvent was removed and the crude residue was purified by column chromatography (1 : 1, EtOAc/petrol) to give title product (0.571 g, 81%) as an oil.

Rf : 0.57 (1 : 1, EtOAc/petrol).

\[ \alpha \]_{25}^{D} +36.9° (c 0.15, CHCl₃).

\( \nu_{\text{max}}/\text{cm}^{-1} \) 1751, 1709, 1439, 1403, 1372, 1250, 1223, 1054, 1045, 912.

\(^1\)H NMR δ 5.83-5.74 (1H, m, H₄'), 5.41 (1H, dd, J = 4.5, 8.5 Hz, H₃), 5.05 (1H, dd, J = 1.5, 17.0 Hz, H₅'), 4.99 (1H, d, J = 10.5 Hz, H₅'), 3.56 (2H, t, J = 7.0 Hz, H₁'), 3.14 (1H, dd, J = 8.5, 18.5 Hz, H₄), 2.66 (1H, dd, J = 4.5, 18.5 Hz), 2.16 (3H, s, CH₃), 2.08 (2H, q, J = 7.0 Hz, H₃'), 1.71 (2H, pentet, J = 7.0 Hz, H₂').
**13C NMR** δ 173.4 (CO), 173.1 (CO), 169.8 (CO), 137.0 (C4'), 115.4 (C5'), 67.4 (C3), 38.7 (C1'), 35.6 (C4), 30.8 (C3'), 26.4 (C2'), 20.5 (CH3).

EIMS m/z 225 (M⁺, 80%).

HREIMS calculated for C₁₁H₁₅NO₄ (M⁺) 225.1856, found 225.1885.

**S)-2-Hydroxy-5-oxo-1-(pent-4-enyl)pyrrolidin-3-yl acetate (170)**

To a solution of 169 (0.300 g, 1.33 mmol) MeOH/CH₂Cl₂ (15 mL, 1 : 1) at 0 °C was added NaBH₄ (0.252 g, 6.66 mmol) portionwise and then the mixture was stirred at this temperature for 1.5 h. An aqueous solution of NaHCO₃ (15 mL) was added and the aqueous layer was extracted with EtOAc (3 x 15 mL). The crude extracts were dried (MgSO₄), filtered and concentrated under vacuo. The crude product was purified by column chromatography (EtOAc) to give the title product (0.183 g, 62%, dr = 90 : 10) as an oil.

Rₚ : 0.22 (1 : 1, EtOAc/petrol).

[α]ᵢ² +34.1° (c 0.17, CHCl₃).

υmax/cm⁻¹ 3356, 2914, 1708, 1450, 1390, 1273, 1050, 1038, 942.

**1H NMR** δ (major isomer) 5.82-5.76 (1H, m, C4'), 5.31 (1H, d, J = 7.0 Hz, H5), 5.15 (1H, dd, J = 6.5, 7.0 Hz, H4), 5.10 (1H, dd, J = 1.5, 17.0 Hz, H5'), 4.98 (1H, d, J = 10.5 Hz, H5'), 4.46 (1H, br. s, OH), 3.49-3.45 (1H, m, H1'), 3.20-3.16 (1H, m, H3), 2.65-2.59 (2H, m, H3), 2.13 (3H, s, CH₃), 2.08-2.04 (2H, m, H3'), 1.70-1.64 (2H, m, H2').

**13C NMR** δ (major isomer) 171.0 (C2), 170.6 (CO), 137.4 (C5'), 115.1 (C4'), 81.5 (C5), 69.9 (C4), 39.8 (C1'), 38.6 (C3), 30.9 (C3'), 26.7 (C2'), 20.6 (CH₃).

EIMS m/z 227 (M⁺ 50%).

HREIMS calculated for C₁₁H₁₇NO₄ (M⁺) 227.1148, found 227.1157.

**S)-4,5-Dihygroxy-1-(pent-4-enyl)pyrrolidin-2-one (157)**

To a solution of 170 (0.200 g, 0.88 mmol) in MeOH (10 mL) was added K₂CO₃ (0.060 g, 0.44 mmol) and the mixture was stirred at rt for 2h. MeOH was removed under vacuo. The crude product was purified by column chromatography (5% MeOH in EtOAc) to give the desired product (0.108 g, 67%) as an oil.
Rf : 0.20 (EtOAc).
$[\alpha]_D^{25} +29.3^\circ$ (c 0.12, CHCl$_3$).

$\nu_{\text{max}}$/cm$^{-1}$ 3329, 2960, 1664, 1465, 1413, 1259, 1081, 1016, 799.

$^1$H NMR $\delta$ 5.83-5.76 (1H, m, H4`), 5.09-4.97 (2H, m, H5`), 4.35 (1H, dd, $J = 6.5$, 7.0 Hz, H4), 4.21-4.17 (1H, d, $J = 7.0$ Hz, H5), 3.50-3.42 (1H, m, H1`), 3.22-3.13 (1H, m, H1`), 2.83 (1H, dd, $J = 6.5$, 17.5 Hz, H3), 2.24 (1H, dd, $J = 2.0$, 17.5 Hz, H3), 2.09-2.04 (2H, m, H3`), 1.73-1.60 (1H, m, H2`).

$^{13}$C NMR $\delta$ 173.7 (C2), 137.5 (C5`), 115.3 (C4`), 82.9 (C5), 71.8 (C4), 39.7 (C1`), 38.5 (C3), 31.0 (C3`), 26.7 (C2`).

EIMS $m/z$ 185 (M$^+$ 70%).
HREIMS calculated for C$_9$H$_{15}$NO$_3$ (M$^+$) 185.1044, found 185.1038.

(4S,5S,E)-4-Hydroxy-1-(pent-4-enyl)-5-styrylpyrrolidin-2-one (171)

To a suspension of 157 (0.100 g, 0.54 mmol) and phenylvinylboronic acid (0.240 g, 1.62 mmol) in CH$_3$CN (5 mL) at 0 °C was added BF$_3$·OEt$_2$ dropwise. The resulting reaction mixture was warmed to rt and stirred at this temperature for 2 h. An aqueous solution of NaHCO$_3$ (5 mL) was added and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 15 mL), dried (MgSO$_4$), filtered and concentrated under vacuo. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title product (0.048 g, 33%) as an oil.

Rf : 0.36 (EtOAc).
$[\alpha]_D^{25} +27.7^\circ$ (c 0.16, CHCl$_3$).

$\nu_{\text{max}}$/cm$^{-1}$ 3349, 2924, 1667, 1449, 1424, 1367, 1255, 1065, 994, 917.

$^1$H NMR $\delta$ 7.44-7.26 (5H, m, ArH), 6.68 (1H, d, $J = 16.0$ Hz, H2`), 6.21 (1H, dd, $J = 8.5$, 16.0 Hz, H1`), 5.79-5.72 (1H, m, H6`), 5.05-4.93 (2H, m, H7`), 4.50 (1H, br. d, $J = 6.0$ Hz, H4), 4.26 (1H, dd, $J = 6.0$, 8.5 Hz, H5), 3.61-3.55 (1H, m, H3`), 2.98-2.92 (1H, m, H3`), 2.70 (1H, dd, $J = 6.5$, 17.0 Hz, H3), 2.47 (1H, dd, $J = 3.5$, 17.0 Hz, H3), 2.08-1.99 (2H, m, H5`), 1.67-1.54 (2H, m, H4`).

$^{13}$C NMR $\delta$ 172.8 (C2), 137.5 (C7`), 136.1 (C2`), 135.6 (ArC), 128.7 (ArCH), 128.4 (ArCH), 126.7 (ArCH), 123.4 (C1`), 115.0 (C6`), 67.8 (C4), 65.9 (C5), 40.2 (C3`), 40.0 (C3), 30.9 (C5`), 26.5 (C4`).
EIMS m/z 271 (M+ 65%).
HREIMS calculated for C₁₇H₂₁NO₂ (M+) 271.1564, found 271.1572.

(1S,Z)-1-Hydroxy-5,6,7,9a-tetrahydro-1H-pyrrolo[1,2-a]azepine-3(2H)-one (172)

To a solution of 171 (0.010 g, 0.037 mmol) in CH₂Cl₂ (10 mL) at rt was added Grubbs’ second generation catalyst (0.004 g, 0.004 mmol). The reaction mixture was stirred at rt for 1 h. The solvent was removed in vacuo and the crude product was purified by column chromatography (2 : 1, EtOAc/petrol) to give the desired product (72%) as a colorless oil.

Rf : 0.34 (2 : 1, EtOAc/petrol).
[α]₂⁰D +33.5° (c 0.24, CHCl₃).

υmax/cm⁻¹ 3359, 2934, 1662, 1444, 1316, 1260, 1101, 1070.

¹H NMR δ 6.04-6.02 (1H, m, H₈), 5.64 (1H, d, J = 10.5 Hz, H₉), 4.40 (1H, br. s, H₉a), 4.38 (1H, br. s, H₁), 4.12 (1H, dt, J = 5.6, 13.8 Hz, H₅), 2.95 (1H, dt, J = 6.6, 13.8 Hz, H₅), 2.61 (1H, dd, J = 5.4, 16.5 Hz, H₂), 2.45 (1H, dd, J = 3.3, 16.5 Hz), 2.39-2.36 (1H, m, H₇), 2.24-2.16 (1H, m, H₇), 1.99 (1H, br. s. OH), 1.88-1.80 (2H, m, H₆).

¹³C NMR δ 172.3 (C₃), 134.3 (C₈), 123.9 (C₉), 67.0 (C₉a), 64.4 (C₁), 41.2 (C₅), 39.9 (C₂), 26.9 (C₆), 26.0 (C₇).

(4S)-1-Benzyl-4-(benzyloxy)-5-hydroxy-5-styrylpyrrolidin-2-one (179)

Magnesium turnings (0.302 g, 12.6 mmol) were stirred overnight under N₂, and anhydrous THF (5 mL) was then added to the flask. Neat trans-β-bromostyrene (0.461 g, 2.52 mmol) was added dropwise at rt. The reaction mixture was stirred at 40 °C for 1 h. The pyrrolidine-2,5-dione 125 (0.50 g, 1.68 mmol) was dissolved in dry THF (10 mL) and the solution was cooled to -78 °C. 2-Phenylvinylimagnesium bromide was then transferred to the solution via syringe. The reaction mixture was stirred at -78 °C for 4 h, and then warmed slowly to -10 °C. Saturated aqueous NH₄Cl solution (20 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by
column chromatography (1 : 1, EtOAc/petrol) to give the title compound as an oil (0.306 g, 45%, dr = 58 : 42).

Rf : 0.54 (1 : 1, EtOAc/petrol).

1H NMR δ (major diastereomer) 7.31-7.17 (15H, m, ArH), 6.79 (1H, d, J = 16.0 Hz, H2’), 5.86 (1H, d, J = 16.0 Hz, H1’), 4.60 (2H, s, H4’), 4.85 (1H, d, J = 15.0 Hz, H3’), 4.42 (1H, d, J = 15.0 Hz, H3’), 4.03 (1H, br. s, OH), 4.00-3.98 (1H, m, H4), 2.70 (1H, dd, J = 7.0, 17.0 Hz, H3), 2.58 (1H, dd, J = 4.5, 17.0 Hz, H3).

13C NMR δ (major diastereomer) 171.6 (C2), 138.3 (ArC), 135.3 (ArC), 132.4 (C2’), 128.5 (ArC), 128.4 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.7 (ArCH), 127.6 (ArCH), 127.3 (ArCH), 126.8 (ArCH), 126.7 (C1’), 90.5 (C5), 77.2 (C4), 72.3 (C4’), 43.0 (C3’), 35.5 (C3).

1H NMR δ (minor diastereomer) 7.30-7.19 (15H, m, ArH), 6.85 (1H, d, J = 16.5 Hz, H2’), 6.25 (1H, d, J = 16.5 Hz, H1’), 4.57-4.49 (3H, m, H4’, H3’), 4.31 (1H, d, J = 15.0 Hz, H3’), 3.99-3.96 (1H, m, H4), 2.87 (1H, dd, J = 6.5, 17.5 Hz, H3), 2.52 (1H, dd, J = 3.0, 17.5 Hz, H3).

13C NMR δ (minor diastereomer) 173.1 (C2), 138.1 (ArC), 137.3 (ArC), 135.7 (C2’), 128.5 (ArC), 128.5 (ArCH), 128.3 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 127.3 (ArCH), 126.8 (C1’), 93.7 (C5), 81.7 (C4), 72.1 (C4’), 42.8 (C3’), 36.6 (C3).

EIMS m/z 399 (M⁺, 100%).

HREIMS calculated for C₂₆H₂₅NO₃ (M⁺) 399.1834, found 399.1819.

(4S, 5R)-1-Benzyl-4-(benzyloxy)-5-phenethylpyrrolidin-2-one (180)

To a solution of 179 (0.98 g, 2.45 mmol) in CH₂Cl₂ (7 mL) at -78 °C, was added dropwise Et₃SiH (1.42 g, 12.25 mmol) and then BF₃·OEt₂ (1.03 g, 7.35 mmol). The mixture was stirred at -78 °C for 6 h and then allowed to warm slowly to rt and stirred overnight. Saturated aqueous NaHCO₃ solution (10 mL) was added, and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by column chromatography (increasing polarity from 1:1, EtOAc/petrol to EtOAc ) to give the title compound as an oil (0.781 g, 83%, dr = 91 : 9).
Rf : 0.26 (1 : 1, EtOAc/petrol).

$^1$H NMR $\delta$ 7.32-7.02 (15H, m, ArH), 4.9 (1H, d, $J = 15.5$ Hz, H3’), 4.45 (1H, d, $J = 11.5$ Hz, H4’), 4.36 (1H, d, $J = 11.5$ Hz, H4’), 3.97 (1H, d, $J = 15.5$ Hz, H3’), 3.93 (1H, d, $J = 6.5$ Hz, H4), 3.52 (1H, br. d, $J = 8.5$ Hz, H5), 2.74 (1H, dd, $J = 6.5$, 17.5 Hz, H3), 2.55-2.52 (2H, m, H3, H1’), 2.48-2.45 (1H, m, H1’), 1.94-1.93 (1H, m, H2’), 1.67-1.69 (1H, m, H2’).

$^{13}$C NMR $\delta$ 172.5 (C2), 140.5 (ArC), 137.3 (ArC), 136.0 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.6 (ArCH), 127.4 (ArCH), 126.1 (ArCH), 76.7 (C4), 70.5 (C4’), 62.8 (C5), 44.1 (C3’), 37.2 (C3), 32.2 (C3), 31.0 (C1’).

EIMS m/z 385 (M$,^+$, 100%).

HREIMS calculated for C$_{26}$H$_{27}$NO$_2$ (M$^+$) 385.2041, found 385.2039.

(4$S$, 5$R$)-1-Benzyl-4-hydroxy-5-phenethylpyrrolidin-2-one (184)

To a solution of 181 (0.050 g, 0.130 mmol) in MeOH (3 mL), was added PdCl$_2$ (0.018 g, 0.10 mmol). The mixture was stirred at rt under an atmosphere of H$_2$ for 1 h, then the flask was flushed with N$_2$ before the mixture was filtered through a pad of celite and the solids were washed with MeOH (2 x 10 mL). The filtrate was evaporated in vacuo, the crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give the title product as an oil (0.030 g, 76%).

Rf : 0.19 (1 : 1, EtOAc/petrol).

$\nu$$_{\text{max}}$/cm$^{-1}$ 3359, 1663, 1474, 1451, 1244, 1081.

$^1$H NMR $\delta$ 7.26-7.04 (10H, m, ArH), 4.94 (1H, d, $J = 15.0$ Hz, H3’), 4.21 (1H, d, $J = 6.0$ Hz, H4), 3.99 (1H, d, $J = 15.0$ Hz, H3’), 3.35 (1H, br. d, $J = 7.0$ Hz, H5), 2.80 (1H, dd, $J = 6.0$, 17.5 Hz, H3), 2.64-2.62 (1H, m, H1’), 2.53-2.50 (1H, m, H1’), 2.39 (1H, d, $J = 17.5$ Hz, H3), 1.95-1.52 (1H, m, H2’), 1.63-1.60 (1H, m, H2’).

$^{13}$C NMR $\delta$ 171.9 (C2), 141.0 (ArC), 136.4 (ArC), 128.9 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 127.8 (ArCH), 126.4 (ArCH), 69.3 (C4), 66.4 (C5), 44.6 (C3’), 40.4 (C3), 32.4 (C2’), 31.4 (C1’).

EIMS m/z 295 (M$,^+$, 80%).

HREIMS calculated for C$_{19}$H$_{21}$NO$_2$ (M$^+$) 295.1572, found 295.1556.

EIMS m/z 167 (M$^+$ 100%).
HREIMS calculated for C\textsubscript{17}H\textsubscript{21}NO\textsubscript{2} (M\textsuperscript{+}) 167.0946, found 167.0954.

7.3. Experimental for Chapter 3

**General Method for Ritter Reaction of 124 and Preparation of (3aR, 6aS)-4-Benzyl-2-methyl-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one (129)**

To a suspension of diol 124 (0.10 g, 0.483 mmol) in acetonitrile (3 mL) at 0 °C was added dropwise BF\textsubscript{3}.Et\textsubscript{2}O (0.192 g, 1.35 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated aqueous solution of NaHCO\textsubscript{3} (10 mL) was added and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 10 mL). The combined extracts were dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc) to give the title compound (0.103 g, 93%) as a colorless waxy solid.

R\textsubscript{f}: 0.22 (EtOAc).

[α]\textsubscript{D}\textsuperscript{+} 21.0 (c 0.19, CHCl\textsubscript{3}).

υ\textsubscript{max}/cm\textsuperscript{-1} 1680, 1433, 1308, 1227, 1065, 1024.

\textsuperscript{1}H NMR δ 7.34-7.32 (5H, m, ArH), 5.38 (1H, d, J = 7.5 Hz, H3a), 5.07 (1H, d, J = 14.5 Hz, H1’), 4.90 (1H, td, J = 2.0, 7.5 Hz, H6a), 4.02 (1H, d, J = 14.5 Hz, H1’), 2.85 (1H, dd, J = 7.5, 18.5 Hz, H6), 2.69 (1H, d, J = 18.5 Hz, H6), 2.03 (3H, s, Me).

\textsuperscript{13}C NMR, δ 170.7 (C5), 168.8 (C2), 135.9 (ArC), 128.7 (ArCH), 128.6 (ArCH), 127.7 (ArCH), 83.2 (C3a), 74.4 (C6a), 44.3 (C1’), 37.5 (C6), 14.1 (CH3).

EIMS m/z 230 (M\textsuperscript{+}, 100%).

HREIMS calculated for C\textsubscript{13}H\textsubscript{14}N\textsubscript{2}O\textsubscript{2} (M\textsuperscript{+}) 230.1055, found 230.1057.

(3aR, 6aR)-4-Benzyl-2-isoproyl-3a,4,6,6a-tetrahydropyrrolo[2,3-d]oxazol-5-one (229a)

The title compound was prepared following the general method described above using 124 (0.10 g, 0.483 mmol), isopropynitrile (3 mL), and BF\textsubscript{3}.Et\textsubscript{2}O (0.192 g, 1.35 mmol). The desired product (0.112 g, 90%) was obtained as a white solid after purification by column chromatography (Et\textsubscript{2}O).

R\textsubscript{f}: 0.49 (Et\textsubscript{2}O).
Mp 43-45 °C.
$[\alpha]_D^{21}+45.4^\circ$ (c 0.11, CHCl$_3$).

$\nu_{\text{max}}$/cm$^{-1}$ 1683, 1639, 1430, 1234, 1120, 1027.

$^1$H NMR $\delta$ 7.22-7.09 (5H, m, ArH), 5.42 (1H, d, $J = 7.5$ Hz, H3a), 4.99 (1H, d, $J = 14.5$ Hz, H1`), 4.89 (1H, td, $J = 1.5$, 7.5 Hz, H6a), 4.12 (1H, d, $J = 14.5$ Hz, H1`), 2.85 (1H, dd, $J = 7.5$, 18.5 Hz, H6), 2.67 (1H, d, $J = 18.5$ Hz, H6), 2.55-2.63 (1H, septet, $J = 7.0$ Hz, H2`), 1.19 (6H, d, $J = 7.0$ Hz, 2 x CH$_3$).

$^{13}$C NMR $\delta$ 175.7 (C5), 170.8 (C2), 136.1 (ArC), 128.5 (ArCH), 128.5 (ArCH), 127.6 (ArCH), 83.3 (C3a), 74.5 (C6a), 44.4 (C1`), 37.4 (C6), 28.2 (C2`), 19.4 (CH$_3$), 19.3(CH$_3$).

EIMS m/z 258 (M$^+$, 75%).

HREIMS calculated for C$_{15}$H$_{18}$N$_2$O$_2$ (M$^+$) 258.1368, found 258.1373.

(3a$R$, 6a$S$)-4-Benzyl-2-phenyl-6,6a-dihydro-3a$H$-pyrrolo[2,3-d]oxazol-5(4$H$)-one (229b)

![229b]

The title compound was prepared following the general method described above using 124 (0.10 g, 0.483 mmol), benzonitrile (3 mL), and BF$_3$.Et$_2$O (0.192 g, 1.35 mmol). The desired product (0.121 g, 86%) was obtained as a white solid after purification by column chromatography (Et$_2$O).

R$_f$ : 0.43 (Et$_2$O).

Mp 96-98 °C.
$[\alpha]_D^{21}+2.46^\circ$ (c 15.0, CHCl$_3$).

$\nu_{\text{max}}$/cm$^{-1}$ 1676, 1638, 1428, 1403, 1356, 1234, 1154, 1089.

$^1$H NMR $\delta$ 7.93 (2H, d, $J = 8.5$ Hz, ArH), 7.51-7.27 (8H, m, ArH), 5.60 (1H, d, $J = 7.5$ Hz, H3a), 5.07 (1H, td, $J = 2.0$, 7.5 Hz, H6a), 5.03 (1H, d, $J = 14.5$ Hz, H1`), 4.16 (1H, d, $J = 14.5$, H1`), 2.91 (1H, dd, $J = 7.5$, 18.5 Hz, H6), 2.79 (1H, d, $J = 18.5$ Hz, H6).

$^{13}$C NMR $\delta$ 170.6 (C5), 166.9 (C2), 136.1 (ArC), 132.2 (ArC), 127.8 (ArCH), 128.7 (ArCH), 128.6 (ArCH), 128.4 (ArCH), 127.6 (ArCH), 126.7 (ArCH), 83.6 (C3a), 75.0 (C6a), 44.5 (C1`), 37.5 (C6).

EIMS m/z 292 (M$^+$, 70%).

HREIMS calculated for C$_{18}$H$_{16}$N$_2$O$_2$ (M$^+$) 292.1211, found 292.1204.
(3aR, 6aS)-4-Benzyl-2-(3,4-dimethoxyphenyl)-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one (229c)

The title compound was prepared following the general method described above using 124 (0.10 g, 0.483 mmol), 3,4-dimethoxybenzonitrile (0.164 g, 1.00 mmol), BF$_3$·Et$_2$O (0.192 g, 1.35 mmol), and nitromethane (3 mL) as solvent. The desired product (0.154 g, 91%) was obtained as a white solid after purification by column chromatography (Et$_2$O).

R$_f$: 0.28 (Et$_2$O).

Mp 147-149 °C.

[α]$^D_{23}$ $+76.7^o$ (c 0.36, MeOH).

$\nu_{\text{max}}$/cm$^{-1}$ 1687, 1634, 1516, 1375, 1216, 1135, 1005.

$^1$H NMR δ 7.52-7.27 (7H, m, ArH), 6.86 (1H, d, J = 8.5 Hz, ArH), 5.60 (1H, d, J = 7.5 Hz, H3a), 5.07 (1H, td, J = 2.0, 7.5 Hz, H6a), 5.01 (1H, d, J = 15.0 Hz, H1''), 4.21 (1H, d, J = 15.0 Hz, H1''), 3.92 (3H, s, OCH$_3$), 3.91 (3H, s, OCH$_3$), 2.90 (1H, dd, J = 7.5, 17.5 Hz, H6), 2.80 (1H, d, J = 17.5 Hz, H6).

$^{13}$C NMR δ 170.7 (C5), 166.7 (C2), 152.4 (ArC), 148.6 (ArC), 136.2 (ArC), 128.6 (ArC), 128.6 (ArCH), 128.5 (ArCH), 127.6 (ArCH), 125.4 (ArCH), 122.3 (ArCH), 111.0 (ArCH), 83.7 (C3a), 75.0 (C6a), 55.9 (OCH$_3$), 55.7 (OCH$_3$) 44.5 (C1''), 37.5 (C6).

EIMS m/z 352 (M$^+$, 65%).

HREIMS calculated for C$_{20}$H$_{20}$N$_2$O$_4$ (M$^+$) 352.1423, found 352.1417.

**General Method for Ritter Reaction of 126 and Preparation of (3aR, 6aS)-4-Benzyl-2-methyl-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one (129)**

To a suspension of diol 126 (0.10 g, 0.483 mmol) in acetonitrile (3 mL) at 0 °C was added dropwise BF$_3$·Et$_2$O (0.192 g, 1.35 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated aqueous solution of NaHCO$_3$ (10 mL) was added and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined extracts were dried (MgSO$_4$), filtered and concentrated in vacuo. The crude product was purified
by column chromatography (EtOAc) to give compounds 129 (0.088 g, 80%) as a colorless waxy solid and 230 (0.052 g, 72%) as a colorless solid.

The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound 129 prepared from diol 124.

**N-Benzylacetamide (230)**

![Chemical Structure of N-Benzylacetamide](image)

Rf: 0.53 (Et₂O).

Mp 59-61 °C (Lit.¹⁵³ Mp 61-62°C)

¹H NMR δ 7.26-7.35 (5H, m, ArH), 5.90 (1H, br. s, NH), 4.41 (2H, d, J = 5.7 Hz, CH₂Ph), 2.01 (3H, s, Me).

¹³C NMR δ 169.6, 137.9, 128.3, 127.5, 43.5, 23.0.

¹H and ¹³C NMR data matched with the published data.

**N-Benzylisobutyramide (234a)**

![Chemical Structure of N-Benzylisobutyramide](image)

Rf: 0.68 (Et₂O).

Mp 73-75 ºC (Lit. ⁸⁵ Mp 75-76°C)

¹H NMR δ 7.32-7.25 (5H, m, ArH), 5.86 (1H, br s, NH), 4.22 (2H, d, J = 5.5 Hz, CH₂Ph), 2.41-2.34 (1H, septet, J = 7.0 Hz,
CH(CH₃)₂, 1.17 (6H, d, J = 7.0 Hz, 2xMe).

¹³C NMR δ 176.7, 138.5, 128.6, 127.3, 43.3, 35.6, 19.5.

¹H and ¹³C NMR data matched with the published data.

EIMS m/z 177 (M⁺, 100%).

HREIMS calculated for C₁₁H₁₅NO (M⁺) 177.1153, found 177.1157.

(3aR, 6aS)-4-Benzyl-2-phenyl-6,6a-dihydro-3aH-pyrrolo[2,3-d]oxazol-5(4H)-one (229b)

The title compound was prepared following the general method described above using 126 (0.10 g, 0.33 mmol), benzonitrile (3 mL), and BF₃.Et₂O (0.190 g, 1.34 mmol). The crude product was purified by column chromatography (Et₂O) to give the title compound (0.079 g, 80%) and N-benzylbenzamide 234b (0.045 g, 63 %) both as a white solid. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound 229b prepared from diol 124.

N-Benzylbenzamide (234b)

Yield : 0.045 g (63%).

Rf : 0.72 (Et₂O).

Mp 99-101°C, (Lit. 86 Mp 103-105°C)

¹H NMR δ 7.78 (2H, d, J = 7.5 Hz, ArH), 7.49-7.24 (8H, m, ArH), 6.62 (1H, br s, NH), 4.61 (2H, d, J = 5.5 Hz, CH₂Ph).

¹³C NMR δ 167.3, 138.1, 134.3, 131.4, 128.6, 128.4, 127.5, 126.9, 44.02.

¹H and ¹³C NMR data matched with the published data.

EIMS m/z 211 (M⁺, 100%).

HREIMS calculated for C₁₄H₁₃NO (M⁺) 211.0997, found 211.1000.

N-((2R, 3S)-1-Benzyl-3-hydroxy-5-oxopyrrolidin-2-yl)acetamide (185)

To a solution of oxazoline 129 (0.020 g, 0.086 mmol) in MeOH (1 mL) at rt was added dropwise 6N HCl (1 mL). The reaction mixture was stirred at rt for 25 min. and concentrated in vacuo, then diluted with water (5 mL), basifidified with solid NaHCO₃ to
pH = 9. The aqueous layer was extracted with EtOAc (3 x 10 mL), dried (Na$_2$SO$_4$) filtered and concentrated in vacuo. The crude product was purified by column chromatography (5% MeOH in EtOAc) to give the title compound (0.009 g, 42%) as a white solid.

R$_f$ : 0.24 (5% MeOH in EtOAc).

M$\text{p}$ 190-193 °C.

$[\alpha]_{D}^{23}$ -160 (c 0.075 MeOH).

$\nu_{\text{max}}$/cm$^{-1}$ 3318, 1577, 1653, 1541, 1446, 1434, 1378, 1275, 1157.

$^1$H NMR δ (CD$_3$OD) 7.31-7.24 (5H, m, ArH), 5.55 (1H, d, $J = 6.5$ Hz, H5), 4.57 (1H, d, $J = 15.0$ Hz, H1’), 4.39 (1H, br q, $J = 6.5$ Hz, H4), 4.23 (1H, d, $J = 15.0$ Hz, H1’), 2.68 (1H, dd, $J = 6.5$, 17.5 Hz, H3), 2.46 (1H, dd, $J = 2.0$, 17.5 Hz, H3), 1.88 (3H, s, Me).

$^{13}$C NMR δ (CD$_3$OD) 174.9 (CO), 173.9 (CO), 138.2 (ArC), 129.5 (ArCH), 129.1 (ArCH), 128.5 (ArCH), 67.6 (C5), 65.8 (C4), 45.0 (C1’), 39.6 (C3), 22.6 (Me).

EIMS $m/z$ 248 (M$^+$, 45%).

HREIMS calculated for C$_{13}$H$_{16}$N$_2$O$_3$ (M$^+$) 248.1160, found 248.1158.

$\text{N-}((2R, 3S)-1$-Benzyl-3-hydroxy-5-oxopyrrolidin-2-yl)$\text{isobutyramide (236)}$

The title compound was prepared in a similar fashion to 185, from oxazoline 229a (0.020g, 0.077 mmol). The desired product (0.015 g, 70%) was obtained as a white solid after purification by column chromatography (5% MeOH in EtOAc).

R$_f$ : 0.53 (5% MeOH in EtOAc).

M$\text{p}$ 161-163 °C.

$[\alpha]_{D}^{23}$ -65.3° (c 0.49, MeOH).

$\nu_{\text{max}}$/cm$^{-1}$ 3291, 1663, 1649, 1536, 1425, 1182, 1070.

$^1$H NMR δ 7.28-7.22 (5H, m, ArH), 6.40 (1H, d, $J = 9.0$ Hz, NH), 5.58 (1H, dd, $J = 5.5$, 9.0 Hz, H5), 4.47 (1H, d, $J = 15.0$ Hz, C1’), 4.34-4.39 (1H, br t, $J = 5.5$ Hz, H4), 4.33 (1H, d, $J = 15.0$ Hz, H1’), 3.87 (1H, d, $J = 4.5$ Hz, OH), 2.69 (1H, dd, $J = 7.0$, 17.5 Hz, H3), 2.48 (1H, dd, $J = 4.0$, 17.5 Hz, H3), 2.20-2.28 (1H, septet, $J = 7.0$ Hz, H2’), 1.03 (3H, d, $J = 7.0$ Hz, Me), 1.00 (3H, d, $J = 7.0$ Hz, Me).
$^{13}$C NMR δ 177.9 (CO), 172.3 (CO), 137.0 (ArC), 128.5 (ArCH), 127.7 (ArCH), 127.4 (ArCH), 66.2 (C5), 65.1 (C4), 44.2 (C1’), 39.1 (C3), 35.5 (C2’), 19.2 (Me), 19.1 (Me).

ESIMS m/z 315 (M+K$,^+$, 100%).

HRESIMS calculated for C$_{15}$H$_{20}$N$_2$O$_3$ (M+K$^+$) 315.1111, found 315.1124.

7.4. Experimental for Chapter 4

**Potassium Styryltrifluoroborate (262)$^{107,108}$**

A solution of phenylacetylene (5.0 g, 49.0 mmol) in dry THF (150 mL) was cooled to -78 °C. nBuLi (2.5 M in hexane, 19.6 mL, 49.0 mmol) was added dropwise, and the solution was stirred for 1 h at this temperature. Trimethylborate (7.57 g, 73.5 mmol) was then added dropwise at -78 °C. The solution was stirred at this temperature for 1 h and then it was allowed to warm to -20 °C for 1 h. A saturated aqueous solution of KHF$_2$ (26.5 g, 0.29 mol) was then added. The resulting mixture was allowed to stir at -20 °C for 1 h and then it was allowed to warmed to rt for 1 h. The solvent was removed, and the resulting white solid was dried under high vacuum for 2 h. The solid was then washed with hot acetone. The resulting organic solution was filtered and the solvent was removed to give the title compound (6.11 g, 60%) as a white solid.

R$_f$ : 0.15 (1 : 1, EtOAc/petrol)

$^1$H NMR δ 7.32-7.22 (4H, m, ArH), 7.20-7.17 (1H, m, ArH).

$^1$H and $^{13}$C NMR data matched with the published data.

(±)-(2S,3S)-Benzyl 3-hydroxy-2-(phenylethynyl)pyrrolidine-1-carboxylate (cis-263) and (±)-(2R,3S)-Benzyl 3-hydroxy-2-(phenylethynyl)pyrrolidine-1-carboxylate (trans-263)

A solution of benzyl 2,3-dihydroxypyrrolidine-1-carboxylate 116$^3$ (0.15 g, 0.63 mmol) and potassium phenylacetylenetrifluoroborate (0.26 g, 1.27 mmol) in MeCN (10 mL) maintained at 0 °C under a nitrogen atmosphere was treated dropwise with BF$_3$·OEt$_2$ (0.36 g,
2.53 mmol). The resulting reaction mixture was stirred for 2 h, then treated with NaHCO₃ (15 mL of a saturated aqueous solution). The separated aqueous layer was extracted with Et₂O (3 x 15 mL), and the combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by column chromatography (1 : 1, EtOAc/petrol) to give *trans-263* (48 mg, 24%) and *cis-263* (133 mg, 65%) both as a pale yellow oils.

Data for *trans-263*

R<sub>f</sub> : 0.55 (1 : 1, EtOAc/petrol)

υ<sub>max</sub>/ cm⁻¹ 3477, 2287, 2900, 1680, 1406, 1393, 1228, 1074.

<sup>1</sup>H NMR δ (major rotamer) 7.40–7.26 (10H, m, ArH), 5.32 (1H, d, J = 12.5 Hz, H1′), 5.90 (1H, d, J = 12.5 Hz, H1′), 4.66 (1H, s, H3), 4.50 (1H, br s, H2), 3.67 (2H, br s, H5), 2.32 (1H, br s, H4), 1.98 (1H, br s, H4).

<sup>13</sup>C NMR δ (major rotamer) 154.9 (CO), 136.7 (ArC), 131.6 (ArC), 128.3 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.6 (ArCH), 127.4 (ArCH), 86.3 (C≡C), 84.2 (C≡C), 77.20 (C3), 66.9 (C1′), 57.4 (C2), 44.1 (C5), 31.7 (C4).

ESIMS <sup>m/z</sup> 322 (M + H<sup>+</sup>, 100%)

HRESIMS calculated for C<sub>20</sub>H<sub>20</sub>NO<sub>3</sub> (M + H<sup>+</sup>) 322.1443, found 322.1501.

Data for *cis-263*

R<sub>f</sub> : 0.50 (1 : 1, EtOAc/petrol).

υ<sub>max</sub>/ cm⁻¹ 3421, 2245, 1685, 1415, 1356, 1209, 1110, 1050.

<sup>1</sup>H NMR δ (major rotamer) 7.38–7.29 (10H, m, ArH), 5.14 (2H, s, H1′), 4.85 (1H, br s, H3), 4.41–4.32 (1H, m, H2), 3.68–3.48 (1H, m, H5), 3.56–3.48 (1H, m, H5), 2.38 (1H, d, J = 10 Hz, OH), 2.18–2.00 (2H, m, H4).

<sup>13</sup>C NMR δ (major rotamer) 154.6 (CO), 136.6 (ArC), 131.9 (ArC), 128.7 (ArCH), 128.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 122.0 (ArCH), 87.2 (C≡C), 84.0 (C≡C), 71.8 (C2), 67.1 (C1′), 54.3 (C3), 43.8 (C5), 31.6 (C4).

ESIMS <sup>m/z</sup> 322 (M + H<sup>+</sup>, 100%).

HRESIMS calculated for C<sub>20</sub>H<sub>19</sub>NO<sub>3</sub> (M + H<sup>+</sup>) 322.1443, found 322.1511.
(+)-(2R, 3S)-Benzyl 3-acetoxy-2-(phenylethynyl)pyrroldidine-1-carboxylate (265)

Compound 265 was prepared in a similar fashion to phenyl alkyne 263, using benzyl 2,3-diacetoxypryrrolidine-1-carboxylate 264\textsuperscript{7} (57 mg, 0.19 mmol), potassium phenylacetylenetrifluoroborate (115 mg, 0.56 mmol), BF\textsubscript{3}·OEt\textsubscript{2} (105 mg, 0.74 mmol) and CH\textsubscript{2}Cl\textsubscript{2} (10 mL), with stirring at 0 °C for 1 h then at rt for 16 h. Column chromatography of the crude product (1 : 3, EtOAc/petrol) afforded the title compound (51 mg, 77%) as a colorless oil. R\textsubscript{f} : 0.5 (1 : 3, EtOAc/petrol).

\[ \nu_{\text{max}}/ \text{cm}^{-1} 2929, 1740, 1705, 1411, 1356, 1236, 1200, 1113, 1050. \]

1\textsuperscript{H} NMR \( \delta \) (major rotamer) 7.41–7.25 (10H, m, ArH), 5.33 (2H, s, H1'), 5.20 (1H, s, H3), 4.74 (1H, s, H2), 3.75–3.67 (1H, m, H4), 3.63–3.55 (1H, m, H4), 2.48–2.40 (1H, m, H5), 2.06 (4H, br s, overlapping signals from Me and H5).

13\textsuperscript{C} NMR \( \delta \) (major rotamer) 170.2 (CO), 154.4 (CO), 154.4 (ArC), 136.6 (ArC), 131.8 (ArC), 128.5 (ArCH), 128.3 (ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.5 (ArCH), 122.2 (ArCH), 85.1 (C2), 66.9 (C1'), 54.9 (C3), 44.2 (C5), 30.8 (C4), 21.0 (CH3).

ESIMS \( m/z \) 364 (M + H\textsuperscript{+}, 100%).

HRESIMS calculated for C\textsubscript{22}H\textsubscript{21}NO\textsubscript{4} (M + H\textsuperscript{+}) 364.1555, found, 364.1549.

(+)-(2R,3S)-Benzyl 3-hydroxy-2-(phenylethynyl)pyrrolidine-1-carboxylate (trans-263)

To a solution of 265 (0.100 g, 0.275 mmol) in MeOH (5 mL) at rt was added K\textsubscript{2}CO\textsubscript{3} (0.018 g, 0.137 mmol) and the reaction mixture was stirred for 1 h. Water (10 mL) and EtOAc (10 mL) were added and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. The crude product was purified by column chromatography to give the title compound (0.064 g, 72%) as a pale yellow oil.

The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound \textit{trans-263} prepared from 116 and 262.
**Method A.** A solution of *cis*-263 (25 mg, 0.08 mmol) in MeOH (2 mL) under a nitrogen atmosphere at rt was treated with AgNO₃ (4 mg, 0.02 mmol). The resulting mixture was stirred for 2 h then water (5 mL) was added, and the aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Column chromatography of the resulting residue (1 : 1, EtOAc/petrol) afforded the title compound 270 (20 mg, 83%) as a colorless oil.

Rᶠ : 0.6 (1 : 1, EtOAc/petrol).

υₘₐₓ/cm⁻¹ 3246, 1695, 1428, 1350, 1234, 1075.

¹H NMR δ (major rotamer) 7.63 (1H, d,  J = 8.5 Hz, ArH), 7.33 – 7.21 (10H, m, ArH), 6.54 (1H, d,  J = 3.5 Hz, H4), 6.13 (1H, d,  J = 3.5 Hz, H3), 5.11 (2H, s, H3’), 4.92 (1H, br. s, NH), 3.55 (2H, dd,  J = 13.0 and 6.5 Hz, H2’), 2.91 (2H, t,  J = 6.5 Hz, H1’).

¹³C NMR δ (major rotamer) 156.3 (CO), 153.0 (ArC), 152.5 (ArC), 132.5 (ArC), 130.8 (ArC), 128.8 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.1 (ArCH), 127.0 (ArCH), 123.4 (ArCH), 108.7 (C3), 105.7 (C4), 66.7 (C3’), 39.7 (C2’), 28.8 (C1’).

ESIMS m/z 322 (M + H⁺, 33%), 344 (M + Na⁺, 100%).

HRESIMS calculated for C₂₀H₁₉NO₃ (M + H⁺) 322.1443, found 322.1486.

**Method B.** A magnetically stirred solution of *cis*-263 (10 mg, 0.03 mmol) in MeOH (2 mL) maintained under a nitrogen atmosphere at rt was treated with Au(PPh₃)Cl₂ (5 mg, 9.3 µmol). The resulting mixture was stirred for 8 h then water (5 mL) was added, and the separated aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. Column chromatography of the resulting residue (1:1, EtOAc/petrol) and concentration of the relevant extracts (Rᶠ 0.6 in 1:1 EtOAc/petrol) afforded the title compound 270 (9 mg, 87%) as a colorless oil.

The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound 270 prepared by Method A.
**Method C.** A solution of *cis*-263 (20 mg, 0.06 mmol) in MeOH (3 mL) maintained under a nitrogen atmosphere at rt was treated with PdCl₂(PPh₃)₂ (2 mg, 0.02 mmol) and CuI (1 mg, 3.1 μmol). The resulting mixture was stirred for 8 h then water (5 mL) was added, and the separated aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. Column chromatography of the resulting residue (1:1, EtOAc/petrol) and concentration of the relevant extracts (*R*ₓ 0.6 in 1:1 EtOAc/petrol) afforded the title compound 270 (14 mg, 69%) as a colorless oil.

The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound 270 prepared by Method A.


To a suspension of CuI (0.077 g, 0.411 mmol), in DMF (4 mL) was added *cis*-263 (0.022 g, 0.068 mmol) and the resulting mixture was heated to 80 °C for 16 h under a nitrogen atmosphere. After the reaction mixture was cooled to rt, water (10 mL) was added and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to give crude product. Column chromatography (CH₂Cl₂) of the crude residue furnished the title product (0.020 g, 65%) as a light pink oil.

![Structure 280](image)

Rₓ : 0.79 (CH₂Cl₂).

υₘᵦₓ/cm⁻¹ 1701, 1414, 1362, 1212, 1096, 1072.

¹H NMR δ (major rotamer) 7.85 (2H, br. s, ArH), 7.46-7.25 (8H, m, ArH), 5.46 (1H, br. s, H₆a), 5.22 (1H, s, H₃a), 5.18 (2H, s, H₁'), 3.99 (1H, br. s, H₅), 3.21 (1H, m, H₆).

¹³C NMR δ (major rotamer) 155.3 (CO), 129.8 (ArC), 129.7 (ArC), 129.3 (ArCH), 128.9 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 128.0 (ArCH), 83.3 (C₃a), 71.7 (C₆a), 67.2 (C₁'), 56.5 (C₆), 42.8 (C₆), 33.1 (C₅).

EIMS *m/z* 447 (M⁺, 40%).
HREIMS calculated for C\textsubscript{20}H\textsubscript{18}NO\textsubscript{3}I (M\textsuperscript{+}) 447.0331, found 447.0318

**Benzyl 2-(4-bromo-5-phenylfuran-2-yl)ethylcarbamate (284)**

Prepared using the general procedure above, from cis-263 (0.020 g, 0.062 mmol), CuBr (0.053 g, 0.373 mmol) and DMF (2 mL). Column chromatography (1 : 5, EtOAc/petrol) of the crude product yielded compound 284 (0.010 g, 41%) as a colorless oil, and compound 270 (0.006 g, 25%) as a colorless oil.

R\textsubscript{f}: 0.60 (1 : 5, EtOAc/petrol).

υ\textsubscript{max}/cm\textsuperscript{-1} 1708, 1395, 1240, 1083, 1072.

\textsuperscript{1}H NMR δ 7.91 (2H, d, \(J = 7.5\) Hz, ArH), 7.42-7.26 (8H, m, ArH), 6.23 (1H, s, H3), 5.2 (2H, s, H3’), 4.91 (1H, br. s, NH), 3.53 (2H, br. d, \(J = 6.0\) Hz, H2’), 2.90 (2H, br. s, H1’).

\textsuperscript{13}C NMR δ 156.3 (CO), 152.6 (ArC), 148.0 (ArC), 136.4 (ArC), 134.3 (ArC), 129.7 (ArC), 128.5 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 125.2 (ArCH), 113.1 (C3), 96.4 (C4), 66.8 (C3’), 39.4 (C2’), 28.7 (C1’).

EIMS m/z 401 (M\textsuperscript{+}, \textsuperscript{79}Br, 50%), 403 (M\textsuperscript{+}, \textsuperscript{81}Br, 50%).

HREIMS calculated for C\textsubscript{20}H\textsubscript{18}NO\textsubscript{3}\textsuperscript{79}Br (M\textsuperscript{+}) 401.0449, found 401.0438.

**Benzyl 2-(5-phenylfuran-2-yl) ethylcarbamate (270)**

Prepared using the general procedure above, from cis-263 (0.020 g, 0.062 mmol), CuCl (0.053 g, 0.373 mmol) and DMF (2 mL). Column chromatography (1 : 5, EtOAc/petrol) of the crude product yielded compound 270 (0.012 g, 61%) as a colorless oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound 270 prepared by Method A.
Benzyl 3-cyano-2-phenyl-6,6a-dihydro-3aH-furo[3,2-b]pyrrole-4(5H)-
carboxylate (285)

Prepared using the general procedure above, from cis-263 (0.025 g, 0.078 mmol), CuCN (0.042 g, 0.468 mmol) and DMF (2 mL).

Column chromatography (1 : 1, EtOAc/petrol) of the crude product yielded compound 285 (0.0079 g, 30%) and compound 270 (0.012 g, 25%) both as colorless oils.

Rf : 0.60 (1 : 1, EtOAc/petrol).

$\nu_{\text{max}}$/cm$^{-1}$ 2202, 1708, 1614, 1414, 1364, 1224, 1103.

$^1$H NMR $\delta$ (major rotamer) 7.96 (2H, d, $J = 7.5$ Hz, ArH), 7.51-7.33 (8H, m, ArH), 5.42-5.35 (3H, m, H3a, H6a, H1’), 5.08 (1H, d, $J = 12$ Hz, H1’), 3.97 (1H, t, $J = 12$ Hz, H5), 3.28 (1H, ddd, $J = 5.5$, 12, 17.5 Hz, H5), 2.32 (1H, dd, $J = 5.5$, 12 Hz, H6), 2.16 (1H, m, H6).

$^{13}$C NMR $\delta$ (major rotamer) 169.5 (CO), 153.7 (C5), 136.3 (ArC), 132.1 (ArC), 129.9 (ArC), 128.8 (ArCH), 128.7 (ArCH), 128.5 (ArCH), 128.2 (ArCH), 127.5 (ArCH), 116.8 (ArCH), 87.1 (C6a), 82.6 (CN), 67.6 (C1’), 65.1 (C3a), 43.0 (C2), 31.7 (C3).

ESIMS $m/z$ 347 (M + H+, 100%).

HRESIMS calculated for C$_{21}$H$_{19}$N$_2$O$_3$ (M + H$^+$) 347.1396, found 347.1475.

(2R, 3S)-Benzyl 2-((E)-1,2-dibromo-2-phenylvinyl)-3-hydroxypyrrolidin-1-
carboxylate (290)

Prepared in a similar fashion to 270 above, from cis-263 (0.020 g, 0.078 mmol), CuBr$_2$ (0.104 g, 0.468 mmol) and DMF (2 mL). Column chromatography (1 : 1, EtOAc/petrol) of the crude product yielded compound 290 as a colorless oil (0.0079 g, 30%) and compound 270 as a colorless oil (0.012 g, 25%).

Rf : 0.60 (1 : 1, EtOAc/petrol)

$\nu_{\text{max}}$/cm$^{-1}$ 3326, 1710, 1548, 1409, 1327.

$^1$H NMR $\delta$ (major rotamer) 7.76-7.75 (2H, m, ArH), 7.45-7.27 (8H, m, ArH), 5.27-5.13 (3H, m, H3’, H2’), 4.99 (1H, app. br. t, $J = 7.0$ Hz, H3), 3.88-3.80 (1H, m, H5), 3.67-3.60 (1H, m, H5), 2.13-2.0 (2H, m, H4).
\(^{13}\)C NMR \(\delta\) (major rotamer) 167.0 (CO), 147.2 (ArC), 134.6 (ArC), 129.5 (ArCH), 128.7 (ArCH), 128.0 (ArCH), 127.6 (ArCH), 127.0 (ArCH), 126.9 (ArCH), 115.0 (C2'), 111.6 (C1'), 80.3 (C3), 74.4 (C2), 67.5 (C3'), 46.9 (C4), 29.1 (C5).

ESIMS \(m/z\) 479 (M + H\(^+\), \(^{79}\)Br\(_2\), 30%), 481 (M+H\(^+\), \(^{79}\)Br\(^{81}\)Br, 50%), 483 (M+H\(^+\), \(^{81}\)Br\(_2\), 30%).

HRESIMS calculated for C\(_{20}\)H\(_{20}\)NO\(_3\)\(^{79}\)Br\(_2\) (M + H\(^+\)) 479.9810, found 479.9656.

**General Method for the Cyclization-Halogenation and Cyclization-Cyanation Reaction of cis-263 under Oxygen Atmosphere and Preparation of Benzyl 2-(4-iodo-5-phenylfuran-2-yl)ethylcarbamate (286)**

To a solution of cis-263 (0.040g, 0.125 mmol) in DMF (1.5 mL) under an oxygen atmosphere (balloon) was added CuI (0.026 g, 0.173 mmol) and the reaction vessel was placed in a pre-heated oil bath at 100 °C. The reaction mixture was stirred at this temperature for 16 h. H\(_2\)O (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 5 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo. The crude product was purified by column chromatography (1 : 5, EtOAc/petrol) to give the title compound (0.041 g, 74%) as a pink oil.

R\(_f\) : 0.52 (1 : 2, EtOAc/petrol)

\(\nu\)\(_{\text{max}}/\text{cm}^{-1}\) 3367, 1683, 1532, 1459, 1274, 1108.

\(\text{H NMR} \delta \) 7.92 (1H, d, \(J = 8.0\) MHz, ArH), 7.40-7.31 (8H, m, ArH), 7.25 (1H, d, \(J = 2.0\) MHz, ArH), 6.27 (1H, s, H3), 5.10 (2H, s, H3'), 4.90 (1H, br. s, NH), 3.54 (2H, dd, \(J = 7.0\), 13.0 MHz, H2'), 2.90 (2H, t, \(J = 7.0\) MHz, H1').

\(\text{C NMR} \delta \) 156.4 (CO), 151.6 (ArC), 136.4 (ArC), 130.3 (ArC), 128.7 (ArC), 128.6 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 127.8 (ArC), 127.1 (ArC), 126.2 (ArCH), 117.6 (C3), 67.0 (CH\(_2\)Ph), 61.4 (C4), 39.6 (C2'), 28.8 (C1').

EIMS \(m/z\) 447 (M\(^+\), 50%);

HREIMS calculated for C\(_{20}\)H\(_{18}\)NO\(_3\)I (M\(^+\)) 447.0320, found 447.0331.
Benzyl 2-(4-iodo-5-phenylfuran-2-yl)ethylcarbamate (286)

Prepared using the general procedure above, from 280 (0.030 g, 0.067 mmol), CuI (0.013 g, 0.074 mmol) and DMF (2 mL). Column chromatography (1 : 2, EtOAc/petrol) of the crude product yielded the title compound (0.026 g, 90%) as a colorless oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound 286 prepared from cis-263.

Benzyl 2-(3-iodo-5-phenylfuran-2-yl)ethylcarbamate (287)

To a solution of 270 (0.025 g, 0.078 mmol) in CH₃CN (2 mL) at -10 °C was added NIS (0.019 g, 0.086 mmol). The resulting mixture was stirred at rt for 16 h. Water (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined extracts were dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by column chromatography (1 : 4, EtOAc/petrol) to give a 1 : 1 mixture of the compounds 286 and 287 (0.029 g, 38%) as pale yellow oil.

Data for 287: ¹H NMR δ 7.94-7.24 (10H, m, ArH), 6.23 (1H, s, H4), 5.19 (2H, s, H3‘), 4.40 (1H, br. s, NH), 3.62 (2H, t, J = 7.0 Hz, H2‘), 3.00 (2H, t, J = 7.0 Hz, H1`).

Benzyl 2-(3-bromo-5-phenylfuran-2-yl)ethylcarbamate (288)

Prepared in a similar fashion to 287 using 270 (0.030, 0.077 mmol), CH₃CN (2 mL) and NBS (0.015 g, 0.085 mmol). Column chromatography (1 : 2, EtOAc/petrol) of the crude product yielded a 1 : 1 mixture of compounds 284 and 288 (0.007 g, 22%) as a colorless oil.

Data for 288: ¹H NMR δ 7.97-7.28 (10H, m, ArH), 6.16 (1H, s, H4), 5.19 (2H, s, H3‘), 3.66 (2H, t, J = 6.0 Hz, H2‘), 2.98 (2H, t, J = 6.0 Hz, H1`).
**Benzyl 2-(4-bromo-5-phenylfuran-2-yl)ethylcarbamate (284)**

Prepared using the general procedure above, from cis-263 (0.040 g, 0.125 mmol), CuBr (0.020 g, 0.137 mmol) and DMF (2 mL). Column chromatography (1 : 2, EtOAc/petrol) of the crude product yielded the title compound (0.035 g, 68%) as a colorless oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound 284 prepared by the general method for cyclization-halogenation and cyclization-cyanation reaction under N₂ atmosphere.

**Benzyl 2-(4-chloro-5-phenylfuran-2-yl)ethylcarbamate (289)**

Prepared using the general procedure above, from cis-263 (0.040 g, 0.125 mmol), CuCl (0.014 g, 0.137 mmol) and DMF (1.5 mL). Column chromatography (1 : 2, EtOAc/petrol) of the crude product yielded compound 289 (0.035 g, 78%) as a colorless oil.

υ<sub>max</sub>/cm<sup>-1</sup> 3359, 1685, 1598, 1526, 1444, 1413, 1265.

R<sub>f</sub>: 0.44 (1 : 2, EtOAc/petrol)

<sup>1 </sup>H NMR δ 7.86 (2H, d, J = 8.0 Hz, ArH), 7.41-7.25 (8H, m, ArH), 6.17 (1H, s, H3), 5.10 (2H, s, H3'), 4.92 (1H, br. s, NH), 3.52 (2H, dd, J = 5.5 Hz, H2'), 2.88 (2H, t, J = 5.5 Hz, H1').

<sup>13 </sup>C NMR δ 156.2 (CO), 151.5 (ArC), 146.4 (ArC), 136.4 (ArC), 129.8 (ArC), 129.4 (ArCH), 128.5 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.5 (ArCH), 124.7 (C4), 111.0 (C3), 66.7 (C3'), 39.3 (C2') 28.7 (Cl').

EIMS m/z 355 (M<sup>+</sup>, 35Cl, 30%).

HREIMS calculated for C<sub>20</sub>H<sub>18</sub>NO<sub>3</sub>Cl (M<sup>+</sup>) 355.0969, found 355.0975.

**Benzyl 3-cyano-2-phenyl-6,6a-dihydro-3aH-furo[3,2-b]pyrrole-4(5H)-carboxylate (285)**

Prepared using the general procedure above, from cis-263 (0.040 g, 0.125 mmol), CuCN (0.013 g, 0.137 mmol) and DMF (2 mL). Column chromatography (1 : 3, EtOAc/petrol) of the crude product yielded compound 285 (0.015 g, 35%) and compound...
270 (0.017g, 40%) both as colorless oils. The spectral data derived from the materials prepared as described above were in good agreement with those obtained from the sample of compound 285 and 270 prepared by the general method for cyclization-halogenation and cyclization-cyanation reaction under N2 atmosphere.

(±)-(3aS, 6aS)-Benzy1 2,3-diphenyl-6,6a-dihydro-3aH-furo[3,2-b]pyrrole-4(5H)-carboxylate (291)

A solution of iodobenzene (51 mg, 0.25 mmol), 2,2′-bipyridine (2 mg, 12.5 μmol), and K₂CO₃ (0.050 g, 0.5 mmol) in CH₃CN (5 mL) maintained under a nitrogen atmosphere at 50 °C was treated with Pd₂(dba)₃ (6 mg, 6.25 μmol). The resulting mixture was stirred for 1 h, before being treated with a solution of compound cis-263 (20 mg, 0.06 mmol) in CH₃CN (2 mL). After being stirred for a further 24 h, the reaction mixture solvent was removed in vacuo and the resulting residue was filtered through a short plug of silica gel using EtOAc. The filtrate was concentrated under reduced pressure and the resulting crude material was purified using column chromatography (1 : 1, EtOAc/petrol) to afford two extracts, A and B. Concentration of fraction A gave biphenyl compound 291 (9 mg, 38%) as a colorless oil. Concentration of fraction B (Rf 0.6 in 1:1 EtOAc/petrol) gave compound 270 (8 mg, 19%) as a colorless oil. The spectral data derived from the material prepared as described above were in good agreement with those obtained from the sample of compound 270 previously prepared.

Data for 291:

Rf : 0.7 (1 : 1, EtOAc/petrol)

υmax/cm⁻¹: 1706, 1593, 1516, 1448, 1260, 1217, 1101, 1026.

¹H NMR δ (major rotamer) 7.31–7.24 (5H, m, ArH), 5.67 (1H, br d, J 5.5 Hz, H6a), 5.24 (1H, br s, H3a), 4.94 (1H, d, J 12.0 Hz, H1'), 4.50 (1H, d, J 12.0 Hz, H1’), 4.10 (1H, br s, H2), 3.33 (1H, br s, H2), 2.24 (1H, br s, H3), 2.10 (1H, br s, H3).

¹³C NMR δ (major rotamer) 154.1 (CO), 136.4 (ArC), 134.4 (ArC), 129.7 (ArC), 129.2 (ArCH), 128.7 (ArCH), 128.5 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 127.4 (ArCH), 127.1 (ArCH), 126.8 (ArCH), 82.4 (C3a), 69.6 (C6a), 66.8 (C1'), 42.9 (C3), 33.4 (C2).

ESIMS m/z 398 (M + H⁺, 100%).
HRESIMS calculated for C_{26}H_{23}NO_{3} (M + H^+) 398.1756, found 398.1767.

7.5. Experimental for Chapter 5

General Method for Preparation of 2-alkynylanilines via the Sonogashira Reaction of 2-Iodoaniline Derivatives: Preparation of 2-(Phenylethynyl)benzeneamine (349)

To a solution of 2-iodoaniline (0.500 g, 2.28 mmol) in Et_{3}N (8 mL) under a nitrogen atmosphere were added PdCl_{2}(PPh_{3})_{2} (0.079 g, 0.11 mmol) and CuI (0.022 g, 0.11 mmol) and the reaction mixture was stirred for 15 min at reflux temperature. Phenylacetylene (0.256 g, 2.51 mmol) was added to the mixture. The reaction mixture was stirred and heated at reflux and was monitored by TLC. After 2 h, H_{2}O (20 mL) was added and the aqueous layer was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were dried (MgSO_{4}), filtered and concentrated in vacuo. The crude product was purified by column chromatography (1 : 10, EtOAc/petrol) to give the title compound (0.391 g, 90%) as a white solid.

R_{f} : 0.38 (1 : 8 EtOAc/petrol).

Mp 85-87 °C (Lit.\textsuperscript{129} Mp 85.5-86 °C).

ν_{max}/\text{cm}^{-1} 3487, 3370, 2202, 1612, 1495, 1438, 1454, 1313, 1260, 1152, 748.

\textsuperscript{1}H NMR δ 7.54-7.51 (2H, m, ArH), 7.38-7.33 (4H, m, ArH), 7.14 (1H, td, J = 1.5, 7.5 Hz, ArH), 6.74-6.69 (2H, m, ArH), 4.28 (2H, br. s, NH_{2}).

ESIMS m/z 194 (M + H^+, 100%).

HRESIMS calculated for C_{14}H_{11}N (M + H^+) 194.0892, found 194.0880.

2-((4-Methoxyphenyl)ethynyl)benzeneamine (350)\textsuperscript{147}

Following the general method, a solution of 2-iodoaniline (0.500 g, 2.28 mmol), PdCl_{2}(PPh_{3})_{2} (0.160 g, 0.22 mmol), CuI (0.043 g, 0.22 mmol) and 4-ethynylanisole (0.36 g, 2.74 mmol) in Et_{3}N (20 mL) was heated at reflux for 2 h. The crude product was purified by column chromatography (1 : 6, EtOAc/petrol) to give the title compound (0.382 g, 83%) as a yellow oil.
Rf : 0.34 (1 : 6 EtOAc/petrol)

$\nu_{\text{max}} \text{ cm}^{-1}$ 3487, 3226, 3385, 2361, 1609, 1506, 1449, 1245, 1174, 1026, 833.

$^1$H NMR $\delta$ 7.45 (2H, d, $J = 9$ Hz, ArH), 7.34 (1H, d, $J = 5.5$ Hz, ArH), 7.10 (1H, t, $J = 5.5$ Hz, ArH), 6.86 (2H, d, $J = 9.0$ Hz, ArH), 6.71- 6.68 (2H, m ,ArH), 4.21 (2H, br. s, NH$_2$), 3.80 (3H, s, CH$_3$O).

$^{13}$C NMR $\delta$ 159.5 (ArC), 147.5 (ArC), 132.8 (ArCH), 131.9 (ArCH), 129.3 (ArCH), 117.9 (ArCH), 115.3 (ArC), 114.2 (ArCH), 113.9 (ArCH), 108.2 (ArC), 94.5 (C≡C), 84.4 (C≡C), 55.2 (CH$_3$O).

ESIMS $m/z$ 224 (M + H$, 100\%$).

HRESIMS calculated. for C$_{15}$H$_{14}$NO (M + H$^+$) 224.1065, found 224,1075.

2-((4-Fluorophenyl)ethynyl)benzeneamine (351)

Following the general method, a solution of 2-iodoaniline (0.500 g, 2.28 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.160 g, 0.22 mmol), CuI (0.043 g, 0.22 mmol) and 1-ethynyl-4-fluorobenzene (0.330 g, 2.74 mmol) in Et$_3$N (20 mL) was heated at reflux for 1.5 h. The crude product was purified by column chromatography (1 : 4, EtOAc/petrol) to give the title compound (0.405 g, 86\%) as an orange solid.

Rf : 0.52 (1 : 4, EtOAc/petrol)

Mp 79-81 °C

$\nu_{\text{max}} \text{ cm}^{-1}$ 2361, 2340, 1613,1504, 1448, 1454, 1306, 1220, 1155, 840.

$^1$H NMR $\delta$ 7.48 (2H, dd, $J = 5.5$, 8.5 Hz, ArH), 7.34 (1H, dd, $J = 1.5$, 8.0 Hz, ArH), 7.12 (1H, dt, $J = 1.5$, 8.0 Hz, ArH), 7.02 (2H, t, $J = 8.0$ Hz, ArH), 6.72-6.69 (2H, m, ArH), 4.23 (2H, br. s, NH$_2$)

$^{13}$C NMR $\delta$ 162.4 (ArC, d, $J = 247$ Hz), 147.7 (ArC), 133.3 (ArCH, d, $J = 8.5$ Hz), 132.0 (ArCH), 129.7 (ArCH), 119.3 (ArC, d, $J = 3.7$ Hz), 117.9 (ArCH), 115.6 (ArCH, d, $J = 22.0$ Hz), 114.3 (ArCH), 107.6 (ArC), 93.5 (C≡C), 85.5 (C≡C).

ESIMS $m/z$ 212 (M + H$, 100\%$).

HRESIMS calculated. for C$_{14}$H$_{11}$NF (M + H$^+$) 212.0864, found 212.0876.
4-Methoxy-2-(phenylethynyl)benzeneamine (356)

Following the general method, a solution of 2-bromo-4-methoxyaniline (0.500 g, 2.05 mmol), PdCl₂(PPh₃)₂ (0.154 g, 0.22 mmol), CuI (0.041 g, 0.22 mmol) and phenylacetylene (0.273 g, 2.67 mmol) in Et₃N (20 mL) was heated at reflux for 6 h. The crude product was purified by column chromatography (1 : 6, EtOAc/petrol) to give the title compound (0.382 g, 83%) as a yellow oil. 

Rₚ : 0.37 (1 : 6, EtOAc/petrol)

ν_max/cm⁻¹ 3298, 2361, 1700, 1613, 1541, 1424, 1275, 1186, 1040, 912.

¹H NMR δ 7.53 (2H, d, J = 6.0 Hz, ArH), 7.35 (3H, d, J = 6.0 Hz, ArH), 6.92 (1H, d, J = 2.5 Hz, ArH), 6.78 (1H, dd, J = 2.5, 8.5 Hz, ArH), 6.68 (1H, d, J = 8.5 Hz, ArH), 4.00 (2H, br. s, NH₂), 3.75 (3H, s, CH₃O).

¹³C NMR δ 151.9 (ArC), 141.9 (ArC), 131.4 (ArCH), 123.1 (ArC), 117.4 (ArCH), 115.9 (ArCH), 115.8 (ArCH), 108.6 (ArC), 94.6 (C≡C), 85.9 (C≡C), 55.8 (CH₃O).

EIMS m/z 223 (M⁺, 100%).

HREIMS calculated. for C₁₅H₁₃NO (M⁺) 223.0998, found 223.0997.

4-Amino-3-(phenylethynyl)benzonitrile (357)

Following the general method, a solution of 4-cyano-2-iodoaniline (0.500 g, 2.05 mmol), PdCl₂(PPh₃)₂ (0.070 g, 0.10 mmol), CuI (0.019 g, 0.10 mmol) and phenylacetylene (0.230 g, 2.25 mmol) in Et₃N (20 mL) was heated at reflux for 2 h. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.439 g, 94%) as a brown solid.

Rₚ : 0.41 (1 : 3, EtOAc/petrol)

Mp 106-108 °C (Lit.,¹³¹ Mp 107-108 °C)

ν_max/cm⁻¹ 3467, 3353, 2215, 11627, 1620, 1503, 1337, 1270, 1029, 821.

¹H NMR δ 7.61 (1H, s, ArH), 7.51 (2H, t, J = 3.5 Hz, ArH), 7.37-7.43 (4H, m, ArH), 6.70 (1H, d, J = 8.5 Hz, ArH), 4.81 (2H, br. s, NH₂).
$^{13}$C NMR $\delta$ 150.9 (ArC), 136.2 (ArCH), 133.1 (ArCH), 131.1 (ArCH), 128.8 (ArCH), 128.4 (ArCH), 122.2 (ArC), 119.3 (ArC), 113.9 (ArCH), 108.1 (ArC), 100.0 (CN), 96.1 (C≡C), 83.3 (C≡C).

EIMS $m/z$ 314 ($M^+$, 30%).

HREIMS calculated for C$_{15}$H$_{10}$N$_2$ ($M^+$) 218.0843, found 218.0843.

2-(Hept-1-ynyl)benzeneamine (358)

Following the general method, a solution of 2-iodoaniline (0.300 g, 1.37 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.048 g, 0.069 mmol), CuI (0.013 g, 0.069 mmol) and heptyne (0.154 g, 1.50 mmol) in Et$_3$N (20 mL) was heated at reflux for 4 h. The crude product was purified by column chromatography (1 : 10, EtOAc/petrol) to give the title compound (0.232 g, 91%) as a yellow oil.

R$_f$ : 0.38 (1 : 7, EtOAc/petrol).

$\nu$$_{\text{max}}$/cm$^{-1}$ 3375, 2955, 2929, 2852, 1690, 1603, 1495, 1455, 1306, 1157, 748.

$^1$H NMR $\delta$ (300 MHz) 7.23 (1H, dd, $J$ = 1.5, 8.0 Hz, ArH), 7.09-7.04 (1H, m, ArH), 6.68-6.62 (2H, m, ArH), 4.15 (2H, br. s, NH$_2$) 2.45 (2H, t, $J$ = 7.0 Hz, CH$_2$), 1.65-1.57 (2H, m, CH$_2$), 1.47-1.30 (4H, m, 2 x CH$_2$), 0.920 (3H, t, $J$ = 7.0 Hz, CH$_3$).

$^{13}$C NMR $\delta$ (75 MHz) 147.5 (ArC), 131.9 (ArCH), 128.7 (ArCH), 127.7 (ArC), 117.8 (ArCH), 114.1 (ArCH), 108.9 (C≡C), 95.7 (C≡C), 31.1 (CH$_2$), 28.6 (CH$_2$), 22.2 (CH$_2$), 19.5 (CH$_2$), 13.9 (CH$_3$).

EIMS $m/z$ 187 ($M^+$, 80%).

HREIMS calculated for C$_{13}$H$_{17}$N ($M^+$) 187.1353, found 187.1361.

General Procedure for the Protection Reactions of Anilines : 2-Ethynylanil ine derivative (1.03 mmol) was dissolved in dry CH$_2$Cl$_2$ (10 mL) and the solution was cooled to 0 °C. Pyridine (2.07 mmol) and tosyl chloride (1.23 mmol) or trifluoroacetic anhydride (1.23 mmol) were then added. The reaction mixture was warmed to rt and then stirred at this temperature until TLC analysis shows consumption of starting material. H$_2$O (10 mL) was added and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. The crude product was purified by column chromatography.
4-Methyl-N-(2-(phenylethynyl)phenyl)benzenesulfonamide (359)

Following the above general procedure, 2-phenylethynylaniline (0.200 g, 1.03 mmol), CH₂Cl₂ (8 mL), pyridine (0.164 g, 2.07 mmol) and tosyl chloride (0.236 g, 1.23 mmol) were stirred for 15 h. The crude product was purified by column chromatography (1 : 8, EtOAc/petrol) to give the title compound (0.340 g, 95%) as a colorless solid.

R_f : 0.52 (1 : 2, EtOAc/petrol)

M_p 110-112 °C (Lit.¹²⁹ M_p 111-112 °C).

ν_max/cm⁻¹ 3267, 2366, 1603, 1538, 1334, 1167, 1091, 917, 814.

¹H NMR δ 7.66 (2H, d, J = 8.0 Hz, ArH), 7.62 (1H, d, J = 8.0 Hz, ArH), 7.46-7.45 (2H, m, ArH), 7.37 (3H, m, ArH), 7.27 (1H, t, J = 8.0 Hz, ArH), 7.23 (1H, br. s, ArH), 7.15 (2H, d, J = 8.0 Hz, ArH), 7.04 (1H, t, J = 8.0 Hz, ArH), 2.31 (3H, s, CH₃).

¹³C NMR δ 143.9 (ArC), 137.4 (ArC), 136.0 (ArC), 131.9 (ArCH), 131.4 (ArCH), 129.5 (ArCH), 128.9 (ArCH), 128.4 (ArCH), 127.1 (ArCH), 124.5 (ArCH), 121.9 (ArC), 120.3 (ArCH), 114.5 (ArC), 96.0 (C≡C), 83.6 (C≡C), 21.4 (CH₃).

ESIMS m/z 348 (M + H⁺, 75%).

HRESIMS calculated. for C₂₁H₁₈NO₂S (M + H⁺) 348.1074, found 348.1058.

2,2,2-Trifluoro-N-(2-(phenylethynyl)phenyl)acetamide (360)

Following the above general procedure, 2-phenylethynylaniline (0.300 g, 1.55 mmol), CH₂Cl₂ (10 mL), pyridine (0.245 g, 3.10 mmol) and trifluoroacetic anhydride (0.390 g, 1.86 mmol) were stirred for 0.5 h. The crude product was purified by column chromatography (1 : 5, EtOAc/petrol) to give the title compound (0.414 g, 93%) as a white solid.

R_f : 0.47 (1 : 3, EtOAc/petrol).

M_p 95-96 °C (Lit.¹²⁹ M_p 96-97 °C)

ν_max/cm⁻¹ 3344, 2366, 1711, 1588, 1541, 1501, 1449, 1280, 1184, 1280, 1157, 767.

¹H NMR δ 8.90 (1H, br. s, NH), 8.38-8.36 (1H, m, ArH), 7.57-7.52 (2H, m, ArH), 7.43-7.40 (3H, m, ArH), 7.25-7.20 (1H, m, ArH).
\[ ^{13}C \text{ NMR} \delta 154.4 (\text{CO, q, } J = 37.6 \text{ Hz}), 136.0 (\text{ArC}), 131.4 (\text{ArCH}), 129.8 (\text{ArCH}), 129.9 (\text{ArCH}), 128.6 (\text{ArCH}), 125.5 (\text{ArCH}), 121.6 (\text{ArC}), 119.5 (\text{ArCH}), 115.8 (\text{CF}_3, q, J = 287.6 \text{ Hz}), 113.4 (\text{ArC}), 98.0 (\text{C}≡\text{C}), 82.8 (\text{C}≡\text{C}). \]

EIMS \( m/z \) 289 (\( M^+ \), 100%).

HREIMS calculated. for \( \text{C}_{16}\text{H}_{10}\text{NOF}_3 (M^+) \) 289.0718, found 289.0732.

**2,2,2-Trifluoro-\( N \)-(2-((4-methoxyphenyl)ethynyl)acetamide (361)**

Following the above general procedure, 2-((4-methoxyphenyl)ethynyl)benzeneamine (0.100 g, 0.45 mmol), \( \text{CH}_2\text{Cl}_2 \) (5 mL), pyridine (0.072 g, 0.90 mmol) and trifluoroacetic anhydride (0.113 g, 0.54 mmol) were stirred for 2 h. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.135 g, 96%) as a white solid.

\( R_f : 0.48 \) (1 : 3, EtOAc/petrol).

\( \text{Mp} \ 99-101^\circ \text{C}. \)

\( \nu_{\text{max}} / \text{cm}^{-1} 3300, 2356, 2330, 1713, 1511, 1291, 1239, 1191, 1166, 1159, 828. \)

\[^1H \text{ NMR} \delta 8.90 \) (1H, br. s, NH), 8.36 (1H, d, \( J = 7.0 \text{ Hz, ArH} \)), 7.54 (1H, dd, \( J = 1.5, 7.0 \text{ Hz, ArH} \)), 7.46 (2H, dt, \( J = 2.0, 8.5 \text{ Hz, ArH} \)), 7.39 (1H, ddd, \( J = 1.5, 7.0, 8.5 \text{ Hz, ArH} \)), 7.20 (1H, ddd, \( J = 1.5, 7.0, 8.5 \text{ Hz, ArH} \)), 6.92 (2H, dt, \( J = 2.0, 8.5 \text{ Hz, ArH} \)), 3.85 (3H, s, CH_3O).

\[^{13}C \text{ NMR} \delta 160.4 (\text{ArC}), 154.3 (\text{CO, q, } J = 37.3 \text{ Hz}), 135.8 (\text{ArC}), 133.0 (\text{ArCH}), 131.4 (\text{ArCH}), 129.4 (\text{ArCH}), 125.4 (\text{ArCH}), 119.5 (\text{ArCH}), 114.3 (\text{ArCH}), 113.8 (\text{ArC}), 113.6 (\text{ArC}), 98.2 (\text{C}≡\text{C}), 81.7 (\text{C}≡\text{C}), 55.3 (\text{CH}_3\text{O}). \)

ESIMS \( m/z \) 319 (\( M + \text{H}^+ \), 100%).

HRESIMS calculated. for \( \text{C}_{17}\text{H}_{12}\text{NO}_2\text{F}_3 (M + \text{H}^+) \) 319.0825, found 319.0820.

**2,2,2-Trifluoro-\( N \)-(2-((4-fluorophenyl)ethynyl)phenyl)acetamide (362)**

Following the above general procedure, 2-((4-fluorophenyl)ethynyl)benzeneamine (0.100 g, 0.48 mmol), \( \text{CH}_2\text{Cl}_2 \) (5 mL), pyridine (0.076 g, 0.96 mmol) and trifluoroacetic anhydride (0.121 g, 0.58 mmol) were stirred for 1 h. The crude product was purified by column
chromatography (1 : 5, EtOAc/petrol) to give the title compound (0.140 g, 96%) as a light yellow solid.
R<sub>f</sub>: 0.61 (1 : 5, EtOAc/petrol).
Mp 79-81 ºC.
ν<sub>max</sub>/cm<sup>-1</sup> 3300, 2361, 1335, 1710, 1509, 1233, 1187, 1173, 1166, 1156, 836.
<sup>1</sup>H NMR δ 8.83 (1H, br. s, NH), 8.35 (1H, d, J = 8.5Hz, ArH), 7.55 (1H, d, J = 8.0 Hz, ArH), 7.52-7.49 (2H, dd, J = 2.5, 8.0 Hz, ArH), 7.41 (1H, t, J = 7.5 Hz, ArH), 7.21 (1H, t, J = 7.5 Hz, 7.09 (2H, t, J = 8.5 Hz, ArH).
<sup>13</sup>C NMR δ 163.0 (ArC, d, J = 250.6 Hz), 154.6 (CO, q, J = 37.8 Hz), 136.0 (ArC), 133.4 (ArCH, d J = 8.7 Hz), 131.6 (ArCH), 129.9 (ArCH), 125.5 (ArCH), 119.6 (ArCH), 117.8 (ArC, d, J = 3.2 Hz), 116.1 (ArCH, d, J = 22.2 Hz), 115.9 (CF<sub>3</sub>, q, J = 287.7 Hz) 113.3 (ArC), 96.8 (C≡C), 82.6 (C≡C).
EIMS m/z 307 (M<sup>+</sup>, 100%).
HREIMS calculated. for C<sub>16</sub>H<sub>9</sub>NOF<sub>4</sub> (M+) 307.0626, found 307.0620.

2,2,2-Trifluoro-N-(4-methoxy-2-(phenylethynyl)phenyl)acetamide (363)

Following the above general procedure, 4-methoxy-2-(phenylethynyl)benzeneamine (0.100 g, 0.45 mmol), CH<sub>2</sub>Cl<sub>2</sub> (5 mL), pyridine (0.071 g, 0.90 mmol) and trifluoroacetic anhydride (0.113 g, 0.54 mmol) were stirred for 1 h. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.129 g, 90%) as a white solid.
R<sub>f</sub>: 0.47 (1 : 3, EtOAc/petrol)
Mp 120-122 ºC.
ν<sub>max</sub>/cm<sup>-1</sup> 3446, 2945, 1603, 1500, 1285, 1226, 1036, 819.
<sup>1</sup>H NMR δ 8.71 (1H, br. s, NH), 8.24 (1H, d, J = 9.0 Hz, ArH), 7.53-7.51 (2H, m, ArH), 7.40-7.38 (3H, m, ArH), 7.06 (1H, d, J = 3.0 Hz, ArH), 6.94 (1H, dd, J = 3.0, 9.0 Hz, ArH), 3.82 (3H, s, CH<sub>3</sub>O).
<sup>13</sup>C NMR δ 156.7 (ArC), 154.3 (CO, q, J = 36.6 Hz), 131.4 (ArCH), 129.5 (ArC), 129.3 (ArCH), 128.6 (ArCH), 121.6 (ArC), 121.2 (ArCH), 116.2 (ArCH), 115.8 (CF<sub>3</sub>, q, J = 287.5 Hz), 115.7 (ArCH) 114.8 (ArC), 97.6 (C≡C), 82.9 (C≡C), 55.5 (CH<sub>3</sub>O).
EIMS m/z 319 (M<sup>+</sup>, 100%).
**N-(4-Cyano-2-(phenylethynyl)phenyl)-2,2,2-trifluoroacetamide (364)**

Following the above general procedure, 4-amino-3-(phenylethynyl)benzonitrile (0.150 g, 0.65 mmol), CH$_2$Cl$_2$ (5 mL), pyridine (0.061 g, 0.78 mmol) and trifluoroacetic anhydride (0.165 g, 0.78 mmol) were stirred for 1 h. The crude product was purified by column chromatography (1 : 4, EtOAc/petrol) to give the title compound (0.195 g, 91%) as a white solid.

$R_f$: 0.37 (1 : 4, EtOAc/petrol).

Mp 115-117 °C.

$\nu$ max/cm$^{-1}$ 3259, 2366, 2233, 1716, 1530, 1485, 1413, 1288, 1190, 1156, 1142, 886.

$^1$H NMR $\delta$ 9.00 (1H, br. s, NH), 8.54 (1H, d, $J$ = 9.0 Hz, ArH), 7.86 (1H, d, $J$ = 1.5 Hz, ArH), 7.69 (1H, dd, $J$ = 1.5, 9.0 Hz, ArH), 7.53 (2H, m, ArH), 7.44 (3H, m, ArH)

$^{13}$C NMR $\delta$ 154.7 (CO, q, $J$ = 37.7 Hz), 139.3 (ArC), 135.1 (ArCH), 133.2 (ArCH), 131.6 (ArCH), 130.07 (ArCH), 128.8 (ArC), 120.6 (ArC), 119.8 (ArCH), 117.4 (ArCH), 115.4 (CF$_3$, q, $J$ = 287.5 Hz), 114.5 (ArC), 109.3 (CN), 100.3 (C≡C), 80.6 (C≡C).

EIMS $m/z$ 314 (M+, 100%).

HREIMS calculated. for C$_{17}$H$_9$N$_2$OF$_3$ (M$^+$) 314.0672, found 314.0666.

**N-(4-Cyano-2-(phenylethynyl)phenyl)-4-methylbenzenesulfonamide (365)**

Following the above general procedure, 4-amino-3-(phenylethynyl)benzonitrile (0.200 g, 0.872 mmol), CH$_2$Cl$_2$ (5 mL), pyridine (0.137 g, 1.74 mmol) and tosyl chloride (0.199 g, 1.04 mmol) were stirred at 40 °C for 6 h. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.190 g, 57%) as a yellow solid.

$R_f$: 0.38 (1 : 3, EtOAc/petrol).

Mp 93-95 °C.

$\nu$ max/cm$^{-1}$ 3257, 2233, 1598, 1496, 1408, 1347, 1291, 1167, 1090, 894.
\[ ^1\text{H NMR } \delta \ 7.66 \ (2\text{H, d, } J = 8.0 \text{ Hz, ArH}), \ 7.57 \ (2\text{H, t, } J = 7.0 \text{ Hz, ArH}), \ 7.49 \ (1\text{H, br. s, ArH}), \ 7.43 \ (3\text{H, m, ArH}), \ 7.33 \ (2\text{H, dd, } J = 9.0, 16.5 \text{ Hz, ArH}), \ 7.17 \ (2\text{H, d, } J = 8.0 \text{ Hz, ArH}), \ 2.94 \ (3\text{H, s, CH}_3) ;\]

\[ ^{13}\text{C NMR } \delta \ 144.8 \ (\text{ArC}), \ 141.2 \ (\text{ArC}), \ 135.6 \ (\text{ArC}), \ 135.5 \ (\text{ArCH}), \ 132.8 \ (\text{ArCH}), \ 131.7 \ (\text{ArCH}), \ 129.9 \ (\text{ArCH}), \ 129.7 \ (\text{ArCH}), \ 128.6 \ (\text{ArCH}), \ 127.1 \ (\text{ArCH}), \ 126.9 \ (\text{ArC}), \ 120.9 \ (\text{ArC}), \ 118.3 \ (\text{ArCH}), \ 114.2 \ (\text{ArC}), \ 107.5 \ (\text{CN}), \ 98.5 \ (\text{C=C}), \ 81.3 \ (\text{C=C}), \ 21.5 \ (\text{CH}_3).\]

EIMS \textit{m/z} 372 (M\(^+\), 100%).

HREIMS calculated. for C\(_{22}\)H\(_{16}\)N\(_2\)O\(_2\)S (M\(^+\)) 372.0933, found 372.0932.

\[
\text{N-(2-(Hept-1-yny1)phenyl)-4-methylbenzenesulfonamide (366)}
\]

Following the above general procedure, 2-(hept-1-ynyl)benzeneamine (0.150 g, 0.80 mmol), CH\(_2\)Cl\(_2\) (5 mL), pyridine (0.126 g, 1.6 mmol) and tosyl chloride (0.183 g, 0.96 mmol) were stirred for 18 h. The crude product was purified by column chromatography (1 : 6, EtOAc/petrol) to give the title compound (0.224 g, 82%) as a yellow oil. 

R\(_f\) : 0.24 (1 : 6, EtOAc/petrol)

\[ \nu_{\text{max}}/\text{cm}^{-1} \ 2965, \ 2924, \ 1603, \ 1490, \ 1398, \ 1342, \ 1259, \ 1166, \ 1091, \ 1017, \ 795\]

\[ ^1\text{H NMR } \delta \ 7.69-7.62 \ (3\text{H, m, ArH}), \ 7.24-7.18 \ (4\text{H, m, ArH}), \ 6.98- \ 6.95 \ (1\text{H, m, ArH}), \ 2.40 \ (2\text{H, t, } J = 7.0 \text{ Hz, CH}_2), \ 2.35 \ (3\text{H, s, CH}_3), \ 1.62-1.57 \ (2\text{H, m, CH}_2), \ 1.43-1.36 \ (4\text{H, m, 2 x CH}_2), \ 0.94 \ (3\text{H, t, } J = 7.0 \text{ Hz, CH}_3) \]

\[ ^{13}\text{C NMR } \delta \ 143.8 \ (\text{ArC}), \ 137.4 \ (\text{ArC}), \ 131.8 \ (\text{ArCH}), \ 129.5 \ (\text{ArCH}), \ 128.6 \ (\text{ArCH}), \ 127.1(\text{ArCH}), \ 124.0 \ (\text{ArC}), \ 119.2 \ (\text{ArCH}), \ 115.7 \ (\text{ArCH}), \ 114.8 \ (\text{ArC}), \ 97.8 \ (\text{C=C}), \ 75.2 \ (\text{C=C}), \ 31.0 \ (\text{CH}_2), \ 28.2 \ (\text{CH}_2), \ 22.1 \ (\text{CH}_2), \ 21.4 \ (\text{CH}_2), \ 19.4 \ (\text{CH}_3), \ 13.8 \ (\text{CH}_3).\]

EIMS \textit{m/z} 341 (M\(^+\), 40%).

HREIMS calculated. for C\(_{20}\)H\(_{23}\)NO\(_2\)S (M\(^+\)) 341.1455, found 341.1449.

\[
\text{2,2,2-Trifluoro-N-(2-(hept-1-yny1)phenyl)acetamide (367)}
\]

Following the above general procedure, 2-(hept-1-ynyl)benzeneamine (0.150 g, 0.80 mmol), CH\(_2\)Cl\(_2\) (5 mL), pyridine (0.126 g, 1.6 mmol) and trifluoroacetic anhydride (0.076 g ,0.96 mmol) were stirred for 1 h. The crude
product was purified by column chromatography (1 : 5, EtOAc/petrol) to give the title compound (0.228 g, 89%) as a yellow oil.

R<sub>f</sub> : 0.64 (1 : 5, EtOAc/petrol).

ν<sub>max</sub>/cm<sup>-1</sup> : 3370, 2955, 2934, 2361, 2335, 1746, 1588, 1541, 1454, 1296, 1260, 1149, 1101, 1015.

<sup>1</sup>H NMR δ : 8.82 (1H, br. s, NH), 8.33 (1H, d, J = 8.0 Hz, ArH), 7.42 (1H, d, J = 8.0 Hz, ArH), 7.34 (1H, t, J = 8.0 Hz, ArH), 7.20-7.12 (1H, m, ArH).

<sup>13</sup>C NMR δ : 154.2 (CO, q, J = 37.1 Hz), 146.7 (ArC), 136.1 (ArCH), 131.6 (ArCH), 129.0 (ArCH), 125.2 (ArCH), 119.2 (ArC), 115.7 (CF<sub>3</sub>, q, J = 287.6 Hz), 99.7 (C≡C), 74.6 (C≡C), 31.0 (CH<sub>2</sub>), 28.2 (CH<sub>2</sub>), 22.1 (CH<sub>2</sub>), 19.4 (CH<sub>2</sub>), 13.8 (CH<sub>3</sub>).

ESIMS m/z : 283 (M + H<sup>+</sup>, 100%).

HRESIMS calculated for C<sub>15</sub>H<sub>16</sub>NOF<sub>3</sub> (M + H<sup>+</sup>) 283.1431, found 283.1184.

General Procedure for the Preparation of Indoles

To a solution of the 2-ethynylaniline derivative (0.30 mmol) in anhydrous DMF (4 mL) under an oxygen atmosphere (balloon) was added CuCN (0.90 mmol) and the reaction vessel was placed in a pre-heated oil bath at 100 °C. The reaction mixture was stirred at this temperature for 16 h. Two different work-up procedures were followed. Work-up procedure A: H<sub>2</sub>O (5 mL) was added and the aqueous layer was extracted with EtOAc (3 x 5 mL), dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. The crude product was purified by column chromatography. Work-up procedure B: The solvent was removed in vacuo at 60 °C. The crude residue was purified by column chromatography.

2-Phenyl-1-(4-methylbenzenesulfonyl)-1H-indole-3-carbonitrile (368)

Using the general indole preparation procedure above, 4-methyl-N-(2-(phenylethynyl)phenyl)benzenesulfonylamide (0.100 g, 0.288 mmol), DMF (4 mL) and CuCN (0.080 g, 0.86 mmol) were stirred at 100 °C for 16 h. Work-up procedure A was applied. The crude product was purified by column chromatography (1 : 5, EtOAc/petrol) to give the compound 368 (0.080 g, 74%) as a white solid and compound 369 (0.003 g, 3%) as a colorless solid.
Data for 368;
R\textsubscript{f} : 0.35 (1 : 5, EtOAc/petrol).
Mp 148-150 °C.
\(v\textsubscript{max}/\text{cm}^{-1}\) 2361, 1342, 2230, 1451, 1375, 1197, 1178.

\(^1\)H NMR \(\delta\) 8.36 (1H, d, \(J = 8.5\) Hz, ArH), 7.65 (1H, d, \(J = 7.5\) Hz, ArH), 7.55-754 (1H, m, ArH), 7.51-7.46 (5H, m, ArH), 7.42 (1H, t, \(J = 7.5\) Hz, ArH), 7.28 (2H, d, \(J = 8.0\) Hz, ArH), 7.10 (2H, d, \(J = 8.0\) Hz, ArH), 2.33 (3H, s, CH\(_3\)).

\(^{13}\)C NMR \(\delta\) 148.6 (ArC), 145.8 (ArC), 136.4 (ArC), 134.6 (ArC), 130.9 (ArCH), 130.5 (ArCH), 129.7 (ArCH), 128.3 (ArC), 127.9 (ArCH), 127.8 (ArC), 126.9 (ArCH), 125.3 (ArCH), 119.6 (ArCH), 116.3 (ArCH), 113.9 (ArC), 96.7 (CN), 21.6 (CH\(_3\)).

EIMS \textit{m/z} 372 (M\textsuperscript{+}, 65%).
HREIMS calculated. for C\(_{22}\)H\(_{16}\)N\(_2\)O\(_2\)S (M\textsuperscript{+}) 372.0935 found 372.0932.

\begin{align*}
2\text{-Phenyl-1-(4-methylbenzenesulfonyl)}\text{-1H-indole1} \ (369) \\
R_f & : 0.52 \ (1 : 3, \text{EtOAc/petrol}). \\
\text{Mp} & 144-146 \ ^\circ\text{C} \ (\text{Lit.}^{85} \text{Mp} 146-148 \ ^\circ\text{C}). \\
\text{v}_{\text{max}}/\text{cm}^{-1} & 1598, 1449, 1367, 1306, 1167, 1060, 978, 809. \\
{^1}\text{H NMR} \ & \delta \ 8.31 \ (1\text{H}, \ d, \ J = 8.5 \ \text{Hz}, \ \text{ArH}), \ 7.50-7.48 \ (2\text{H}, \ m, \ \text{ArH}), \ 7.43 \ (4\text{H}, \ m, \ \text{ArH}), \ 7.35 \ (1\text{H}, \ t, \ J = 7.5 \ \text{Hz}, \ \text{ArH}), \ 7.27-7.24 \ (3\text{H}, \ m, \ \text{ArH}), \ 7.03 \ (2\text{H}, \ d, \ J = 8.5 \ \text{Hz}, \ \text{ArH}), \ 6.54 \ (1\text{H}, \ s, \ \text{ArH}), \ 2.28 \ (3\text{H}, \ s, \ \text{CH}_3). \\
\text{ESIMS} \ & \text{m/z} \ 348 \ (\text{M} + \text{H}^+, \ 100\%). \\
\text{HRESIMS calculated. for C}_{21}\text{H}_{18}\text{NO}_2\text{S} \ (\text{M} + \text{H}^+) \ 348.1042, \ \text{found} \ 348.1058.
\end{align*}

\begin{align*}
2\text{-Phenyl-1H-indole-3-carbonitrile} \ (370) \\
\text{Using the general indole preparation procedure above, 2,2,2\text{-trifluoro-N-(2-(phenylethynyl)phenyl)acetamide (0.100 g, 0.34 mmol), DMF (4 mL), and CuCN (0.093 g, 1.02 mmol) were stirred at 100 °C for 16 h. Work-up procedure A was applied. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.059 g, 80%) as a white solid.} \\
R_f & : 0.22 \ (1 : 3, \text{EtOAc/petrol}). \\
\text{Mp} & 224-226 \ ^\circ\text{C}.
\end{align*}
$\nu_{\text{max}}$/cm$^{-1}$ 3221, 2361, 2335, 2217, 1654, 1490, 1451, 1424, 1250, 732.

$^1$H NMR $\delta$ (d$_6$-acetone) 11.5 (1H, br. s, NH), 8.05-8.02 (2H, m, ArH), 7.71-7.68 (1H, m, ArH), 7.61-7.56 (4H, m, ArH), 7.35-7.26 (2H, m, ArH).

$^{13}$C NMR $\delta$ (d$_6$-acetone) 145.5 (ArC), 136.6 (ArC), 130.7 (ArC), 130.6 (ArCH), 130.1 (ArCH), 129.7 (ArC), 127.8 (ArCH), 124.8 (ArCH), 122.9 (ArCH), 119.4 (ArCH), 117.1 (ArC), 113.2 (ArCH), 83.7 (CN).

ESIMS $m/z$ 219 (M + H$^+$, 100%).

HREIMS calculated for C$_{15}$H$_{10}$N$_2$ (M + H$^+$) 219.0846, found 219.0843.

2-(4-Methoxyphenyl)-1$H$-indole-3-carbonitrile (371)

Using the general indole preparation procedure above, 361 (0.100 g, 0.32 mmol), DMF (4 mL), and CuCN (0.086 g, 0.95 mmol) were stirred at 100 $^\circ$C for 16 h. Work-up procedure B was applied. The crude product was purified by column chromatography (EtOAc) to give the title compound (0.061 g, 77%) as a white solid.

R$_f$ : 0.15 (3 : 1, EtOAc/petrol).

Mp 99-101 $^\circ$C.

$\nu_{\text{max}}$/cm$^{-1}$ 3257, 2212, 1613, 1499, 1446, 1255, 1245, 1173, 1040, 836.

$^1$H NMR $\delta$ (d$_6$-acetone) 11.4 (1H, br. s, NH), 7.99 (2H, d, $J$ = 8.5 Hz, ArH), 7.67 (1H, d, $J$ = 7.5 Hz, ArH), 7.53 (1H, d, $J$ = 7.5 Hz, ArH), 7.30-7.24 (2H, m, ArH), 7.15 (2H, d, $J$ = 8.5 Hz, ArH), 3.89 (3H, s, CH$_3$O).

$^{13}$C NMR $\delta$ (d$_6$-acetone) 161.3 (ArC), 145.1 (ArC), 135.8 (ArC), 129.1 (ArC), 128.7 (ArCH) 123.8 (ArCH), 122.4 (ArC), 122.1 (ArCH), 118.6 (ArCH), 116.8 (ArC), 114.9 (ArCH), 112.3 (ArCH), 81.9 (CN), 55.2 (CH$_3$O).

EIMS $m/z$ 248 (M$^+$, 80%).

HREIMS calculated for C$_{16}$H$_{12}$N$_2$O (M$^+$) 248.0943, found 248.0949.

2-(4-Fluorophenyl)-1$H$-indole-3-carbonitrile (372)

Using the general indole preparation procedure above, 362 (0.080 g, 0.26 mmol), DMF (3 mL), CuCN (0.072 g, 0.79 mmol) were stirred at 100 $^\circ$C for 16 h. Work-up procedure B was applied. The crude product was purified by column...
chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.041 g, 65%) as a white solid.

\( R_f : 0.26 \) (1 : 3, EtOAc/petrol).

\( \text{Mp} \ 239-241 \ ^\circ \text{C}. \)

\( \nu_{\text{max}}/\text{cm}^{-1} \ 3257, 2213, 1675, 1613, 1498, 1448, 1241, 1173, 830. \)

\( ^1\text{H NMR} \ \delta (\text{d}_6\text{-acetone}) \ 11.5 \ (1\text{H, br. s, NH}), 8.08-8.06 \ (2\text{H, m, ArH}), 7.69 \ (1\text{H, d, } J = 7.5 \ \text{Hz, ArH}), 7.56 \ (1\text{H, d, } J = 7.5 \ \text{Hz, ArH}), 7.39-7.34 \ (2\text{H, m, ArH}), 7.32-7.27 \ (2\text{H, m, ArH}). \)

\( ^{13}\text{C NMR} \ \delta (\text{d}_6\text{-acetone}) \ 164.2 \ (\text{ArC, d, } J = 247.6 \ \text{Hz}), 144.5 \ (\text{ArC}), 136.6 \ (\text{ArC}), 113.1 \ (\text{ArCH}), 83.7 \ (\text{CN}). \)

\( \text{EIMS } m/z \ 236 \ (\text{M}^+, 100\%). \)

HREIMS calculated. for C\(_{15}\)H\(_9\)N\(_2\)F (M\(^+\)) 236.0760, found 236.0749.

5-Methoxy-2-phenyl-1H-indole-3-carbonitrile (373)

Using the general indole preparation procedure above, 2,2,2-trifluoro-N-(4-methoxy-2-(phenylethynyl)phenyl)acetamide (0.100 g, 0.32 mmol), DMF (4 mL), CuCN (0.086 g, 0.95 mmol) were stirred at 100 °C for 16 h at 130 °C. Work-up procedure B was applied. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.062 g, 78%) as a white solid.

\( R_f : 0.35 \) (1 : 3, EtOAc/petrol).

\( \text{Mp} \ 120-122 \ ^\circ \text{C}. \)

\( \nu_{\text{max}}/\text{cm}^{-1} \ 3216, 2965, 2909, 2358, 2341, 2217, 1685, 1652, 1558, 1540, 1456, 1055, 752; \)

\( ^1\text{H NMR} \ \delta (\text{d}_6\text{-acetone}) \ 11.4 \ (1\text{H, br. s, NH}), 8.01 \ (2\text{H, d, } J = 7.0 \ \text{Hz, ArH}), 5.95 \ (2\text{H, t, } J = 7.0 \ \text{Hz, ArH}), 7.53 \ (1\text{H, d, } J = 7.0 \ \text{Hz, ArH}), 7.46 \ (1\text{H, d, } J = 8.5 \ \text{Hz, ArH}), 7.16 \ (1\text{H, s, ArH}), 6.94 \ (1\text{H, d, } J = 8.5 \ \text{Hz, ArH}), 3.90 \ (3\text{H, s, CH}_3\text{O}); \)

\( ^{13}\text{C NMR} \ \delta (\text{d}_6\text{-acetone}) \ 156.7 \ (\text{ArC}), 145.1 \ (\text{ArC}), 131.2 \ (\text{ArC}), 130.5 \ (\text{ArC}), 130.3 \ (\text{ArCH}), 130.2 \ (\text{ArCH}), 129.8 \ (\text{ArCH}), 127.3 \ (\text{ArCH}), 117.1 \ (\text{ArC}), 115.1 \ (\text{ArCH}), 113.8 \ (\text{ArC}), 100.4 \ (\text{ArCH}), 83.2 \ (\text{CN}), 55.6 \ (\text{CH}_3\text{O}). \)
EIMS m/z 248 (M+, 100%).
HREIMS calculated for C_{16}H_{12}N_{2}O (M+) 248.0938, found 248.0949.

**Phenyl-1H-indole-3,5-dicarbonitrile (374)**

Using the general indole preparation procedure above, 364 (0.070 g, 0.21 mmol), DMF (3 mL), CuCN (0.059 g, 0.64 mmol) were stirred at 100 °C for 16 h. Work-up procedure B was applied. The crude product was purified by column chromatography (2 : 1, EtOAc/petrol) to give the title compound (0.031 g, 60%) as a white solid.

R_f : 0.64 (EtOAc).

Mp 265-267 °C.

ν_{max}/cm^{-1} 3231, 2360, 2235, 2224, 1685, 1654, 1475, 1449, 1367, 1255, 1070, 906.

^1H NMR δ (d_6-acetone) 12.1 (1H, br. s, NH), 8.13 (1H, d, J = 1.5 Hz, ArH), 8.06 (2H, dd, J = 1.5, 7.0 Hz, ArH), 7.76 (1H, d, J = 7.0 Hz, ArH), 7.68-7.59 (4H, m, ArH).

^13C NMR δ (d_6-acetone) 147.8 (ArC), 138.0 (ArC), 131.1 (ArCH), 130.0 (ArCH), 129.4 (ArC), 129.0 (ArC), 127.8 (ArCH), 127.4 (ArCH), 124.3 (ArCH), 119.7 (ArC), 115.7 (ArC), 114.2 (ArCH), 106.0 (CN), 84.1 (CN).

EIMS m/z 243 (M+, 100%).
HREIMS calculated for C_{16}H_{9}N_{3} (M+) 243.0813, found 243.0796.

**2-Phenyl-1-(4-methylbenzenesulfonyl)-1H-indole-5-carbonitrile (375)**

Using the general indole preparation procedure above, N-(4-cyano-2-(phenylethynyl)phenyl)-4-methylbenzenesulfonamide (0.100 g, 0.26 mmol), DMF (4 mL) and CuCN (0.072 g, 0.78 mmol) were stirred at 100 °C for 16 h. Work-up procedure A was applied. The crude product was purified by column chromatography (1 : 4, EtOAc/petrol) to give the compound 375 (0.037 g, 38%) and compound 376 (0.023 g, 22%) both as white solids.

Data for 375:

R_f : 0.34 (1 : 4, EtOAc/petrol).

Mp 78-80 °C.
ν<sub>max</sub>/cm<sup>-1</sup> 2970, 2361, 1340, 1654, 1375, 1173, 1091, 1081, 756.

<sup>1</sup>H NMR δ 8.42 (1H, d, J = 8.0 Hz, ArH), 7.70 (1H, s, ArH), 7.60 (1H, dd, J = 1.5, 8.0 Hz, ArH), 7.45-7.42 (5H, m, ArH), 7.24 (2H, d, J = 7.0 Hz, ArH), 7.07 (2H, d, J = 7.0 Hz, ArH), 6.56 (1H, s, ArH), 2.31 (3H, s, CH₃).

<sup>1</sup>C NMR δ 150.6 (ArC), 146.6 (ArC), 138.0 (ArC), 134.1 (ArC), 131.3 (ArCH), 130.2 (ArCH), 129.6 (ArCH), 128.3 (ArCH), 127.7 (ArC), 127.3 (ArCH), 124.4 (ArCH), 118.2 (ArC), 117.4 (ArCH), 112.7 (ArC), 109.1 (CN), 96.0 (CN), 21.6 (CH₃).

ESIMS <i>m/z</i> 373 (M + H<sup>+</sup>, 100%).

HRESIMS calculated. for C<sub>22</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub>S (M + H<sup>+</sup>) 373.1018, found 373.1011.

2-Phenyl-1-(4-methylbenzenesulfonyl)-1H-indole-3,5-dicarbonitrile (376)

<sup>1</sup>H NMR δ 8.50 (1H, d, J = 8.5 Hz, ArH), 7.99 (1H, s, ArH), 7.59 (1H, t, J = 7.0 Hz, ArH), 7.49 (2H, t, J = 7.0 Hz, ArH), 7.42 (2H, d, J = 7.0 Hz, ArH), 7.25 (2H, d, J = 8.0 Hz, ArH), 7.14 (2H, d, J = 8.0 Hz, ArH), 2.36 (3H, s, CH₃).

<sup>1</sup>C NMR δ 150.6 (ArC), 146.6 (ArC), 138.0 (ArC), 134.1 (ArC), 131.3 (ArCH), 130.2 (ArCH), 129.6 (ArCH), 128.3 (ArCH), 127.7 (ArC), 127.3 (ArCH), 124.4 (ArCH), 118.2 (ArC), 117.4 (ArCH), 112.7 (ArC), 109.1 (CN), 96.0 (CN), 21.6 (CH₃).

ESIMS <i>m/z</i> 398 (M + H<sup>+</sup>, 100%).

HRESIMS calculated. for C<sub>23</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub>S (M + H<sup>+</sup>) 398.0944, found 398.0963.

2-Pentyl-1H-indole-3-carbonitrile (377)

Using the general indole preparation procedure above, 2,2,2-trifluoro-N-(2-(hept-1-ynyl)phenyl)acetamide (0.100 g, 0.32 mmol), DMF (4 mL), CuCN (0.088 g, 0.96 mmol) were stirred at 100 °C for 16 h. Work-up procedure A was
applied. The crude product was purified by column chromatography (1 : 3, EtOAc/petrol) to give the title compound (0.050 g, 73%) as a white solid.

\[ R_f : 0.31 \ (1 : 3, \text{EtOAc/petrol}). \]

Mp 49-51 °C.

\[ \nu_{\text{max}}/\text{cm}^{-1} \ 3262, 2955, 2929, 2858, 2208, 1557, 1490, 1452, 1332, 1239, 742. \]

\[ ^1H \text{ NMR} \ \delta \ 8.70 (1H, \text{ br. s, } \text{NH}), 7.65 (1H, d, J = 8.5 \text{ Hz, ArH}), 7.38 (1H, d, J = 8.5 \text{ Hz, ArH}), 7.25-7.22 (2H, m, ArH), 2.94 (2H, t, J = 7.0 \text{ Hz, CH}_2), 1.80-1.78 (2H, m, CH2), 1.38-1.35 (4H, m, 2 x CH2), 0.90 (3H, t, J = 7.0 \text{ Hz, CH}_3). \]

\[ ^{13}\text{C NMR} \ \delta \ 149.3 (\text{ArC}), 134.5 (\text{ArC}), 127.6 (\text{ArC}), 123.3 (\text{ArCH}), 121.9 (\text{ArCH}), 118.9 (\text{ArCH}), 116.4 (\text{ArC}), 111.3 (\text{ArCH}), 84.7 (\text{CN}), 31.1 (\text{CH}_2), 28.7 (\text{CH}_2), 27.5 (\text{CH}_2), 22.2 (\text{CH}_2), 13.8 (\text{CH}_3). \]

ESIMS \[ m/z \ 213 (\text{M} + \text{H}^+, \text{100} \%). \]

HRESIMS calculated. for C_{14}H_{17}N_{2} (M + H^+) \ 213.1360, found \ 213.1392.

2-Pentyl-1-(4-methylbenzenesulfonyl)-1H-indole-3-carbonitrile (378)

Using the general indole preparation procedure above, \( N \)-(2-(hept-1-ynyl)phenyl)-4-methylbenzenesulfonamide (0.0.080g, 0.23 mmol), DMF (3 mL), CuCN (0.063 g, 0.69 mmol) were stirred at 100 °C for 16 h. Work-up procedure A was applied. The crude product was purified by column chromatography (1 : 5, EtOAc/petrol) to give the compound 378 (0.046 g, 55%) as a colorless oil and compound 379 (0.019 g, 24%) as a white solid with a ratio of 378 : 379 = 70 : 30.

Data for 378

\[ R_f : 0.42 (1 : 5, \text{EtOAc/petrol}). \]

\[ \nu_{\text{max}}/\text{cm}^{-1} \ 2955, 2924, 2863, 2228, 1598, 1451, 1384, 1191, 1178, 1155, 1098, 969. \]

\[ ^1H \text{ NMR} \ \delta \ 8.17 (1H, d, J = 8.5 \text{ Hz, ArH}), 7.65 (1H, d, J = 8.5 \text{ Hz, ArH}), 7.58 (1H, d, J = 8.0 \text{ Hz, ArH}), 7.39-7.33 (2H, m, ArH), 7.25 (3H, d, J = 8.0 \text{ Hz, ArH}), 3.20 (2H, t, J = 7.5 \text{ Hz, CH}_2), 2.37 (3H, s, CH_3), 1.82-1.77 (2H, m, CH_2), 1.43-1.35 (4H, m, 2 x CH_2), 0.91 (3H, t, J = 7.5 \text{ Hz, CH}_3). \]

\[ ^{13}\text{C NMR} \ \delta \ 151.4 (\text{ArC}), 145.9 (\text{ArC}), 135.6 (\text{ArC}), 135.3 (\text{ArC}), 130.2 (\text{ArCH}), 127.2 (\text{ArC}), 126.4 (\text{ArCH}), 125.7 (\text{ArCH}), 124.8 (\text{ArCH}), 119.1 (\text{ArCH}), 115.1 (\text{ArCH}), 114.1 (\text{ArC}), 94.5 (\text{CN}), 31.4 (\text{CH}_2), 30.4 (\text{CH}_2), 28.5 (\text{CH}_2), 22.2 (\text{CH}_2), 21.6 (\text{CH}_3), 13.9 (\text{CH}_3). \]
ESIMS m/z 367 (M + H⁺, 100%).
HRESIMS calculated. for C₂₁H₂₃N₂O₂S (M + H⁺) 367.1470, found 367.1480.

2-Pentyl-1-(4-methylbenzenesulfonyl)-1H-indole (379)

\[
\text{Rf : 0.55 (1 : 5, EtOAc/petrol).}
\]

\[
\text{Mp 57-59 °C.}
\]

\[
\nu_{\text{max/cm}^{-1}} 2955, 2924, 2356, 2330, 1444, 1369, 1224, 1170, 1139, 1092, 1060, 804.
\]

\[
\text{H NMR } \delta 8.16 (1H, d, J = 8.0 \text{ Hz, ArH}), 7.61 (2H, d, J = 8.0 \text{ Hz, ArH}), 7.39 (1H, d, J = 8.0 \text{ Hz, ArH}), 7.25-7.16 (4H, m, ArH), 2.97 (2H, t, J = 7.5 \text{ Hz, CH}_2), 2.32 (3H, s, CH₃), 1.75-1.72 (2H, m, CH₂), 1.39-1.35 (4H, m, 2 x CH₂), 0.91 (3H, t, J = 7.5 \text{ Hz, CH}_3).
\]

\[
\text{C NMR } \delta 144.2 (\text{ArC}), 142.5 (\text{ArC}), 137.1 (\text{ArC}), 136.2 (\text{ArC}), 129.7 (\text{ArCH}), 126.6 (\text{ArCH}), 126.2 (\text{ArC}), 123.7 (\text{ArCH}), 123.4 (\text{ArCH}), 119.9 (\text{ArCH}), 114.7 (\text{ArCH}), 108.5 (\text{ArCH}), 31.5 (\text{CH}_2), 28.9 (\text{CH}_2), 28.5 (\text{CH}_2), 22.4 (\text{CH}_2), 21.5 (\text{CH}_3), 14.0 (\text{CH}_3).
\]

EIMS m/z 341 (M⁺, 50%).
HREIMS calculated. for C₂₀H₂₃NO₂S (M⁺) 341.1451, found 341.1449.
REFERENCES


34. Wikipedia. url: [http://commons.wikimedia.org/wiki/Astragalus_lentiginosus](http://commons.wikimedia.org/wiki/Astragalus_lentiginosus).


147. Ding, Q.; Wu, J. *J. Comb. Chem.* **2008**, *10*, 541-545.


APPENDIX 1: INTERMOLECULAR ADDITION REACTIONS OF N-ACYLIMINIIUM IONS (PART I)
Intermolecular Addition Reactions of N-Acyliminium Ions (Part I)\(^1\)

Arife Yazici, Stephen G. Pyne\(^*\)

School of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia
Fax +61(2)42214987; E-mail: spyne@uow.edu.au

Received 22 September 2008; revised 7 October 2008

Abstract: This review highlights the advances in the literature up to July 2008 on the intermolecular reactions of acyclic and cyclic N-acyliminium ions. This is an update of an earlier review in 2000 on this topic and does not include intramolecular addition reactions to N-acyliminium ions which was recently reviewed. This review is presented in two parts, with the first part dealing with acyclic and pyrrolidine-based N-acyliminium ions. Part II continues with other five-membered heterocyclic derivatives and higher systems.

Part I
1 Introduction
2 Acyclic N-Acyliminium Ions
   2.1 Synthesis of Acyclic N-Acyliminium Ion Precursors
   2.2 Reactions of Acyclic N-Acyliminium Ions
      2.2.1 Reactions with Nucleophiles
      2.2.1.1 Silicon-Based Nucleophiles
      2.2.1.2 Aromatic Nucleophiles
      2.2.1.3 Organostannanes
      2.2.1.4 Organometallic Reagents
      2.2.1.5 Thiols
      2.2.1.6 Alkenes
      2.2.1.7 Nitrogen Nucleophiles
      2.2.1.8 Alkyl Radicals
      2.2.2 Cycloaddition Reactions
      2.2.3 Cationic Carboxylation Reactions
   3 Cyclic N-Acyliminium Ions
      3.1 Synthesis of Cyclic N-Acyliminium Ion Precursors
      3.1.1 Preparation of Iminium Ions in situ by Anodic Oxidation
      3.2 Five-Membered-Ring N-Acyliminium Ions
      3.2.1 Reactions of Pyrrolidine-Based N-Acyliminium Ions
         3.2.1.1 Silicon-Based Nucleophiles
         3.2.1.2 Aromatic Nucleophiles
         3.2.1.3 Organostannanes
         3.2.1.4 Organometallic Reagents
         3.2.1.5 Active Methylene Compounds
         3.2.1.6 Nitrile Nucleophiles (Ritter Reaction)
   Part II
   3.2.2 Reactions of N-Acylpyrrolidine-Based N-Acyliminium Ions with Nucleophiles
   3.2.3 Reactions of Oxazolidinone-Based N-Acyliminium Ions with Nucleophiles
   3.2.4 Cyclocondensation Reaction of N-Aminimidyl Iminium Ions
   3.3 Reactions of Six-Membered-Ring N-Acyliminium Ions
      3.3.1 Reactions of Piperidinone-Based N-Acyliminium Ions with Nucleophiles
      3.3.3 Reactions of Piperazine-Based N-Acyliminium Ions with Nucleophiles
      3.3.4 Reactions of Pyridine-Based N-Acyliminium Ions with Nucleophiles

SYNTHESIS 2009, No. 3, pp 0339–0368
Advanced online publication: 26.01.2009
DOI: 10.1055/s-0028-1083325; Art ID: E22608SS
© Georg Thieme Verlag Stuttgart · New York

1 Introduction

This review highlights the advances in the literature up to July 2008 on the intermolecular reactions of acyclic and cyclic N-acyliminium ions. This is an update of an earlier review in 2000\(^2\) on this topic and does not include intramolecular addition reactions to N-acyliminium ions which was recently reviewed.\(^3\) A review article on addition reactions to related, but less reactive, N-acylimines has also been recently published.\(^4\)

The highly reactive nature of N-acyliminium ions require that they are generated in situ usually in the presence of the other reactive, electron-rich, nucleophilic partner (NuY, Y = metal, SiR\(_3\), SnR\(_3\), etc.). In general these intermediates are generated from more stable and isolatable α-substituted N-acylamines of the type 1 by treatment with a Lewis acid or sometimes a protic acid (Scheme 1). The reaction of 2 with a nucleophilic species (NuY) then gives α-substituted N-acylamine 3. Compounds 1–3 can be acyclic systems or R\(_1\) and R\(_2\), R\(_2\) and R\(_3\), R\(_1\) and R\(_3\) can be taken together to form part of a ring system as shown in the general structures 4, 5, and 6.

Compounds like 1 (X = OH and NH\(_2\)CO\(_2\)R) are most likely formed in situ from the Lewis acid promoted three-component, one-pot coupling reactions of carboxamides, aldehydes (or acetals) and silyl nucleophiles or electron-rich aromatic nucleophiles (Scheme 2).\(^5\)

N-Acyliminium ions like 11 can also be generated in dichloromethane solution, in the absence of nucleophiles, by the electrochemical oxidation of N-trimethylsilylmethyl carbamates like 10 (Scheme 3). These intermediates have been characterised spectroscopically and were sub-
sequently treated with nucleophiles or dipolarophiles to give addition products.\textsuperscript{7–9}

**Biographical Sketches**

**Arife Yazici** obtained her MSc degree in chemistry at Hacettepe University-Ankara (Turkey) in 2005. She is currently doing her PhD studies with Professor Stephen Pyne at the University of Wollongong. Her area of study is the total synthesis of Stemona alkaloids.

**Stephen G. Pyne** is a Professor of Chemistry at the University of Wollongong (UOW) and Chair of the Division of Organic Chemistry of the Royal Australian Chemical Institute. He obtained his BSc (Hons) degree at the University of Adelaide with Dr. Ralf Massey-Westrop and his PhD degree with Professor Lew Mander (Australian National University) in 1979. After post-doctoral positions with Professor Phil Fuchs (Purdue) and Professor E. J. Corey (Harvard), he was appointed as a lecturer at UOW in 1985. His research interests include the total synthesis of bioactive alkaloids, natural products chemistry, drug design and synthesis, and fullerene chemistry.
um ions since they are often stable solids. They can be prepared by the coupling reaction of amides or carbamates with an aldehyde in the presence of benzenesulfinic acid or its salt (Scheme 4).\textsuperscript{11,13}

\[
\begin{align*}
\text{A} + \text{B} \rightarrow \text{C} + \text{D}
\end{align*}
\]

Scheme 4

\alpha-Carbamylalkylbenzotriazole derivatives 13 and 14 can be prepared from the coupling of carbamates, benzotriazole and aldehydes (Scheme 5). These benzotriazole adducts are usually formed as a mixture of 1-yl 13 and 2-yl 14 isomers. These regioisomers, however, are both readily converted into the same N-acyliminium ion.\textsuperscript{6,14,15}

\[
\begin{align*}
\text{A} + \text{B} \rightarrow \text{C} + \text{D}
\end{align*}
\]

Scheme 5

\alpha-Alkoxy carbamates 15 and 16 can be obtained from the electrochemical oxidation of carbamates in methanolic solution\textsuperscript{16} (Scheme 6, equation 1) or from the reaction of primary amines with aldehydes, followed by reaction with diethyl pyrocarbonate (Scheme 6, equation 2).\textsuperscript{17,18}

\[
\begin{align*}
\text{A} + \text{B} \rightarrow \text{C} + \text{D}
\end{align*}
\]

Scheme 6

\alpha-Acetoxy carbamate and amide derivatives 17 can be synthesised from the corresponding N-methylenecarbamates and amides by palladium-catalysed oxidation (Scheme 7).\textsuperscript{19}

\[
\begin{align*}
\text{A} + \text{B} \rightarrow \text{C} + \text{D}
\end{align*}
\]

Scheme 7

\alpha-Hydroxy carbamate derivatives 18 can be prepared by the partial reduction of imides using diisobutylaluminium hydride (Scheme 8). Although other reducing agents, such as sodium borohydride are effective for the reduction of cyclic imides, only diisobutylaluminium hydride was effective for acyclic imides.\textsuperscript{20,21}

\[
\begin{align*}
\text{A} + \text{B} \rightarrow \text{C} + \text{D}
\end{align*}
\]

Scheme 8

\alpha-Alkylthiocarbamates 19 can be synthesised from the three-component condensation of amides or carbamates with isopropylmercaptan and glyoxylic acid or its ester derivatives (Scheme 9).\textsuperscript{22}

\[
\begin{align*}
\text{A} + \text{B} \rightarrow \text{C} + \text{D}
\end{align*}
\]

Scheme 9

Weinreb amide derivatives 20 can be obtained from the condensation of carbamates with the corresponding hemiacetal (Scheme 10).\textsuperscript{23}

\[
\begin{align*}
\text{A} + \text{B} \rightarrow \text{C} + \text{D}
\end{align*}
\]

Scheme 10

Carbamates 21, having a N-silylmethyl substituent, can be easily synthesised from the reaction of carbamates with \alpha-silylalkyl iodides under basic conditions (Scheme 11,
equation 1). They can be used to generate N-acyliminium ions by anodic oxidation (Scheme 3). Alternatively, these compounds can be prepared by N-alkylation of amines with α-silylalkyl chlorides and then N-acylation of the resulting N-silylmethylamine (Scheme 11, equation 2). The N-trimethylsilylmethyl amides 22 can be converted into N-methoxymethyl carbamates 23 upon anodic oxidation in methanol or by oxidation with ceric ammonium nitrate (see Scheme 18).  

Scheme 11

2.2 Reactions of Acyclic N-Acyliminium Ions

2.2.1 Reactions with Nucleophiles

2.2.1.1 Silicon-Based Nucleophiles

Allylsilanes and silyl enol ethers constitute the largest class of silicon-based nucleophiles that have been treated with in situ generated N-acyliminium ions. The α-trimethylsilyloxy carbamates 24 reacted with trimethylsilyl cyanide in the presence of trimethylsilyl triflate (0.2 equiv) at −78 °C to −20 °C to give nitriles 25 in high yields (Scheme 12).  

Scheme 12

In a limited study the α-trimethylsilyloxy carbamate 26 gave products 27 upon treatment with three different silicon-based nucleophiles (Scheme 13).  

Scheme 13

The α-amido sulfones 28 reacted with silicon nucleophiles (1.5 equiv) in the presence of titanium(IV) chloride (2 equiv) to give adducts 29 in 70–89% yields. Halogen-containing substrates were also efficient in the allylation reaction (Scheme 14, equation 1). The bisamido sulfones 30 and 32 were treated with allytrimethylsilane under the same reaction conditions to give the corresponding bisallylated products 31 and 33 in good yields (Scheme 14, equations 2 and 3).  

The N-acyliminium ions 11 and 34, which were generated by electrochemical oxidation from the corresponding N-silylmethylcarbamates (Scheme 3), reacted with ally trimethylsilane and 3-trimethylsilylcyclohexene to give the corresponding adducts 35 in 57–72% yields (Scheme 15).  

The one-pot three-component coupling reaction of N-acyliminium ion 11 with enamine 36 and silicon nucleophiles afforded products 39 in 52–68% yields. The N-acyliminium ion 11 first reacted with the enamine 36 to form the new cationic species 37. The resulting cation, which was assumed to be an equilibrium mixture of 37 and 38, was then treated with nucleophiles to give the products 39 as diastereomeric mixtures. The major trans isomer most likely was a result of attack on the iminium 37 from the face anti to the ring C-3 substituent or from an Sn2-like attack on the bridged cationic intermediate pyrrolidine 38. The reaction of the N-acyliminium ion 11 with six-membered-ring analogues of enamine 36 and allytrimethylsilane gave the corresponding six-membered analogues of product 39 in 62% yield and with a trans/cis ratio of 91:9. Treatment of the N-cyclohexyl analogue of the N-butyl N-acyliminium ion 11 with allytrimethylsilane afforded the corresponding N-cyclohexyl analogue of 39 in 70% yield and with a diastereomeric ratio of 91:9. The analogous tert-butyl carbamate of 36 gave the tert-butyl analogue of 39 in the same yield and with the same trans/cis diastereoselectivity (Scheme 16).  

The use of vinyl sulfide 40 as an olefinic component in the three-component coupling reaction of the N-acyliminium ion 11 and silicon nucleophiles gave the products 41 in 56–75% yields (Scheme 17).
**Scheme 14**

An N-acyliminium ion was selectively generated in the polymer-supported dipeptide 42 by oxidation of the N-silylmethyl group with ceric ammonium nitrate in methanol. The resulting N-methoxymethyl carbamate reacted with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to give the polymer-supported allylated product 43. The yield of 43 was determined to be 66% yield (Scheme 18).24,27
Similarly, anodic oxidation of the trimethylsilyl group in peptide 44 gave the corresponding N-methoxymethyl carbamate, which was treated with allytrimethylsilane and boron trifluoride–diethyl ether complex to give product 45 (Scheme 19).\textsuperscript{24,28}

\[ \text{Scheme 19} \]

![Scheme 19](image)

The reaction of the α-benzotriazole carbamate 46 with allytrimethylsilane gave the allylated product 47 in 80% yield (Scheme 20). The analogous reactions of 46 with buta-2,3-dienylsilane and (furan-2-yl)trimethylsilane were less efficient and gave the corresponding adducts 47 in 53% and 51% yields, respectively.\textsuperscript{5}

\[ \text{Scheme 20} \]

![Scheme 20](image)

The reaction of the α-hydroxy carbamates 48a and 48b with allytrimethylsilane in the presence of titanium(IV) chloride provided the corresponding allylated products 49a and 49b in 80% and 72% yields, respectively (Scheme 21).\textsuperscript{21}

\[ \text{Scheme 21} \]

![Scheme 21](image)

The Lewis acid catalysed reactions of the N,O-acetals 50 and 53 gave the corresponding ring-opened acyclic N-acyliminium ions 51. These reacted smoothly with allytrimethylsilane, trimethylsilyl cyanide, and ketene silyl acetics to afford the adducts 52 (Scheme 22) and the diastereomeric products 54 and 55 (Scheme 23) in good yields.\textsuperscript{29}

\[ \text{Scheme 22} \]

![Scheme 22](image)

High syn selectivity was observed in the adducts from the reactions of the 3-benzyloxybenzyl acetal 53. A hydrogen-bonded transition-state model 56, involving hydrogen-bonding between the proton bound to the iminium nitrogen and the α-oxygen substituent group, was proposed. The nucleophile preferentially attacked from the less-hindered face of the iminium ion (from the side of the α-hydrogen) to give the syn product (Scheme 23).\textsuperscript{29} The syn/anti ratio did not vary dramatically with the nature of R in 53.

Allenyltrimethylsilane reacted with the α-methoxy and α-acetoxy carbamates 57 in the presence of boron trifluoride–diethyl ether complex to give dienes 58 in 75–88% yields (Scheme 24).\textsuperscript{30}

The one-pot reaction of carbamates 59 with aldehydes or their acetals and silyl nucleophiles in the presence of boron trifluoride–diethyl ether complex gave adducts 60 in yields ranging from 5% to 92% (Scheme 25). In the same study, treatment of carbamate 59 (R = Bn) with vinyl acetate and benzaldehyde in the presence of a catalytic amount of scandium(III) triflate provided product 60 in 28% yield. The reaction did not work with boron trifluoride–diethyl ether complex.\textsuperscript{6}

The (benzylsulfonyl)ethyl and (benzylsulfinyl)ethyl carbamates 61a and 61b underwent one-pot reactions with aldehydes or their acetals and allytrimethylsilane in the presence of boron trifluoride–diethyl ether complex to afford products 62 in 45–89% yields (Scheme 26).\textsuperscript{6}

Similarly, the reaction of carbamate 63 with diethyl acetal 64 and allytrimethylsilane in the presence of boron trifluoride–diethyl ether complex afforded a mixture of the
desired allylated product 65 and the bis-carbamate 66 in 75% yield (Scheme 27). Treatment of 66 with allyltrimethylsilyl and boron trifluoride–diethyl ether complex resulted in a 6:4 mixture of compounds 65 and 66.6

Treatment of resin-bound 67a with aromatic aldehydes and allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the corresponding allylated products 69 in a range of yields, <5% to 80%, after base-promoted cleavage from the resin (Scheme 28). Use of 4-methoxybenzaldehyde and benzaldehyde resulted in 79% and 80% yields of 69, respectively, while the use of benzaldehydes having electron-withdrawing groups, 4-cyanobenzaldehyde and 4-nitrobenzaldehyde, gave poor yields of 69 (< 5% and 39%, respectively). The three-component, one-pot reactions of compounds 67b and 67c with benzaldehyde and allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex gave the corresponding allylated products 69 in 83% and 57% yields, respectively, after cleavage from the resin.5

In a similar study, the one-pot reaction of resin-bound 67a with aldehydes or their acetals and silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex provided products 70 in 3–80% yields, after cleavage from the resin (Scheme 29).6

The reaction of Weinreb amide 71 with allyltrimethylsilane under boron trifluoride–diethyl ether complex catalysis gave product 72 in 89% yield (Scheme 30).23
The reaction of immobilised α-benzotriazolyl carbamates 73a and 73b with allytrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the desired allylated products 74a and 74b in 71% and 36% yields, respectively, after cleavage from the resin by sodium methoxide (Scheme 31).6

Tin(IV) chloride mediated allylation reaction of oxazolidinone 75 with allytrimethylsilane provided product 76 in 78% yield (Scheme 32).31

The reactions of oxazolidinone 77 with silicon nucleophiles under boron trifluoride–diethyl ether complex catalysis led to the formation of the desired products 78 in 85–94% yields (Scheme 33).32
The boron trifluoride–diethyl ether complex catalysed reaction of chiral oxazolidinones 79 with CH₂=CH₂ on OTMS(OEII) yielded products 80 in yields of 47–
99% with very high diastereoselectivity (dr = 91:9 to
96:4) (Scheme 34). 32

The oxazolidinone 81 reacted with CH₂=CH₂ on OTMS(OEII)
in the presence of boron trifluoride–diethyl ether complex
and provided the products 82 and 83 in a ratio of 95:5
(Scheme 35, equation 1); while the reaction of diastereomer
84 of the oxazolidinone 81 under the same reaction
conditions yielded product 82 and 83 in a ratio of 6:94
(Scheme 35, equation 2). 32

The oxazolidinone 85 was treated with allyltrimethylsi-
lane in the presence of titanium(IV) chloride to provide
adducts 86 and 87 in yields of 46–93%, in favour of product
86 (Scheme 36). 33

Treatment of the imidazolidinones 88 with silicon nucleo-
philes under tin(IV) chloride catalysis led to the formation
of adducts 89 and 90 in yields of 30–80% (Scheme 37). 31

2.2.1.2 Aromatic Nucleophiles

The reaction of the N-acyliminium ion 11 with substituted
benzenes and heteroaromatic compounds afforded the
corresponding monoalkylated and dialkylated products
91–94 (Scheme 38). The use of a conventional batch reac-
tor resulted in the formation of both mono- and dialkyli-
ed products, except in the cases of toluene, 1,4-
dimethylbenzene and 1,3,5-trimethylbenzene, where the
monoalkylated products 91 were obtained exclusively, in
yields of 62–69%. When the reactions were performed in
a micromixer-type reactor, however, only the monoalkyl-
lated products 91 and 93 were obtained, in 26–92% and 39–84% yields, respectively.9

The above method, using a micromixer together with pre-generated N-acyliminium ions, has been extended to the selective introduction of two different alkyl groups onto aromatic compounds (Scheme 39). Monoalkylation of thiophene was carried out in a micromixer, and the product 95 was directly treated with a different N-acyliminium ion 34, to give the dialkylated product 96 in 64% yield.9

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{Bu} \\
\text{N} & \quad \text{N} \\
\text{Bu} & \quad \text{Bu} \\
\text{CO}_2\text{Me} & \\
\end{align*}
\]

Scheme 39

The α-amido sulfones 97 gave the corresponding arylated adducts 98 in good yields when treated with electron-rich aromatic compounds in the presence of titanium(IV) chloride (Scheme 40).10

\[
\begin{align*}
\text{Me}_2\text{OC} & \quad \text{N} \\
\text{Bu} & \quad \text{Bu} \\
\text{CO}_2\text{Me} & \\
\end{align*}
\]

Scheme 38

Treatment of bisamido sulfones 32 and 30 with aromatic compounds (1.5 equiv) in the presence of titanium(IV) chloride (2 equiv) resulted in poor yields of monoarylated products due to the formation of bisarylated products and side products. Bisarylation took place efficiently when excess amounts of the aromatic nucleophiles (3 equiv) and titanium(IV) chloride (4 equiv) were used (Scheme 41).10

The α-amido sulfones 102 reacted with indoles 101 in the presence of montmorillonite K-10 without solvent to give the 3-substituted indole derivatives 103 (Scheme 42). Unexpectedly, these products retained the toluenesulfonyl group of 102, instead of its carbamoyl group. The formation of these products 103 has been explained by the mechanism shown in Scheme 43. The N-acyliminium ion
104 forms from the α-amido sulfone under acidic conditions. The indole 105 attacks the N-acyliminium ion 104 to form the expected product 106, which is then protonated and eliminates the carbamate group. The resulting iminium ion 108 can react with another molecule of indole to give the bisindole 109, or with the arenesulfonic acid to give the observed product 103. Since the formation of the bisindole is reversible and product 103 is more stable than the bisindole, the reaction favours the formation of 103.\(^\text{34}\)

Scheme 41

The α-amido sulfones 110 gave products 111 when they were treated with 1,2,4-trimethoxybenzene in the presence of ytterbium(III) triflate at room temperature (Scheme 44). Heteroaromatic compounds gave lower yields of adducts than electron-rich benzene derivatives, which might be the result of formation of a deactivating complex between the heteroaromatic compounds and the Lewis acid.\(^\text{35}\)

Scheme 43

Trifluoromethanesulfonic acid catalysed the reaction of α-chloro amide 112 with benzene and gave the benzhydryl
product 114 in 88% yield (Scheme 45).\textsuperscript{36} Evidence for the dicationic intermediate 113 has been reported.\textsuperscript{37}

\[
\begin{align*}
\text{Cl} &\quad \text{N} \quad \text{O} \\
\text{Ph} &\quad \text{Ph} \\
112
\end{align*}
\]

\[
\begin{align*}
\text{CF}_2\text{SO}_3 \quad \text{H} \\
\text{O}_2\text{SCF}_3 \\
113
\end{align*}
\]

\[
\begin{align*}
\text{C}_6\text{H}_8 (3.7 \text{ equiv}) \quad \text{CH}_2\text{Cl}_2, \text{ r.t.} \\
\text{Ph} &\quad \text{N} \quad \text{O} \\
114
\end{align*}
\]

\textbf{Scheme 45}

Treatment of the α-benzotriazole carbamate 46 with furan in the presence of camphorsulfonic acid monohydrate afforded product 115 in 55% yield (Scheme 46).\textsuperscript{6}

\[
\begin{align*}
\text{HN} &\quad \text{Ph} \\
\text{Cbz} &\quad \text{CSA} (1.0 \text{ equiv}) \quad \text{r.t.} \\
\text{HN} &\quad \text{Ph} \\
115
\end{align*}
\]

\textbf{Scheme 46}

In the same study, the reaction of immobilised α-benzotriazole carbamate 73a with furan and 1,3-dimethoxybenzene in the presence of camphorsulfonic acid gave products 116 in 50% and 20% yields, respectively, after cleavage from the resin (Scheme 47).\textsuperscript{6}

\[
\begin{align*}
\text{HN} &\quad \text{Ph} \\
\text{Cbz} &\quad \text{CSA} (1.0 \text{ equiv}) \quad \text{CH}_2\text{Cl}_2, \text{ r.t.} \\
\text{HN} &\quad \text{Ph} \\
116
\end{align*}
\]

\textbf{Scheme 47}

Treatment of the α-hydroxy carbamates 48a and 48b with aromatic nucleophiles under titanium(IV) chloride catalysis afforded the desired arylated products 117 in yields ranging from 68% to 78% (Scheme 48).\textsuperscript{21}

The oxazolidinones 118 reacted with methoxybenzene and 1,3-dimethoxybenzene in the presence of titanium(IV) chloride to afford the corresponding adducts 119 and 120 in 62–95% yields (Scheme 49).\textsuperscript{37}

\textbf{2.2.1.3 Organostannanes}

Racemic allyllic stannanes 122 reacted with N-acyliminium ions derived from α-ethoxy carbamate 121 to give the racemic adducts 123 and 124 in good to excellent yields, and with good diastereoselectivities (Scheme 50).\textsuperscript{17,18}

The racemic (E)-γ-OTBS derivative of allylic stannane 126 gave only the racemic syn adduct 127 from its reaction with α-ethoxy carbamates 125. The E- or Z-geometry of the stannane and the nature of the substituents on the iminium ion did not affect the syn preference of the reaction (Scheme 51).\textsuperscript{17}

The N-(2-methoxyphenyl) carbamates 128, however, underwent highly diastereoselective reactions (dr > 95:5) with the enantiomERICALLY enriched (S)-γ-silyloxyallylic stannane 129 to give the syn products 130 (Scheme 52). The reason for this enhanced diastereoselectivity, apparently due to the presence of the 2-methoxy group, was not clear.\textsuperscript{15}

The boron trifluoride–diethyl ether complex promoted reaction of (R)-131 and (S)-132 gave the syn,anti adduct 133 as the exclusive product (the matched case) while the corresponding reaction of (S)-131 and (S)-132 gave a 60:40
The reaction of the N-acyliminium ion 11 with allyltributyldistannane and enamine 36 led to the formation of product 136 in a yield of 76% \((\text{trans/cis} = 93:7)\) (Scheme 54).\textsuperscript{25}

Scheme 54

In the same study, the three-component coupling reaction of the N-acyliminium ion 11 with vinyl phenyl sulfide 40 and allyltributyldistannane provided the corresponding product 137 in 64% yield (Scheme 55).\textsuperscript{25}
Treatment of α-silyloxy carbamates 24 with allyltributylstannane in the presence of boron trifluoride–diethyl ether complex provided the desired adducts 138 in yields of 80–91% (Scheme 56).\textsuperscript{20}

The one-pot reaction of allyl carbamate 139 with benzaldehyde and an allenylstannane nucleophile in the presence of boron trifluoride–diethyl ether complex gave the alkyne product 140 in only 10% yield (Scheme 57).\textsuperscript{6}

Phenylmagnesium bromide and triethylaluminium each gave the corresponding three-component coupling products 143, with good diastereoselectivity, when they were added to a solution of 37 and 38 (Scheme 16), formed in situ from the reaction of 11 and 36 (Scheme 59).\textsuperscript{25}

A 3-alkoxyallenylzinc reagent reacted with the N-acyliminium ion 145, which was generated in situ from the treatment of the imine 144 with acyl chlorides, to provide products 146 in yields of 31–96% and with syn/anti ratios of 61:39 to 74:26 (Scheme 60).\textsuperscript{39}

2.2.1.4 Organometallic Reagents

The N-acyliminium ion 141, generated from the corresponding carbamate by electrochemical oxidation (Scheme 3), was treated with phenylmagnesium bromide to give the desired adduct 142 in 72% yield (Scheme 58).\textsuperscript{38}
2.2.1.5 Thioles

Treatment of N-methoxymethyl dipeptides 147 with thiol nucleophiles afforded thiol-substituted dipeptides 148 in 64–91% yields (Scheme 61).24

Scheme 61

2.2.1.6 Alkenes

Generation of N-acyliminium ions by low-temperature electrochemical oxidation and the use of a micromixer system were successfully applied to the synthesis of polymers of tert-butyl vinyl ether 150 (Scheme 62). The method allowed for the control of molecular-weight distribution.40

Scheme 62

2.2.1.7 Nitrogen Nucleophiles

Treatment of the α-isopropylthioglycine derivative 151 with N-bromosuccinimide provided bromosulfonylum salt 152 which formed the corresponding N-acyliminium ion 153. This intermediate underwent reaction with amines, amides and carbamates to afford products 154 in yields ranging from 12% to 80% (Scheme 63).22

Scheme 63

2.2.1.8 Alkyl Radicals

The N-acyliminium ion 141, generated from the corresponding carbamate by low-temperature electrochemical oxidation, was treated with heptyl iodide in the presence of hexabutyldistannane to afford product 155 in 57% yield (Scheme 64). Decreasing the rate of addition of the distannane had increased the yield from 31% to 57%.21,42

Scheme 64

2.2.2 Cycloaddition Reactions

The N-acyliminium ion 11 underwent smooth [4+2]-cycloaddition reactions with various alkenes and alkynes (Scheme 65). (E)-But-2-ene, (E)-1,2-diphenylethane and (Z)-propenylbenzene each gave the corresponding trans cycloadduct exclusively in 68%, 87%, and 88% yields, respectively, while (Z)-but-2-ene gave the cis cycloadduct exclusively. These results were consistent with a concerted reaction mechanism. The loss of stereoselectivity in the reaction of (Z)-1,2-diphenylethane (transcis = 45:55) and (E)-propenylbenzene (transcis = 44:56) suggested a stepwise mechanism in which bond rotation competed with cyclisation in the intermediate 160. It was concluded that the stereospecificity of the reactions of alkyl-substituted alkenes was consistent with a concerted mechanism, while that observed with aryl-substituted alkenes was consistent with a stepwise mechanism.8,43

2.2.3 Cationic Carboxyhydroxylation Reactions

Alkenes underwent cationic carboxyhydroxylation reaction with the N-acyliminium ion 161 to afford products 162 and 163 in combined yields of 60–85% (Scheme 66). The reaction of electrochemically generated 161 with hept-1-ene in the presence of water and triethylamine gave products 162 and 163 in 42% (dr = 74:26) and 25% (dr = 60:40) yields, respectively, while the reaction of vi-
The N-acyliminium ion 161 reacted with alkynes in water and triethylamine to give the corresponding cationic carbohydroxylating products 164 in yields of 47–70% (Scheme 67).\textsuperscript{44}

\[
\begin{align*}
\text{Bu}_3\text{N}^+ & \xrightarrow{\text{alkyne}} \text{Bu}_3\text{NI} \quad \text{(11, alkene/alkyne)} \\
\text{1-dodecene, (E)-2-buten, (Z)-2-buten,} & \quad \text{vinyltrimethysilane, vinyl acetate, cyclohexene,} \\
\text{1,3-cyclohexadiene, (E)-1,2-diphenylethene,} & \quad \text{(Z)-1,2-diphenylethene, (E)-1-propanethiobenzene,} \\
& \quad \text{(Z)-1-propanethiobenzene, 1-octyne, ethynylbenzene,} \\
& \quad \text{vinyltrimethysilane}
\end{align*}
\]

Scheme 65

3 Cyclic N-Acyliminium Ions

3.1 Synthesis of Cyclic N-Acyliminium Ion Precursors

Earlier methods for the synthesis of these precursors were reported in the previous review.\textsuperscript{2} 5-Alkoxypyrrolidinones 166 were synthesised from the reaction of 5-alkylidenepyrrolidinones 165 with \( m \)-chloroperoxybenzoic acid or dimethylidioxirane (DMD) (Scheme 68).\textsuperscript{45}

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{alkene}} \text{H}_2\text{O, Et}_3\text{N} \\
\text{161} & \xrightarrow{\text{alkene}} \text{R}^1 = \text{C}_8\text{H}_{11}, \text{TMS}
\end{align*}
\]

Scheme 66

nyltrimethysilane with 161 afforded products 162 and 163 in 25% and 54% yields, respectively. The reactions of (Z)-1,2-diphenylethene and (E)-1,2-diphenylethene with 161 afforded the 162-type products exclusively in 85% and 71% yields, respectively. The corresponding ketone of product 162 was obtained in 60% yield from the reaction of 161 with vinyl acetate under the same reaction conditions.\textsuperscript{44}

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{alkene}} \text{H}_2\text{O, Et}_3\text{N} \\
\text{161} & \xrightarrow{\text{alkene}} \text{R}^1 = \text{C}_8\text{H}_{11}, \text{TMS}
\end{align*}
\]

Scheme 66

3.1.1 Preparation of Iminium Ions in situ by Anodic Oxidation

Five-membered-ring N-acyliminium ions like 168 can be generated in situ by a one-pot radical decarboxylation–oxidation process using (diacetoxyiodo)benzene (DIB) and iodine. Decarboxylation–oxidation of 167 first formed the N-acyliminium ion 168 in situ, then addition of a nucleophile gave addition products 169 (Scheme 69).\textsuperscript{46,47} This one-pot decarboxylation–oxidation–nucleophilic addition reaction can be used for the preparation of \( \alpha \)-functionalised piperazinediones. Treatment of piperazinedione 170 with (diacetoxyiodo)benzene and iodine in methanol or acetic acid provided the corresponding \( \alpha \)-methoxy or \( \alpha \)-acetoxy diketopiperazines 171 in 55–83% yields.\textsuperscript{48}

Anodic oxidation of compounds 172 in a 1 M lithium perchlorate/nitromethane electrolyte solution in the presence of 50 mM acetic acid generated the N-acyliminium ions 173, which were trapped with thiophenol to give 2-phenylsulfonyl derivatives 174. Subsequent oxidation of these 2-phenylsulfonyl derivatives also gave rise to the corresponding N-acyliminium ions which, when generated in the presence of a nucleophile, gave the expected adducts 175 (Scheme 70, equation 1).\textsuperscript{49} The N-acyliminium...
ions 177 (R = H) can also be formed by low-temperature oxidation of the corresponding carbamates 176 in dichloromethane solution in the absence of nucleophiles (Scheme 70, equation 2). \(^{36,41,42,50}\)

Scheme 70

3.2 Five-Membered-Ring N-Acyliminium Ions

3.2.1 Reactions of Pyrrolidinone-Based N-Acyliminium Ions with Nucleophiles

3.2.1.1 Silicon-Based Nucleophiles

Allenylmethysilanes 179 react with 5-ethoxypyrrolidinones 178 in the presence of boron trifluoride–diethyl ether complex in acetone to give the corresponding dienes 180 (Scheme 71, equation 1). Reaction of allenylmethysilane (179, R² = R³ = H) with 178 gave 5-substituted pyrrolidinone products in 42–74% yields. Substituted allenylsilanes 179 resulted in formation of products 180 in yields of 65–85%. Product 180 with R¹ = H, R² = Me, R³ = H was obtained as the pure E-isomer, while product 180 with R¹ = H, R² = Ph, R³ = H was obtained as a 1:1 mixture of isomers. Treatment of the 5-hydroxypropylidenone 181 with allenylmethysilane under the same reaction conditions provided product 182 in 74% yield (Scheme 71, equation 2). \(^{51}\)

The reaction of 5-ethoxypyrrolidinone 183 with propargylsilanes 184a–c led to the formation of the 5-allenylpyrrolidinones 185a–c. Propargyltrimethylsilane (184a) and but-2-ynyltrimethylsilane (184b) gave allenyl products 185a and 185b in 55% and 64% yields, respectively, while phenyl-substituted propargylsilane 184c gave 128c in 18% yield (Scheme 72, equation 1). The reaction of 4-acetoxy-5-ethoxypyrrolidinone 186 with propargylsilane 184b under the same reaction conditions afforded the corresponding product 187 in 37% yield and with very high trans selectivity (trans/cis = 98:2) (Scheme 72, equation 2). \(^{51}\)

The N-acyliminium ion generated from 188 was trapped with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to give allylated product 189 in 71% yield (Scheme 73). \(^{46}\)

The zinc triflate catalysed reaction of allyltrimethylsilane with the 5-hydroxy-, 5-methoxy-, 5-acetoxy- and 5-sulfonylpyrrolidinones 190 afforded 5-allylated products 191 in moderate to good yields (Scheme 74). The 5-methoxy-pyrrolidinone derivative of 190 (R = OMe) underwent an addition reaction with a silyl enol ether \([\text{CH}_3=\text{C} (\text{OTMS})(\text{Ph})]\) to give the desired product in 69% yield. \(^{52}\)
Scheme 72

Scheme 73

Scheme 74

Pyrrolidinones 192, having a chiral C–N axis, reacted with allyltrimethylsilane or propargyltrimethylsilane in the presence of trimethylsilyl triflate to give products 193 in ≥99% ee (Scheme 75).54

Scheme 75

The reaction of 194a with silyl enol ether 195a in the presence of trisopropylsilyl triflate (5 mol%) afforded the corresponding ketone 196 in 42% yield and as a 75:25 mixture of diastereomers. The use of toluene as a solvent increased the yield (78%) but lowered the diastereoselectivity (60:40). Treatment of 194b with 195a under the same reaction conditions provided the desired ketone product as a mixture of isomers (dr = 60:40) in 55% yield. In that case, using toluene as a solvent did not change the diastereoselectivity but increased the yield to 74%. The reaction of 194b with 195b in dichloromethane or toluene afforded the desired ketone 196 with the same diastereomeric ratio of 63:37 and in 30% and 32% yields, respectively (Scheme 76).55 The reaction of the pyrrolidinone 194b with 195a under catalysis by bis(trifluoromethane)sulfinamide (5 mol%) or scandium(III) triflate (5 mol%) afforded the expected ketone as a mixture of isomers (60:40 and 58:42) and in yields of 78% and 81%, respectively.55

Scheme 76

The reaction of the 5-alkoxy pyrrolidinone 197 with triethylsilane in the presence of boron trifluoride–diethyl ether complex yielded products 198 in yields of ranging from 86% to 97% favouring the threo isomer (Scheme 77, equation 1). Pyrrolidinones 199 with triethylsilane yield-
ed exclusively the *three* isomer of product 200 under the same experimental conditions (Scheme 77, equation 2).\(^{45}\)

\[
\begin{align*}
\text{Ph} & \quad \text{TMS} \\
\text{O} & \quad \text{Ph} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

Scheme 77

Allyltrimethylsilane and trimethylsilyl cyanide reacted with the pyrrolidinone 201 under titanium(IV) chloride catalysis to give the corresponding 5-allylpyrrolidinone and 5-cyanoarylpyrrolidinones 202 in 83% (dr = 87:13) and 89% (dr = 90:10) yields, respectively (Scheme 78).\(^{56}\)

Treatment of pyrrolidinone 201 with CH\(_3\)=C(Ph)(OTMS) in the presence of bis(trifluoromethane)sulfonimide (5 mol%) or scandium(III) triflate (5 mol%) gave the corresponding ketone as a 1:1 mixture of isomers and in 81% and 40% yields, respectively. The reaction of 201 with CH\(_3\)=C(Ph)(TMS), CH\(_3\)=C(OTMS)(r-Bu), and Me\(_2\)=C(OMe)(OTMS) under catalysis by trisopropylsilyl triflate afforded the corresponding ketones in 93%, 50%, and 89% yields, respectively.\(^{54,55}\)

The boron trifluoride–diethyl ether complex catalysed reaction of 2-silyloxyfuran 204 and pyrrolidinone 203a afforded adduct 205a as a mixture of diastereomers (dr = 67:33) in 80% yield. The reaction of pyrrolidinone 203b under the same reaction conditions gave 205b in 27% yield and as a 1:1 mixture of diastereomers (Scheme 79).\(^{57,58}\)

Scheme 78

Scheme 79

Pyrrolidinones 206a,b reacted with trimethylsilyl cyanide in the presence of boron trifluoride–diethyl ether complex to give the 5-cyano-3-phenylpyrrolidinones 207 in 89% (dr = 87:13) and 90% (dr = 89:10) yields, respectively (Scheme 80).\(^{59}\)

The 5-methoxypyrrolidinone 208 underwent addition reactions with silyl enol ethers and allylsilanes in the presence of titanium(IV) chloride to give 5-allylpyrrolidinones 209 with good *cis* selectivity (Scheme 81).\(^{60}\)
The reaction of the 5-acetoxypyrrolidinones 210a with 195b (1.4 equiv) in the presence of triisopropylsilyle trifluorotrichlorosilane in dichloromethane or toluene gave the products 212 in 74% and 64% yields, and with a diastereomeric ratio of $>97:3$ and 90:10, respectively, in favour of the trans isomer (Scheme 82, equation 1). Treatment of 210a with 211a (2.0 equiv) in dichloromethane or toluene afforded the corresponding products 212 in 94% and 72% yields, respectively, and with moderate trans selectivity (74:26, 63:37, respectively). The reaction of 210a with 211b (1.4 equiv) provided product 212 in 74% yield and with a trans/cis ratio of $>97:3$. The reaction of 210b with 195a and 211a under the same reaction conditions provided the desired products in 80% and 67% yields and with diastereomeric trans/cis ratios of 87:13 and 30:70, respectively (Scheme 82, equation 1). Although the reactions of 210a with 195a,b and 211a afforded the desired products with high trans selectivity, the reaction of 210a with trimethylsilyl cyanide in the presence of triisopropylsilyle trifluorotrichlorosilane in dichloromethane or toluene gave 5-cyanopyrrolidinone 213 with cis/trans ratios of 57:43 and 60:40, in yields of 82% and 94%, respectively (Scheme 82, equation 2).\(^\text{54}\)

In a very similar study, treatment of the 4,5-diacetoxypyrrolidinones 210a, 206b, 214 with silyl nucleophiles in the presence of bis(trifluoromethane)sulfonimide (5 mol\%) in dichloromethane or acetonitrile provided the desired products 215 with moderate to excellent trans diastereoselectivity (Scheme 83, equation 1). The reaction of pyrrolidinone 210a with trimethylsilyl cyanide under the same reaction conditions yielded the 4,5-cis-pyrrolidinone 213 in 87% yield and with a diastereomeric ratio of 66:34 (Scheme 83, equation 2).\(^\text{55}\)

The pyrrolidinone 210a reacted with allyltrimethylsilane and the silyl enol ether of acetophenone in the presence of niobium(V) chloride to afford adducts 215 in 86% and 81% yields and with moderate trans selectivity (Scheme 84).\(^\text{61}\) The bismuth(III) triflate catalysed reaction of the pyrrolidinone 210a with allyltrimethylsilane provided the 5-allylated pyrrolidinone in 82% yield (trans/cis = 70:30).\(^\text{62}\)
The reactions of pyrrolidinones 206a, 210b with silicon nucleophiles in the presence of bis(trifluoromethane)sulfonimide (5 mol%) in acetonitrile gave products 216 in yields ranging from 55% to 95% (Scheme 85).55,61

Pyrrolidinone 217 reacted with triethylsilane in the presence of boron trifluoride–diethyl ether complex to give the product 218 in a yield of 83% and with high 4,5-trans diastereoselectivity (Scheme 86).64a

The reaction of pyrrolidinone 219 with triethylsilane in the presence of boron trifluoride–diethyl ether complex provided products 220 and 221 in 72–90% yields, in favour of the erythro isomer (erythro/threo = 87.5:12.5 to 79:21) (Scheme 87).55

Treatment of imides 222 with Grignard reagents afforded 5-hydroxy-5-alkylpyrrolidinones 223 which were treated with triethylsilane in the presence of boron trifluoride–diethyl ether complex to give the 4,5-trans adducts 224 exclusively in yields of 93–98% (Scheme 88).66

The reaction of imide 225 with Grignard reagents led to the formation of 5,5-disubstituted pyrrolidinones 226 in yields of 76–91%. Treatment of pyrrolidinones 226 with triethylsilane and boron trifluoride–diethyl ether complex provided the 4,5-trans isomer 227, exclusively, in 85–90% yields (Scheme 89).67

While the addition of Grignard reagents and hydrides to imides 222 was regioselective and gave adducts of the
type 223 (Scheme 88), the reactions of organolithium reagents in the presence of cerium(III) chloride with imides 228 afforded regioisomeric mixtures of adducts 229 and 230. The major adducts are 229. These were treated with triethylsilane (Scheme 90, equation 1) in the presence of boron trifluoride–diethyl ether complex to give 3,5-trans alkyl-substituted pyrrolidinones. Reaction of triethylsilane with pyrrolidinones 229a,230a and 229b,230b gave products in 55% and 63% yields, respectively, in ratios of (231+232)/233 = 73:27 and 75:25, respectively, while products 231c,232c were isolated exclusively in 51% yield from the reaction of pyrrolidinone 229c with triethylsilane. Similarly the reaction of trimethylsilyl cyanide with pyrrolidinones 229a,230a, 229b,230b, and 229d,230d gave products in 50%, 68%, and 55% yields, respectively, with ratios of (234+235)/236 = 73:27, 75:25 and 75:25. Products 234c,235c were obtained exclusively, in 52% yield, from the reaction of imide 229c with trimethylsilyl cyanide (Scheme 90, equation 2). 68

Whereas the C-2 and C-5 carbonyl groups of imides 228a–d reacted with organolithium reagents to give mixtures of the adducts 229 and 230 (Scheme 90), imides 237a–d reacted only at C-2 and gave products of type 238a–d with lithium trimethylsilylacetylide. Reduction of these 5-hydroxyppyrrolidinones 238a–d with triethylsilane and boron trifluoride–diethyl ether complex afforded products 239a–d with very high 4,5-trans selectivity (Scheme 91, equation 1). In contrast, the reduction of pyrrolidinones 238a–c with sodium cyanoborohydride and acetic acid afforded products 239a–c with moderate 4,5-cis selectivity (Scheme 91, equation 2); 238d gave the trans product as major isomer (trans/cis = 60:40). 69 The 4,5-cis isomer 239a was prepared as a single diastereomer from the titanium chloride catalysed reaction of 240 (Scheme 91, equation 3). 69

The addition reactions of allyltrimethylsilane to the 5-acetoxy-N-allylpyrrolidinones 214a and 241 afforded products 215 and 242 with 4,5-trans selectivity (Scheme 92, equation 1). The highest trans selectivity (88:12) was observed from the reaction of pyrrolidinone 214a with allytrimethylsilane in the presence of titanium(IV) chloride. The use of indium(III) chloride, tin(IV) chloride or trimethylsilane triflate as the Lewis acid in this reaction resulted in trans/cis product ratios of 80:20, 76:24 and 78:22, respectively. Treatment of pyrrolidinone 241 with allytrimethylsilane under catalysis by boron trifluoride–diethyl ether complex or titanium(IV) chloride gave 242 in 64:56 and 69:31 diastereomeric ratios, respectively. In the same study, the reaction of the pyrrolidinone 243a

![Diagram](image-url)

Scheme 90

Treatment of pyrrolidinone 248, the enantiomer of 245b, with trimethylsilyl cyanide provided products 249 and 250 in 93% yield and as a mixture of isomers (249/250 = 80/20) (Scheme 93, equation 2).71

The addition of the Grignard reagent benzylxoylmethylmagnesium chloride to imide 251 in the presence of mercury(II) chloride afforded the 5-hydroxypyrrolidinone 252 as a diastereomeric mixture. Treatment of this mixture with triethylsilane gave exclusively the 4,5-trans pyrrolidinone 253 in 61% yield (Scheme 94).72

Organolithium reagents were treated with imide 254 to afford 5-hydroxy-5-alkylpyrrolidinones 255. The 4,5-trans pyrrolidinones 256 were obtained from the reaction of these 5-hydroxypyrrolidinones 255 with triethylsilane in the presence of boron trifluoride–diethyl ether complex (Scheme 95). Similarly, the reaction of pyrrolidinone 257 with lithium reagents and then triethylsilane under the same reaction conditions provided 4,5-trans products 259 in yields of 50–66%.73

Treatment of 214a with 260 (1.5 equiv) under trisopropylsilyl triflate catalysis in dichloromethane or diethyl ether gave the desired product 261a in 50% yield and as a mixture of isomers (trans/cis = 85:15). The reaction of 243 with 195a (1.4 equiv) provided the product 261b with cis selectivity (cis/trans = 73:27) in 73% yield, while the reaction of 243 with 260 afforded product 261c with no selectivity (dr = 50:50) and in a yield of 55% (Scheme 96).74
Scheme 93

Scheme 94

Scheme 95

Scheme 96
The boron trifluoride–diethyl ether complex promoted reaction of acetonide 262 with allyltrimethylsilane or the trimethylsilyl enol ether of pinacolone provided the corresponding products 263 in 96% and 70% yields, as the single isomers, whereas the reaction of 262 with trimethylsilyl cyanide gave product 263 as a mixture of diastereomers [(2S,3S,4S)/ (2R,3S,4S) = 80:20] in 72% yield (Scheme 97).  

\[
\text{Scheme 97}
\]

3.2.1.2 Aromatic Nucleophiles

The reaction of benzene and its derivatives with the 5-hydroxypyrrrolidinone 264 in the presence of trifluoromethanesulfonic acid or trifluoroacetic acid provided 5-arylpyprrrolidinones 265 (Scheme 98). The reaction of benzene with 264 in the presence of trifluoromethanesulfonic acid gave 265 in 86% yield, while the less nucleophilic 1,4-dichlorobenzene gave 265 in 60% yield. 1,4-Dichlorobenzene did not react under trifluoroacetic acid catalysis; however, the more nucleophilic 1,4-dimethoxybenzene gave 265 in 67% yield.  

\[
\text{Scheme 98}
\]

Indole compounds 266a,b reacted with 4,5-diacetoxypyrrrolidinone 210a in the presence of niobium(V) chloride to give trans adducts 267a,b (Scheme 99). From 266a, a 90% yield of 267a (trans/cis = 86:14) was obtained, while 266b afforded 267b in 75% yield with a higher selectivity, trans/cis = 94:6.  

A boron trifluoride–diethyl ether complex mediated addition of 2-naphthol to 4,5-diacetoxypyrrrolidinone 268 gave exclusively the trans arylated product 269 in 76% yield (Scheme 100).  

\[
\text{Scheme 99}
\]

3.2.1.3 Organostannanes

5-Acetoxypyrrrolidinone 206a was subjected to cyanation reaction conditions with tributyltin cyanide under boron trifluoride–diethyl ether complex catalysis, and afforded the 5-cyanopyrrrolidinone 270 in 40% yield and with low 4,5-cis diastereoselectivity (cis/trans = 58:42) (Scheme 101).  

High 4,5-cis diastereoselectivity was obtained from the cyanation reaction of the 5-acetoxypyrrrolidinone 245a with tributyltin cyanide in the presence of boron trifluoride–diethyl ether complex. The use of dichloromethane or toluene as a solvent gave product 246 in 98% and 94% yields and with a cis/trans ratio of 89:11 and 90:10, respectively (Scheme 102).  

Treatment of the 5-acetoxypyrrrolidinone 271 with allyltributylstannane in the presence of magnesium bromide yielded exclusively the 4,5-cis product 272, and in quantitative yield (Scheme 103).  

Pyrrrolidinones 214a,b reacted with allylstannanes in the presence of Lewis acids to give the 5-allylated products 273a,b (Scheme 104, equation 1). In the reaction of 214a, titanium(IV) chloride gave the product 273a with a cis/trans ratio of 67:33, boron trifluoride–diethyl ether com-
Scheme 102

Complex gave a cis/trans ratio of 64:36 and titanium(IV) fluoride gave no selectivity (cis/trans = 50:50). In the reaction of pyrrolidinone 214b, boron trifluoride–diethyl ether complex and magnesium bromide each gave a 69:31 mixture of isomers, favouring the cis isomer, while titanium(IV) chloride gave a 64:36 mixture of cis/trans isomers. The reaction of pyrrolidinone 243b with allyltributyltin in the presence of boron trifluoride–diethyl ether complex provided the 5-allylated product 244b as a mixture of isomers (cis/trans = 80:20) (Scheme 104, equation 2).70

Scheme 103

Scheme 104

5-Hydroxypyrrolidinones 255, obtained from the reaction of organolithium reagents with imides 254, reacted with allyltributyltin in the presence of boron trifluoride–diethyl ether complex to afford 5-allyl-5-alkylypyrrolidinones 274. The reaction of the 5-butyl-substituted pyrrolidinone with allyltributylstannane provided 274 in the highest yield (65%, dr = 98:2) (Scheme 105, equation 1). The N-allyl analogue, pyrrolidinone 257, underwent addition reactions under the same conditions to afford products 275 in yields of 48–66% (Scheme 105, equation 2).73

The addition of organolithium compounds to imides 228a,b gave a mixture of the regioisomers 276 and 277. These isomers were subjected to allylation reactions with allyltributyltin in the presence of boron trifluoride–diethyl ether complex to give 5-alkyl-5-alkylypyrrolidinones 278, 279 and 280, respectively. The reaction of pyrrolidinone 228a with methylithium and then allyltributyltin gave a mixture of 278, 279 and 280 [(278+279)+280 = 73:27] in 53% yield. Treatment of 228b with butyllithium and then allyltributyltin gave only products 278 and 279 (278/279 = 88:12) in 55% yield (Scheme 106).68

3.2.1.4 Organometallic Reagents

Zinc alkynylides, generated in situ, reacted with 5-methoxyppyrrolidinone 281 in the presence of zinc triflate to afford the corresponding propargylic adducts 282 (Scheme 107).52
The reactions of organocupper reagents with pyrrolidinone 201 gave products 283 with good diastereoselectivities (dr = 87:13 to 88:12). Methyl and butyl cuprates gave 283 in 85% and 95% yields, respectively, while phenyl cuprate gave 283 in only 32% yield but also good diastereoselectivity (dr = 88:12) (Scheme 108).56

Treatment of the pyrrolidinone 284 with vinylmagnesium bromide in the presence of zinc chloride yielded the product 285 in 65% yield and with a trans/cis ratio of 80:20 (Scheme 109).77

The zinc chloride–diethyl ether complex promoted reaction of pyrrolidinone 286 with Grignard reagents led to the formation of products 287 in yields of 50–89%, with 4,5-trans selectivity (Scheme 110).78

Treatment of 4-benzzyloxy-5-hydroxytryptophan 288 with boron acids in the presence of boron trifluoride–diethyl ether complex afforded the corresponding trans-4,5-disubstituted pyrrolidinones 289. The use of 2-furanboronic acid, 2-benzofuranboronic acid, styrlyboronic acid, and potassium trans-styryl trifluoroborate all resulted in good to high trans selectivity. Phenylboronic acid did not react with the pyrrolidinone, but its electron-rich derivatives 4-methoxyphenylboronic acid and 3,4-dimethoxyphenylboronic acid provided 5-arylated pyrrolidinones in 48% and 74% yields (Scheme 111, equation 1). Reaction of 290, the 4-hydroxy analogue of pyrrolidinone 288, with 2-furanboronic acid and 3,4-dimethoxyphenylboronic acid gave 4,5-trans pyrrolidinones 291 in 65% (dr = 77:23) and 72% (dr = 72:28) yields, respectively. The use of 2-benzofuran boronic acid gave the 4,5-cis product in 56% yield and with a diastereomeric ratio of 92:8 (Scheme 111, equation 2).64a

The reaction of pyrrolidinones 210a.b and 292 with phenyl acetylenetrifluoroborate in the presence of boron trifluoride–diethyl ether complex afforded the corresponding products 293 in 69–89% yield, with very high 4,5-trans selectivity (trans/cis = 90:10) (Scheme 112).54b
The reaction of 294 with phenylacetylenetri fluoroborate under boron trifluoride–diethyl ether complex catalysis yielded the 4,5-\textit{cis} adduct 295 exclusively in 70% yield (Scheme 113).\textsuperscript{64b}

In a similar study, 5-acetoxy-2-pyrrolidinone 296 reacted with potassium organotrifluoroborates under boron trifluoride–diethyl ether complex catalysis to afford the corresponding products 297 and 298 with good 4,5-\textit{syn} diastereoselectivity and in yields of 65–87% (Scheme 114).\textsuperscript{79}

Scheme 114

3.2.1.5 Active Methylene Compounds

The reaction of 4-tert-butylmethyisilyloxy-5-methoxy-pyrrolidinone 208 with titanium enolates derived from the active methylene compounds 299a–d gave 4,5-disubstituted pyrrolidinones 300a–d. Except for the reaction of the enolate derived from 299b with 208, high 4,5-\textit{trans} selectivity was observed in these reactions (Scheme 115).\textsuperscript{50}

Scheme 115

3.2.1.6 Nitrile Nucleophiles (Ritter Reaction)

Treatment of pyrrolidinones 288 and 290 with nitriles in the presence of boron trifluoride–diethyl ether complex afforded the pyrrolo[2,3-\textit{d}]oxazoles 301 in yields of 80–93% (Scheme 116).\textsuperscript{80}

Scheme 116

ÎÛÊ×ÛÉ

×²¬»®³±´»½«´¿® ß¼¼·¬·±² Î»¿½¬·±²­ ±º Òóß½§´·³·²·«³ ×±²­ øÐ¿®¬ ×÷

Ì¸·­ ®»ª·»© ½±²¬·²«»­ ©·¬¸ ¬¸» ½¸»³·­¬®§ ±º Òó¿½§´·³·²·ó
«³ ·±²­ ¼»®·ª»¼ º®±³ ±¬¸»® º·ª»ó³»³¾»®»¼ ¸»¬»®±½§½´·½
¿²¼ ¸·¹¸»® ­§­¬»³­ ·² ¬¸» ²»¨¬ ·­­«» ±º Í§²¬¸»­·­òï

ß½µ²±©´»¼¹³»²¬
É» ¬¸¿²µ ¬¸» ß«­¬®¿´·¿² Î»­»¿®½¸ Ý±«²½·´ º±® ­«°°±®¬·²¹ ±«® ®»ó
­»¿®½¸ ·² ¬¸·­ ¿®»¿ò

Î»º»®»²½»­
øï÷ Ú±® Ð¿®¬ ××ô ­»»æ Ç¿¦·½·ô ßòå Ð§²»ô Íò Ùò Í§²¬¸»­·­ îððçô ëïíò
øî÷ Í°»½µ¿³°ô Éò Òòå Ó±±´»²¿¿®ô Óò Öò Ì»¬®¿¸»¼®±² îðððô ëêô
íèïéò
øí÷ Ó¿®§¿²±ººô Þò Ûòå Æ¸¿²¹ô Øò Ýòå Ý±¸»²ô Öò Øòå Ì«®½¸·ô ×ò Öòå
Ó¿®§¿²±ººô Ýò ßò Ý¸»³ò Î»ªò îððìô ïðìô ïìíïò
øì÷ Ð»¬®·²·ô Óòå Ì±®®»¹·¿²·ô Ûò Í§²¬¸»­·­ îððéô ïëçò
øë÷ ª¿² Ó¿¿®­»ª»»²ô Öò Øòå Ó»»­¬»®ô Éò Öò Òòå Ê»»®³¿²ô Öò Öò Òòå
Õ®«­»ô Ýò Ùòå Ø»®³µ»²­ô Ðò Øò Øòå Î«¬¶»­ô Úò Ðò Öò Ìòå
Ø·»³­¬®¿ô Øò Öò Ý¸»³ò Í±½òô Ð»®µ·² Ì®¿²­ò ï îððïô ççìò
øê÷ Ó»»­¬»®ô Éò Öò Òòå ª¿² Ó¿¿®­»ª»»²ô Öò Øòå Õ·®½¸­¬»·¹»®ô Õòå
Ø»®³µ»²­ô Ðò Øò Øòå Í½¸±»³¿µ»®ô Øò Ûòå Ø·»³­¬®¿ô Øòå
Î«¬¶»­ô Úò Ðò Öò Ìò ßÎÕ×ÊÑÝ îððìô ø··÷ô ïîîò
øé÷ Í«¹¿ô Íòå Ò¿¹¿µ·ô ßòå Ç±­¸·¼¿ô Öòó·ò Ý¸»³ò Ý±³³«²ò îððíô
íëìò
øè÷ Í«¹¿ô Íòå Ì­«¬­«·ô Çòå Ò¿¹¿µ·ô ßòå Ç±­¸·¼¿ô Öòó·ò Þ«´´ò Ý¸»³ò
Í±½ò Ö°²ò îððëô éèô ïîðêò
øç÷ Ò¿¹¿µ·ô ßòå Ì±¹¿·ô Óòå Í«¹¿ô Íòå ß±µ·ô Òòå Ó¿»ô Õòå Ç±­¸·¼¿ô
Öò Öò ß³ò Ý¸»³ò Í±½ò îððëô ïîéô ïïêêêò
øïð÷ Ð»¬®·²·ô Óòå Ì±®®»¹·¿²·ô Ûò Ì»¬®¿¸»¼®±² Ô»¬¬ò îððëô ìêô ëçççò
øïï÷ Þ»®¹»±¬ô Ñòå Ý±®­·ô Ýòå Ï¿½»³·ô Óò Ûòå Æ¿®¼ô Íò Æò Ñ®¹ò
Þ·±³±´ò Ý¸»³ò îððêô ìô îéèò
øïî÷ Ó»½±¦¦·ô Ìòå Ð»¬®·²·ô Óò Öò Ñ®¹ò Ý¸»³ò ïçççô êìô èçéðò
øïí÷ Ð»¿®­±²ô Éò Øòå Ô·²¼¾»½µô ßò Ýòå Õ¿³°ºô Öò Éò Öò ß³ò Ý¸»³ò
Í±½ò ïççíô ïïëô îêîîò
øïì÷ Õ¿¬®·¬¦µ§ô ßò Îòå Ë®±¹¼·ô Ôòå Ó¿§»²½»ô ßò Öò Ñ®¹ò Ý¸»³ò
ïççðô ëëô îîðêò
øïë÷ Õ¿¬®·¬¦µ§ô ßò Îòå Ó¿²¶«ô Õòå Í·²¹¸ô Íò Õòå Ó»¸»®ô Òò Õò
Ì»¬®¿¸»¼®±² îððëô êï îëëëò
øïê÷ Í¸±²±ô Ìòå Ó¿¬­«³«®¿ô Çòå Ì­«¾¿¬¿ô Õò Öò ß³ò Ý¸»³ò Í±½ò
ïçèïô ïðíô ïïéîò
øïé÷ Ý¸»ª¿´´·»®ô Úòå Þ»¿«¼»¬ô ×òå Ô» Ù®±¹²»½ô Ûòå Ì±«°»¬ô Ôòå
Ï«·²¬¿®¼ô ÖòóÐò Ì»¬®¿¸»¼®±² Ô»¬¬ò îððìô ìëô éêïò
øïè÷ Ó¿®­¸¿´´ô Öò ßòå Ù·´´ô Õòå Í»´»¬­µ§ô Þò Óò ß²¹»©ò Ý¸»³ò ×²¬ò
Û¼ò îðððô íçô çëíò
øïç÷ É¿²¹ô ÜòóØòå Ø¿±ô ÈòóÍòå É«ô ÜòóÚòå Ç«ô ÖòóÏò Ñ®¹ò Ô»¬¬ò
îððêô èô ííèéò
øîð÷ Í«¸ô ÇòóÙòå Í¸·²ô ÜòóÇòå Ö«²¹ô ÖòóÕòå Õ·³ô ÍòóØò Ý¸»³ò
Ý±³³«²ò îððîô ïðêìò
øîï÷ Ü»Ò·²²±ô Óò Ðòå Û´´»®ô Ýòå Û¬·»²²»ô Öò Þò Öò Ñ®¹ò Ý¸»³ò îððïô
êêô êçèèò
øîî÷ Ç¿±«¿²½¯ô Ôòå Î»²»ô Ôòå Ü¿«ô ÓòóÛò Ìò Øòå Þ¿¼»¬ô Þò Öò Ñ®¹ò
Ý¸»³ò îððîô éêô ëìðèò
øîí÷ É·³ô Öò Òòå ª¿² Ü·¶µô Îòå ª¿² Ó¿¿®­»ª»»²ô Öò Øòå Î«¬¶»­ô Úò
Ðò Öò Ìòå Ø»®³µ»²­ô Ðò Øò Øòå Ø·»³­¬®¿ô Øò Öò Ý¸»³ò Í±½òô
Ð»®µ·² Ì®¿²­ò ï îððïô îçðçò
øîì÷ Í«²ô Øòå Ó¿®¬·²ô Ýòå Õ»­­»´®·²¹ô Üòå Õ»´´»®ô Îòå Ó±»´´»®ô Õò
Üò Öò ß³ò Ý¸»³ò Í±½ò îððêô ïîèô ïíéêïò
øîë÷ Í«¹¿ô Íòå Ò·­¸·¼¿ô Ìòå Ç¿³¿¼¿ô Üòå Ò¿¹¿µ·ô ßòå Ç±­¸·¼¿ô Öò
Öò ß³ò Ý¸»³ò Í±½ò îððìô ïîêô ïìííèò
øîê÷ Ò·´­±²ô Óò Ùòå Ú«²µô Îò Ôò Ñ®¹ò Ô»¬¬ò îððêô èô íèííò
øîé÷ Í«²ô Øòå Ó±»´´»®ô Õò Üò Ñ®¹ò Ô»¬¬ò îððíô ëô íïèçò
øîè÷ Í«²ô Øòå Ó±»´´»®ô Õò Üò Ñ®¹ò Ô»¬¬ò îððîô ìô ïëìéò
øîç÷ Í«¹·«®¿ô Óòå Ø¿¹·±ô Øòå Ø·®¿¾¿§¿­¸·ô Îòå Õ±¾¿§¿­¸·ô Íò
Öò ß³ò Ý¸»³ò Í±½ò îððïô ïîíô ïîëïðò

íêé

øíð÷ ø¿÷ Ó»²¬·²µô Ùòå Ê¿² Ó¿¿®­»ª»»²ô Öò Øòå Ø·»³­¬®¿ô Øò Ñ®¹ò
Ô»¬¬ò îððîô ìô íìçéò ø¾÷ Þ»®µ¸»·¶ô Óòå Ü·¶µ·²µô Öòå Ü¿ª·¼ô Ñò
Îò Ðòå Í±²µ»ô Ìòå ×¶¦»²¼±±®²ô Üò Îòå Þ´¿¿«©ô Îò Øòå
Ê¿² Ó¿¿®­»ª»»²ô Öò Øòå Í½¸±»³¿µ»®ô Øò Ûòå Ø·»³­¬®¿ô Øò
Û«®ò Öò Ñ®¹ò Ý¸»³ò îððèô çïìò
øíï÷ Ù·¿®¼·²¿ô ßòå Ó»½±¦¦·ô Ìòå Ð»¬®·²·ô Óò Öò Ñ®¹ò Ý¸»³ò îðððô
êëô èîééò
øíî÷ Í¸·²ô ÜòóÇòå Ö«²¹ô ÖòóÕòå Í»±ô ÍòóÇòå Ô»»ô ÇòóÍòå Ð¿»µô ÍòóÓòå
Ý¸«²¹ô Çò Õòå Í¸·²ô Üò Óòå Í«¸ô ÇòóÙò Ñ®¹ò Ô»¬¬ò îððíô ëô
íêíëò
øíí÷ Ó¿®½¿²¬±²·ô Ûòå Ó»½±¦¦·ô Ìòå Ð»¬®·²·ô Óò Öò Ñ®¹ò Ý¸»³ò îððîô
êéô îçèçò
øíì÷ Þ¿´´·²·ô Îòå Ð¿´³»·»®·ô ßòå Ð»¬®·²·ô Óòå Ì±®®»¹·¿²·ô Ûò Ñ®¹ò
Ô»¬¬ò îððêô èô ìðçíò
øíë÷ Õ«¸¿µ¿®²ô Ýòå Ì¿²¹¼»²°¿·­¿´ô Õòå Õ±²¹­¿»®»»ô Ðòå Ð®¿¾°¿·ô
Íòå Ì«½¸·²¼¿ô Ðòå Ð±¸³¿µ±¬®ô Óòå Î»«¬®¿µ«´ô Êò Ì»¬®¿¸»¼®±²
Ô»¬¬ò îððéô ìèô îìêéò
øíê÷ Æ¸¿²¹ô Çòå Ü»Í½¸»°°»®ô Üò Öòå Ù·´¾»®¬ô Ìò Óòå Õ«³¿®ô Õò Íò
Íòå Õ´«³°°ô Üò ßò Ý¸»³ò Ý±³³«²ò îððéô ìðíîò
øíé÷ Ó»½±¦¦·ô Ìòå Ð»¬®·²·ô Óòå Ð®±º»¬¿ô Îò Ì»¬®¿¸»¼®±²æ
ß­§³³»¬®§ îððíô ïìô ïïéïò
øíè÷ Í«¹¿ô Íòå Ñµ¿¶·³¿ô Óòå Ç±­¸·¼¿ô Öòó·ò Ì»¬®¿¸»¼®±² Ô»¬¬ò
îððïô ìîô îïéíò
øíç÷ Î±§ô Þòå Ð»®»¦óÔ«²¿ô ßòå Ú»®®»·®¿ô Úòå Þ±¬«¸¿ô Ýòå Ý¸»³´¿ô Úò
Ì»¬®¿¸»¼®±² Ô»¬¬ò îððèô ìçô ïëíìò
øìð÷ Ò¿¹¿µ·ô ßòå Õ¿©¿³«®¿ô Õòå Í«¹¿ô Íòå ß²¼±ô Ìòå Í¿©¿³±¬±ô
Óòå Ç±­¸·¼¿ô Öò Öò ß³ò Ý¸»³ò Í±½ò îððìô ïîêô ïìéðîò
øìï÷ Ó¿®«§¿³¿ô Ìòå Í«¹¿ô Íòå Ç±­¸·¼¿ô Öòó·ò Ì»¬®¿¸»¼®±² îððêô
êîô êëïçò
øìî÷ Ó¿®«§¿³¿ô Ìòå Í«¹¿ô Íòå Ç±­¸·¼¿ô Öò Öò ß³ò Ý¸»³ò Í±½ò îððëô
ïîéô éíîìò
øìí÷ Í«¹¿ô Íòå Ò¿¹¿µ·ô ßòå Ì­«¬­«·ô Çòå Ç±­¸·¼¿ô Öò Ñ®¹ò Ô»¬¬ò
îððíô ëô çìëò
øìì÷ Í«¹¿ô Íòå Õ¿¹»§¿³¿ô Çòå Þ¿¾«ô Ùòå ×¬¿³·ô Õòå Ç±­¸·¼¿ô Öòó×ò
Ñ®¹ò Ô»¬¬ò îððìô êô îéðçò
øìë÷ Õ±­»µ·ô Çòå Õ«­¿²±ô Íòå ×½¸·ô Üòå Ç±­¸·¼¿ô Õòå Ò¿¹¿­¿µ¿ô Ìò
Ì»¬®¿¸»¼®±² îðððô ëêô èèëëò
øìê÷ Þ±¬±ô ßòå Ø»®²¿²¼»¦ô Îòå Í«¿®»¦ô Ûò Öò Ñ®¹ò Ý¸»³ò îðððô êëô
ìçíðò
øìé÷ Þ±¬±ô ßòå Ø»®²¿²¼»¦ô Îòå Í«¿®»¦ô Ûò Ì»¬®¿¸»¼®±² Ô»¬¬ò îðððô
ìïô îèççò
øìè÷ Ý¸¿·ô Ýò Ôò Ôòå Û´·¨ô Öò ßòå Ø«´»¿¬¬ô Ðò Þò Ì»¬®¿¸»¼®±² îððëô
êïô èéîîò
øìç÷ Õ·³ô Íòå Ø¿§¿­¸·ô Õòå Õ·¬¿²±ô Çòå Ì¿¼¿ô Óòå Ý¸·¾¿ô Õò Ñ®¹ò
Ô»¬¬ò îððîô ìô íéíëò
øëð÷ Ó¿®«§¿³¿ô Ìòå Ó·¦«²±ô Çòå Í¸·³·¦«ô ×òå Í«¹¿ô Íòå Ç±­¸·¼¿ô
Öòó·ò Öò ß³ò Ý¸»³ò Í±½ò îððéô ïîçô ïçðîò
øëï÷ Õ¿®­¬»²­ô Éò Úò Öòå Õ´±³°ô Üòå Î«¬¶»­ô Úò Ðò Öò Ìòå Ø·»³­¬®¿ô
Øò Ì»¬®¿¸»¼®±² îððïô ëéô ëïîíò
øëî÷ Î±²¿´¼±ô ßòå Î±¾»´´±ô Ôò Ùò Í§²´»¬¬ îððëô îîçéò
øëí÷ Ù±¼º®»§ô Ýò Îò ßòå Í·³°µ·²­ô Òò Íòå É¿´µ»®ô Óò Üò Í§²´»¬¬
îðððô íèèò
øëì÷ Þ»² Ñ¬¸³¿²ô Îòå Þ±«­¯«»¬ô Ìòå Ú±«­­»ô ßòå Ñ¬¸³¿²ô Óòå
Ü¿´´¿ô Êò Ñ®¹ò Ô»¬¬ò îððëô éô îèîëò
øëë÷ Þ»² Ñ¬¸³¿²ô Îòå Þ±«­¯«»¬ô Ìòå Ñ¬¸³¿²ô Óòå Ü¿´´¿ô Êò Ñ®¹ò
Ô»¬¬ò îððëô éô ëííëò
øëê÷ Þ¿«­­¿²²»ô ×òå Ý¸·¿®±²·ô ßòå Î±§»®ô Öò Ì»¬®¿¸»¼®±²æ
ß­§³³»¬®§ îððïô ïîô ïîïçò
øëé÷ Õ»²¼»ô ßò Íòå Ø»®²¿²¼±ô Öò ×ò Óòå Ó·´¾¿²µô Öò Þò Öò
Ì»¬®¿¸»¼®±² îððîô ëèô êïò
øëè÷ Õ»²¼»ô ßò Íòå Ø»®²¿²¼±ô Öò ×ò Óòå Ó·´¾¿²µô Öò Þò Öò Ñ®¹ò Ô»¬¬ò
îððïô íô îëðëò
øëç÷ Ñ¾¿ô Óòå Ó·¬¿ô ßòå Õ±²¼±ô Çòå Ò·­¸·§¿³¿ô Õò Í§²¬¸ò
Ý±³³«²ò îððëô íëô îçêïò
øêð÷ Ô»²²¿®¬¦ô Óòå Í¬»½µ¸¿²ô Ûò Í§²´»¬¬ îðððô íïçò
øêï÷ ß²¼®¿¼»ô Ýò Õò Æòå Î±½¸¿ô Îò Ñòå Î«­­±©­µ§ô Üòå Ù±¼±§ô Óò
Òò Öò Þ®¿¦ò Ý¸»³ò Í±½ò îððëô ïêô ëíëò

Í§²¬¸»­·­ îððçô Ò±ò íô ííçŠíêè

w Ì¸·»³» Í¬«¬¬¹¿®¬ i Ò»© Ç±®µ


(64) (a) Morgan, I. R.; Yazici, A.; Pyne, S. G. Tetrahedron 2008, 64, 1409. (b) Unpublished results from these laboratories.
APPENDIX 2: INTERMOLECULAR ADDITION REACTIONS OF N-ACYLIMINIUM IONS (PART 2)
Intermolecular Addition Reactions of N-Acyliminium Ions (Part II)\textsuperscript{1}

Arife Yazici, Stephen G. Pyne\textsuperscript{*}

School of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia
Fax +61(2)42214987; E-mail: spyne@uow.edu.au

Received 22 September 2008; revised 7 October 2008

Abstract: This review highlights the advances in the literature up to July 2008 on the intermolecular reactions of acyclic and cyclic N-acyliminium ions. This is an update of an earlier review in 2000 on this topic and does not include intramolecular addition reactions to N-acyliminium ions which was recently reviewed. This review is presented in two parts, with the first part having dealt with acyclic and pyrrolidinone-based N-acyliminium ions. Part II continues with other five-membered heterocyclic derivatives and higher systems.

Part I

1 Introduction
2 Acyclic N-Acyliminium Ions
2.1 Synthesis of Acyclic N-Acyliminium Ion Precursors
2.2 Reactions of Acyclic N-Acyliminium Ions
2.2.1 Reactions with Nucleophiles
2.2.2 Cycloaddition Reactions
2.2.3 Cationic Carboxylation Reactions
3 Cyclic N-Acyliminium Ions
3.1 Synthesis of Cyclic N-Acyliminium Ion Precursors
3.1.1 Preparation of Iminium Ions in situ by Anodic Oxidation
3.2 Five-Membered-Ring N-Acyliminium Ions
3.2.1 Reactions of Pyrrolidinone-Based N-Acyliminium Ions

Part II

3.2.2 Reactions of N-Acylpyrrolidine-Based N-Acyliminium Ions with Nucleophiles
3.2.2.1 Silicon-Based Nucleophiles
3.2.2.2 Aromatic Nucleophiles
3.2.2.3 Organostannanes
3.2.2.4 Organometallic Reagents
3.2.2.5 Carbonyl Compounds
3.2.2.6 Alkyl Radicals
3.2.2.7 Thiols
3.2.2.8 Active Methylene Compounds
3.2.3 Reactions of Oxazolidinone-Based N-Acyliminium Ions with Nucleophiles
3.2.3.1 Silicon-Based Nucleophiles
3.2.3.2 Organometallic Reagents
3.2.3.3 Active Methylene Compounds
3.2.4 Cyclocondensation Reaction of N-Aminodinyl Iminium Ions
3.3 Reactions of Six-Membered-Ring N-Acyliminium Ions
3.3.1 Reactions of Piperidinone-Based N-Acyliminium Ions with Nucleophiles
3.3.1.1 Silicon-Based Nucleophiles
3.3.1.2 Organostannanes
3.3.1.3 Organometallic Reagents
3.3.2 Reactions of N-Acylpyrrolidine-Based N-Acyliminium Ions
3.3.2.1 Reactions with Nucleophiles
3.3.2.2 Cycloaddition Reactions

SYNTHESIS 2009, No. 4, pp 0513–0541
Advanced online publication: 02.02.2009
DOI: 10.1055/s-0028-1083346; Art ID: E22708SS
© Georg Thieme Verlag Stuttgart - New York

3.3.3 Reactions of Piperazine-Based N-Acyliminium Ions with Nucleophiles
3.3.3.1 Silicon-Based Nucleophiles
3.3.3.2 Aromatic Nucleophiles
3.3.4 Reactions of Pyridine-Based N-Acyliminium Ions with Nucleophiles
3.3.4.1 Organometallic Reagents
3.3.5 Reactions of N,O-Acetal Oxathiazinan N-Sulfonyliminium Ions with Nucleophiles
3.3.5.1 Organometallic Reagents
3.4 Reactions of Seven-Membered-Ring N-Acyliminium Ions
3.4.1 Reactions with Silicon-Based Nucleophiles
3.4.2 Cycloaddition Reactions
3.5 Reactions of Bicyclic N-Acyliminium Ions
3.5.1 Reactions with Nucleophiles
3.5.1.1 Silicon-Based Nucleophiles
3.5.1.2 Organometallic Reagents
3.5.1.3 Enamines
3.5.2 Cycloaddition Reactions
3.6 Other Systems
3.6.1 Silicon-Based Nucleophiles
4 Stereochemical Outcomes
5 Conclusions

Key words: N-acyliminium ion, nucleophilic addition, cycloaddition, aromatic electrophilic substitution, radical addition, peptides, pyrrolidines, piperidines

3.2.2 Reactions of N-Acylpyrrolidine-Based N-Acyliminium Ions with Nucleophiles

3.2.2.1 Silicon-Based Nucleophiles

Treatment of the N-acyliminium ion 302 with benzyltrimethylsilanes afforded 2-benzylated pyrrolidines 303, 4-fluorobenzyl-, benzyl-, and 2-methylbenzyltrimethylsiline did not react with the N-acyliminium ion. Reactions of 3,5-dimethylbenzyl-, 4-methylbenzyl-, 2,4,6-trimethylbenzyl-, 4-methoxybenzyl-, and 2,3,4,5,6-pentamethylbenzyltrimethylsilanes gave the corresponding products in 12–88% yields. Use of 4-methylbenzyllstannanes (0.1 equiv.), as an additive in the reactions of 4-fluorobenzyltrimethylsilane and 4-methylbenzyltrimethylsilane, resulted in 50% and 97% yields of 303, respectively (Scheme 117).\textsuperscript{30}

The reaction of N-Boc-2-methoxyxpyrrolidine (304) with silicon nucleophiles in an ionic liquid, BMI InCl\textsubscript{3}, led to the formation of 2-substituted pyrrolidines 305 in yields of 76–80% (Scheme 118).\textsuperscript{81}

Treatment of pyrrolidinone 304 with similar silicon nucleophiles in the presence of indium(III) chloride under solvent-free conditions afforded the corresponding prod-
ucts 305 in 92–100% yields (Scheme 119). The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.\textsuperscript{82b}

In a similar study, pyrrolidine 304 reacted with silicon nucleophiles under catalysis by zinc triflate to afford the desired adducts 305 in 68–80% yields (Scheme 120).\textsuperscript{32}

The reactions of silicon nucleophiles with pyrrolidine 304 in the presence of bis(trifluoromethane)sulphonimide or trisopropylsilil triflate under solvent-free conditions afforded the corresponding adducts 305 in good to excellent yields (Scheme 121). It was found that 0.3 mol% of bis(trifluoromethane)sulphonimide catalysed the reaction of allytrimethylsilane, while the silyl enol ether of aceto-phenone required 1.0 mol% of catalyst. The trimethylsilyl enol ether of cyclohexanone and the trisopropylsilyl ether of methyl isobutyrate and trimethylsiloxyfuran required 5 mol% of bis(trifluoromethane)sulphonimide. The use of 1 mol% of trisopropylsilyl triflate as a Lewis acid in these reactions gave the desired adducts in the same or similar yields.\textsuperscript{83}

Chiral 2-methoxypyrrrolidines 306a,b underwent addition reactions with 2-\textit{tert}-butylmethylsiloxyfuran in the presence of a catalytic amount of titanium(IV) chloride or trimethylsilyl triflate in dichloromethane at –78 °C to form only two out of four possible diastereomeric prod-

### Biographical Sketches

**Arife Yazici** obtained her MSc degree in chemistry at Hacettepe University- Ankara (Turkey) in 2005. She is currently doing her PhD studies with Professor Stephen Pyne at the University of Wollongong. Her area of study is the total synthesis of Stemona alkaloids.

**Stephen G. Pyne** is a Professor of Chemistry at the University of Wollongong (UOW) and Chair of the Division of Organic Chemistry of the Royal Australian Chemical Institute. He obtained his BSc (Hons) degree at the University of Adelaide with Dr. Ralf Massey-Westrop and his PhD degree with Professor Lew Mander (Australian National University) in 1979. After post-doctoral positions with Professor Phil Fuchs (Purdue) and Professor E. J. Corey (Harvard), he was appointed a lecturer at UOW in 1985. His research interests include the total synthesis of bioactive alkaloids, natural products chemistry, drug design and synthesis, and fullerene chemistry.
Scheme 121

NuTMS or NuTIPS (1.4 equiv) → R

47–100%

Scheme 122

Silyloxyfurans 310 reacted with 2-alkoxypyrrolidines 309 upon exposure to trimethylsilyl triflate. The N-Boc-protected pyrrolidine derivative 309a gave the best yield of 82% and the highest diastereomeric ratio of 95:5 when R¹ = H (Scheme 123).84

The reaction of allenyltrimethylsilane with the 2-ethoxy-pyrrolidine 313 in the presence of boron trifluoride–diethyl ether complex provided the 2-substituted pyrrolidine 314 in 49% yield (Scheme 124). Treatment of N-tosyl-2-hydroxy- pyrrolidinone under the same reaction conditions afforded the N-tosyl analogue of piperidine 314 in 74% yield.80

Scheme 123

N-Carbo- benzylcloroxy-2-hydroxy pyrrolidine (315) reacted with a silyl enol ether in the presence of trimethylsilyl triflate (1.0 equiv) in dichloromethane to afford the 2-substituted pyrrolidine 316 in 96% yield (Scheme 125).85

Scheme 124

The N-acyliminium ion which was generated by anodic oxidation of 317 was treated with silicon nucleophiles and afforded the corresponding alkylated products 318 (Scheme 126, equation 1). Similarly, the reactions of allyltrimethylsilane with the in situ generated N-acyliminium ion of amides and carbamates 319 under the same reaction conditions gave products 320 in 73–97% yields (Scheme 126, equation 2).89

Treatment of the immobilised amines 321a,b with boron trifluoride–diethyl ether complex led to the formation of N-acyliminium ions 322a,b which were trapped with al- lytrimethylsilane to give the desired adducts 323 (Scheme 127). Cleavage of the adduct from the resin with 1 M sodium methoxide in tetrahydrofuran–methanol gave the trans,2,4-disubstituted pyrrolidines 324a,b in 81% and 52% yields, respectively.5
Decarboxylation and oxidation of the proline derivative 325 with (diacetoxyiodo)benzene and iodine gave the corresponding N-acryliminium ion. The reaction of allyltrimethylsilane with the latter under boron trifluoride-diethyl ether complex catalysis gave the 2-allylated product 326 in 91% yield (Scheme 128). The reaction did not take place in the absence of the Lewis acid: only the corresponding 2-hydroxyxypyrrolidine was isolated. Treatment of 325 with (trimethylsilyloxy)cyclohexene and trimethylsilyloxofuran under the same reaction conditions gave addition products in 68% and 81% yields, respectively. In a similar study, treatment of 325 with isopropenyl acetate (5.0 equiv) in the presence of boron trifluoride-diethyl ether complex afforded the expected product in 58% yield.

When the one-pot decarboxylation–oxidation–alkylation methodology was applied to the 4-trimethylacetoxy-L-proline derivative 167a, the desired allylated product 327 was isolated in 91% yield with a cis/trans ratio of 85:15 (Scheme 129).

The reaction of the N-acylprolines 328a and 328b with allyltrimethylsilane in the presence of titanium(IV) chloride yielded the allylated products 329a and 329b in 80% and 53% yields, respectively (Scheme 130). The 3-substituted N-Cbz pyrrolidines 330a–e reacted with allyltrimethylsilane, cyanotrimethylsilane, and tert-butyll(1-ethoxyvinyl)oxydime-thylsilane in the presence of boron trifluoride-diethyl ether complex to give products 331a–e. 3-Carbamoyl-2-methoxypyrrolidines 330a–c and 3-iodo-2-methoxypyrrolidine 330d gave the adducts in moderate to excellent yields and with 2,3-trans selectivity (Scheme 131, equation 1), while 3-azido-2-methoxypyrrolidine 330e gave the adduct 331e in 49% yield and with high 2,3-cis selectivity (88:12) (Scheme 131, equation 2). The 2,3-trans selectivity in the reactions of 330a–d was suggested to arise from neighbouring-group participation of the R1 group (R1 = NHCO₂H or I). The reaction of 2-ethoxy-4-butylpyrrolidine 332 with allylsilanes afforded the corresponding adducts 333 in 30–40% yields as isomeric mixtures (Scheme 132). The diastereomeric ratios were not determined. However, when R = Me, the mixture was converted into a 80:20 mixture of indolizidines, with the major isomer having arisen from the initial 2,5-trans adduct.
The reaction of pyrrolidine 334 with silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex provided the desired adduct 335 with complete 2,4-cis selectivity (Scheme 133).\(^7\)

Treatment of pyrrolidine 336 with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the 2,3-trans product 337 in 99% yield (Scheme 134).\(^9\)

The cyano group was introduced into the N-Boc pyrrolidines 338a,b stereoselectively (Scheme 135). The reaction of 338a with trimethylsilyl cyanide (3.0 equiv) in the presence of trifluoromethanesulfonic acid (1.5 equiv) in acetonitrile at \(-40^\circ\text{C}\) resulted in the best yield (90%) and diastereomeric ratio (96:4). The use of tetrahydrofuran, toluene and dichloromethane as solvents in this reaction gave the product 339a in poor to good yields (19–60%) with reduced diastereoselectivities (dr = 87:13 to 90:10). Using trimethylsilyl triflate as catalyst gave product 339a in 67% yield with a diastereomeric ratio of 93:7. The reaction of 338b with trimethylsilyl cyanide in the presence of boron trifluoride–diethyl ether complex (1.5 equiv) in dichloromethane afforded product 339b in the highest yield (89%) and diastereomeric ratio of 92:8. The use of tin(IV) chloride and trimethylsilyl triflate as Lewis acids in toluene provided product 339b in 32% and 68% yields and with diastereomeric ratios of 66:33 and 75:25, respectively. The high diastereoselectivity was suggested to be the result of attack of the nucleophile from the face anti to the C-5 substituent. This substituent was proposed to adopt a pseudo-axial orientation to minimise A\(^1,2\) strain with the N-Boc group.\(^4\)

Scheme 131

Scheme 132

Scheme 133

Scheme 134

Scheme 135

The 2,3-O-isopropylidene-protected pyrrolidine 340 reacted with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to give the 2-allylated pyrrolidine 341 in 52% yield and with complete 2,3-trans selectivity (trans/cis = 100:0) (Scheme 136). Magnesium bromide, tin(IV) chloride, dichlorodisopropoxypyritani-um(IV), and ytterbium(III) triflate were found to be ineffective in this reaction.\(^5\)
Scheme 136

The 5-substituted 2,3-O-isopropylidene-protected pyrrolidines 342 and 344 gave allylated products 343 and 345, respectively, with exclusive 2,3-trans selectivity and good yields, when they were treated with allyltrimethylsilane in the presence of boron trifluoride-diethyl ether complex (Scheme 137). The allyltrimethylsilane attacked from the exo face of the bicyclic aminal, independent of the C-4 and C-5 substituents and their configurations. The lower diastereoselectivities observed when the stronger Lewis acid mixture of boron trifluoride-diethyl ether complex and trimethylsilyl triflate was employed was thought to be due to initial cleavage of the bicyclic aminal prior to nucleophilic attack.92

Scheme 137

Treatment of pyrrolidinone 346 with Grignard reagents and then triethylsilane in the presence of boron trifluoride-diethyl ether complex afforded adducts 347 and 348. This reaction sequence using methylmagnesium iodide gave adduct 347 in 80% yield and with high 3,5-cis selectivity, while that using of 4-benzoyloxyphenylmagnesium bromide provided only the 3,5-trans adduct 348 in 58% yield (Scheme 138).72

3.2.2.2 Aromatic Nucleophiles

Treatment of benzene derivatives with the proline derivatives 328a–d in the presence of titanium(IV) chloride or tin(IV) chloride gave the arylated adducts 349 in 31–71% yields. The prolines 328a, c (R1 = CO2Me or Cbz) gave exclusively the 2,5-cis products (Scheme 139, equation 1), whereas the prolines 328b, d (R1 = CHO or Bz) yielded the arylated adducts 349 as a mixture of isomers favouring the trans isomer (Scheme 139, equation 2).86
3.2.2.3 Organostannanes

Treatment of benzylationbutylstannane and 4-methylbenzyltributylstannane with the N-acyliminium ion 302 provided the 2-benzylated pyrrolidines 350 in 51% and 71% yields, respectively (Scheme 140).\textsuperscript{50}

\[
\text{CO}_2\text{Me} + \text{Bu}_3\text{Sn} + \text{X} \rightarrow 50^\circ\text{C} \rightarrow \text{CH}_2\text{Cl}_2 \rightarrow \text{CO}_2\text{Me}
\]

Scheme 140

A cinnamylstannane reacted with pyrrolidines 351a–c in the presence of boron trifluoride–diethyl ether complex to give adducts 352a–c. While pyrrolidine 351a gave the product 352a in 75% yield and as a single diastereomer, 351b and 351c gave the products 352b and 352c in yields of 73% and 54%, and with a diastereomeric ratio of 70:30 and 75:25, respectively (Scheme 141, equation 1). When pyrrolidine 353 was treated under the same reaction conditions, the addition product 354 was obtained in 56% yield as a 50:50 mixture of diastereomers (Scheme 141, equation 2). In contrast to the reactions reported in Schemes 136 and 137, a ring-opened monocyclic iminium ion intermediate was proposed for the reactions of 351a–c.\textsuperscript{93}

3.2.2.4 Organometallic Reagents

The N-acyliminium ion 302 underwent reactions with Grignard reagents to afford 2-substituted pyrrolidines 355 in moderate to good yields. The reaction took place with alkyl-, alkenyl-, alkynyl- and arylmagnesium halides (Scheme 142).\textsuperscript{58}

Treatment of organozinc and organoaluminium reagents with the N-acyliminium ion 302 provided 2-ethylpyrrolidine 356 in 55–74% yields (Scheme 143). The use of diethylzinc, ethylzinc iodide, triethyaluminium and diethylaluminium chloride gave the ethylated product in 74%, 65%, 72%, and 55% yields, respectively.\textsuperscript{38}

The reactions of zinc alkynylides, prepared in situ, with 2-methoxypyrrolidine 304 in the presence of zinc trflate afforded the corresponding 2-substituted products 357 (Scheme 144).\textsuperscript{52}

Alkynes reacted with 2-methoxypyrrolidines 309b,c in the presence of copper(1) bromide in water at 40–50 °C under sonication conditions to afford 2-substituted pyrrolidines 358 (Scheme 145).\textsuperscript{94}

As an extension of an earlier study,\textsuperscript{95b} the reaction of the racemic 2,3-dihydroxypryrrolidine 359 with an alkenylboronate led to the 2,3-\textit{cis} product 360 in 99% yield and with high 2,3-\textit{cis} selectivity (\textit{cis/trans} = 98:2) (Scheme 146).\textsuperscript{95b}

Organocopper reagents were treated with 3-substituted 2-methoxypryrrolidines 361 in the presence of boron trifluoride–diethyl ether complex to afford adducts 362 in 50–97% yields after Boc deprotection. These reactions showed 2,3-\textit{trans} selectivity (\textit{trans/cis} = 60:40 to 91:9) (Scheme 147). The \textit{trans} selectivity increased with the use of bulky organocopper reagents.\textsuperscript{36}
reaction took place between 2-phenylsulfonylpyrrolidine and the silylcuprate reagent even in the absence of the Lewis acid. It was postulated that either the copper behaves as a Lewis acid to generate the N-acyliminium ion, or the reaction follows an S_N2 mechanism.\(^{34}\)

![Scheme 143](image)

The 3,5-disubstituted N-Boc proline 365 reacted with 2-methylpropenyl lithium and trans-1-lithiopropene in the presence of copper bromide–dimethylsulfide complex and boron trifluoride–diethyl ether complex to give the 2,5-trans products 366 (Scheme 149).\(^{97}\)

![Scheme 147](image)

3.2.2.5 Carbonyl Compounds

The reaction of N-Boc-2-ethoxypyrrrolidine 309a with the N,O-silyketene acetal, itself prepared in situ by treatment of N-propionylxazolidin-2-one 367 with trimethylsilyl triflate and triethylamine, provided a 67:33 mixture of the 2-substituted pyrrolidines 368 and 369 in 45% yield (Scheme 150).\(^{38}\)

The 5-methoxypyrrroline derivative 371 reacted with trimethylsilyloxofuran compounds, themselves generated in situ by treatment of butenolides 370 with trimethylsilyl triflate under basic conditions, in the presence of trimethylsilyl triflate at –78 °C to give a mixture of diastereomeric adducts. Addition of an excess amount of trimethylsilyl triflate to these adducts afforded deprotected pyrrolidines 372 as a mixture of four diastereomers (Scheme 151).\(^{99}\)

The titanium enolates of N-acrylazolidinones 373a–d reacted with N-tert-butoxycarbonyl-2-ethoxypyrrrolidine (309a) to afford the corresponding 2-substituted pyrrolidines 374a–d and 375a–d. Treatment of pyrrrolidine 309a with 373a and 373b in the presence of titanium(IV)
The reaction of 2-alkoxy pyrroline 309b with N-acloyloxazolidinones 373a and 373b in the presence of titanium(IV) chloride provided the corresponding products in 67% and 57% yields, and with product ratios (376/377) of 91:9 and 83:17, respectively. Treatment of 309c with 373a and 373b under the same reaction conditions resulted in 33% and 50% yields, respectively and with product ratios (376/377) of 91:9 and 86:14, respectively (Scheme 153).  

The titanium enolates of 378a and 378b reacted with 2-alkoxy pyrrolines 309a and 309b to afford the N-Boc- and N-Cbz-2-substituted pyrrolines 379 and 380. The reactions of 309a with 378a and 378b in the presence of titanium(IV) chloride and diisopropylethylamine gave products 379 and 380 with high selectivity >95:<5 in yields of 70% and 81%, respectively. Treatment of 309b with 378b under the same experimental conditions afforded 379 and 380 in 73% yield, with the same selectivity (Scheme 154).  

The 2-alkoxy pyrrolines 304 and 309a, when treated with the titanium enolate of N-acloxyazolidinone 381a (X = O) or its thio analogue 381b (X = S), respectively,
Scheme 155

gave the addition products 382a,b as single isomers in 82–84% yields (Scheme 155).100

The titanium enolate of 2-pyridylthio ester 384 was treated with 2-methoxypropyrrrolidine 383 in the presence of titanium(IV) chloride to give the 2,3-trans product 385 in 25% yield and with a diastereomeric ratio of 92:8 (Scheme 156).101

Scheme 156

The boron enolates of the oxazolidin-2-ones 373a,b were treated with N-tert-butylxoycarbonyl-2-ethoxypropyrrrolidine (309a) in the presence of dibutylboryl triflate (2.0 equiv) to afford the corresponding N-Boc-2-substituted pyrrolidines 374a,b and 375a,b. The reaction using 373a gave a mixture of 374a and 375a (dr = 93:7) in 50% yield, while the reaction with 373b under the same reaction conditions provided products 374b/375b in 55% yield (dr = 98:2) (Scheme 157).106

Scheme 157

3.2.2.7 Thiols

Anodic oxidation of pyrrrolidine 386 in a 1 M lithium perchlorate/nitromethane electrolytic solution in the presence of 50 mM acetic acid gave an intermediate N-acyliminium ion, which was trapped with thiophenol to afford the 2-phenylsulfonyl pyrrrolidine 317 in 91% yield (Scheme 159).107

Scheme 159

Treatment of amide or carbamate proline derivatives 319a and 319b with thiophenol under the same electrolytic oxidative conditions gave adducts 319c,d in 86% yield as a 50:50 mixture of diastereomers (Scheme 160).108

Scheme 160

Synthesis 2009, No. 4, 513–541 © Thieme Stuttgart · New York
3.2.2.8 Active Methylene Compounds

1,3-Dicarbonyl compounds were treated with \( \alpha \)-methoxy-pyrrolidine 304 in the presence of indium(III) chloride under solvent-free conditions to afford the 2-substituted pyrrolidines 387 (Scheme 161). Use of ethyl acetylacetone (\( R^1 = Me, R^2 = OEt \)), acetylacetone (\( R^1 = R^2 = Me \)) and diethyl malonate (\( R^1 = R^2 = OEt \)) gave products in 92\%, 94\%, and 83\% yields, respectively. The use of indium(IV) chloride in sodium dodecylsulfate and water has also been described for these reactions.\(^{82b}\)

![Scheme 161](image)

The reaction of 3-iodo-2-methoxy-pyrrolidine 330d with dimethyl malonate in the presence of titanium(IV) chloride afforded product 388 in 68\% yield and high selectivity (\( \text{trans/cis} = 98:2 \)) (Scheme 162).\(^{95}\)

![Scheme 162](image)

3.2.3 Reactions of Oxazolidinone-Based \( N \)-Acylinium Ions with Nucleophiles

3.2.3.1 Silicon-Based Nucleophiles

Treatment of the chiral oxazolidinones 389 with allyltrimethylsilane and 2-bromoallyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex or titanium(IV) chloride afforded 4,5-\( \text{trans} \) products 390 with very high selectivity (\( \text{trans/cis} = 87:13 \) to 98:2) in 85–92\% yields (Scheme 163).\(^{102}\)

![Scheme 163](image)

The reaction of bisoxazolidinone 391 with silicon nucleophiles in the presence of titanium(IV) chloride gave substituted products 392 in yields of 17–59\%, in favour of the di-\( \text{trans} \) products (Scheme 164).\(^{103}\)

![Scheme 164](image)

3.2.3.2 Organometallic Reagents

Treatment of oxazolidinone 393 with organocopper reagents in the presence of boron trifluoride–diethyl ether complex led to the formation of products 394 in 52–62\% yields and good 4,5-\( \text{trans} \) diastereoselectivities (Scheme 165).\(^{102}\)

![Scheme 165](image)

The boron trifluoride–diethyl ether complex catalysed reaction of oxazolidinones 389a and 393 with Grignard reagents provided products 395 in 58–78\% yields with very high 4,5-\( \text{trans} \) selectivity (Scheme 166).\(^{102}\)

Oxazolidinone 393 was treated with organocopper–zinc reagents in the presence of boron trifluoride–diethyl ether.
3.3 Six-Membered-Ring N-Acyliminium Ions

3.3.1 Reactions of Piperidine-Based N-Acyliminium Ions with Nucleophiles

3.3.1.1 Silicon-Based Nucleophiles

The reaction of 6-ethoxy-piperidine (400) with but-2-ynyltrimethylsilane under catalysis by boron trifluoride–diethyl ether complex yielded 6-methylallene-piperidinone (401) in 68% yield (Scheme 170). The addition reaction of silicon nucleophiles with 6-methoxy-piperidine (404) in the presence of zinc triflate provided the desired 6-substituted piperidinones (405) in 50–52% yields (Scheme 172). The reaction of racemic 6-methoxy-piperidine (406) with silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex in dichloromethane or acetonitrile afforded the corresponding racemic products (407) in 42–100% yields, in favour of the 4,6-trans isomer (trans/cis = 57:43 to 89:11) (Scheme 173). In the same study, piperidinone (406) reacted with CH₂=C(OTMS)(Ph) in the complex to give the 4,5-trans products (396) in 48–72% yields (Scheme 167).

3.2.3.3 Active Methylene Compounds

Bisoxazolidinone (391) reacted with a titanium enolate, prepared in situ from the treatment of diethyl malonate with titanium(IV) chloride in the presence of triethylamine, to afford predominantly the di-trans product (trans/cis = 94:6) in 57% yield (Scheme 168).

6-Acetoxy-piperidinone (402) underwent reaction with propargyltrimethylsilane to provide the allene product (403) in 90% yield (Scheme 171).

3.2.4 Cyclocondensation Reaction of N-Aminidinyl Iminium Ions

The cyclocondensation reaction of (398) with alkenes and dienes provided the desired cycloadducts (399) in 37–83% yields (Scheme 169).
presence of scandium(III) triflate in acetonitrile to give product 407 in 88% yield and with a trans/cis ratio of 78:22.106

3.3.1.2 Organostannanes

Treatment of racemic piperidinone 406 with allenlytributylstannane in the presence of boron trifluoride–diethyl ether complex afforded the racemic product 408 as a mixture of isomers (trans/cis = 51:49) in quantitative yield. The use of dichloromethane as a solvent decreased the yield to 85%, but increased the diastereoselectivity slightly (trans/cis = 59:41) (Scheme 174).106

3.3.1.3 Organometallic Reagents

Treatment of piperidinone 404 with an in situ generated zinc alkynylide in the presence of zinc triflate yielded the propargyl adduct 409 in 42% yield (Scheme 175).52

Scheme 176

3.3.2 Reactions of N-Acylpiperidine-Based N-Acyliminium Ions

3.3.2.1 Reactions with Nucleophiles

3.3.2.1.1 Silicon-Based Nucleophiles

The zinc triflate mediated reaction of N-tert-butyloxycarbonyl-2-methoxy piperidine (412) with silicon nucleophiles afforded the expected 2-substituted piperidines 413 in 52–68% yields (Scheme 177).32

Scheme 177
Treatment of piperidine 412 with similar silicon nucleophiles in the presence of indium(III) chloride under solvent-free conditions gave the desired 2-alkylated piperidines 413 in 79–92% yields (Scheme 178). The use of indium(IV) chloride in sodium dodecysulfate and water has also been described for these reactions.\textsuperscript{2b}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{Scheme_178}
\caption{Scheme 178}
\end{figure}

Piperidine 412 also reacted with silicon nucleophiles in an ionic liquid (BMI InCl₃) to yield the corresponding 2-substituted piperidines 413 in 65–76% yields (Scheme 179).\textsuperscript{81}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{Scheme_179}
\caption{Scheme 179}
\end{figure}

The one-pot decarboxylation–oxidation–allylation reaction of N-methoxy carbonyl piperidine 414 afforded 2-allylpiperidine 415 in 67% yield (Scheme 180).\textsuperscript{47}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{Scheme_180}
\caption{Scheme 180}
\end{figure}

Treatment of N-acylpiperidines 416a–c with 2-silyloxyfurans under trimethylsilyl triflate catalysis afforded products 417, 418 and 419 in 58–75% yields (Scheme 181). The reactions of 416a–c with 2-silyloxyfuran (R² = H, R³ = TBS) gave products 417 and 418 in 58%, 63%, and 74% yields, and with product ratios (417/418) of 88:12, 67:33, and 75:25, respectively. The reaction of piperidines 416a–c with another silyloxyfuran (R³ = Me, R⁴ = TIPS) afforded products 417, 418, and 419 in 67%, 75%, and 70% yields, with 417/418/419 product ratios of 3:60:36, 33:67:0, and 16:84:0, respectively. The relative stereochemistry of 419 was not determined.\textsuperscript{84}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{Scheme_181}
\caption{Scheme 181}
\end{figure}

In a very similar study, piperidine 416a reacted with 2-[(trisopropyl)silyl]oxy]-5-methylfuran in a tetrahydrofuran and dichloromethane solvent mixture in the presence of trimethylsilyl triflate or boron trifluoride–diethyl ether complex to afford products 420, 421 and 422 in 67% and 40% yields, respectively with product ratios (420/421/422) of 60:4:36 and 58:4:38, respectively. The reaction of piperidine 416b with silyloxyfuran in the presence of trimethylsilyl triflate, titanium(IV) chloride, and boron trifluoride–diethyl ether complex in dichloromethane, diethyl ether, tetrahydrofuran, and tetrahydrofuran–dichloromethane gave products 420 and 421 in 42–85% yields and with 420/421 product ratios of 52:48 to 67:33. The regioisomer 422 was not obtained from the reaction of piperidine 416b (Scheme 182).\textsuperscript{107}

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{Scheme_182}
\caption{Scheme 182}
\end{figure}

The reaction of chiral 2-methoxy piperidines 423a,b with 2-tert-butyl(dimethyl)silyloxyfuran under titanium(IV) chloride or trimethylsilyl triflate catalysis provided the

Synthesis 2009, No. 4, 513–541 © Thieme Stuttgart · New York
adducts 424a,b and 425a,b (Scheme 183). Treatment of 423a with the silyloxyfuran in the presence of titanium(IV) chloride or trimethylsilyl triflate gave products 424a and 425a in 55% and 75% yields (424a/425a = 88:12). Reaction of 423b with the silyloxyfuran under trimethylsilyl triflate catalysis gave the adducts 424b and 425b in 73% yield, with a diastereomeric ratio of 67:33.86

Scheme 183

The reaction of racemic 3-azido-2-methoxy Piperidine 426 with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex provided the racemic 2-allylated piperidine 427 as a mixture of isomers with a cis/trans ratio of 88:12 in 50% yield (Scheme 184).87,88

Scheme 184

Treatment of racemic piperidine 428 with silicon nucleophiles 195a, 211a and 429 in the presence of scandium(III) triflate in acetonitrile yielded products 430 in 89%, 92%, and 86% yields, respectively, and with cis/trans ratios of 52:48, 54:46 and 74:26, respectively. When the reaction of piperidine 428 with 211a and 429 was performed under boron trifluoride–diethyl ether complex catalysis in acetonitrile, products 430 were obtained in yields of 92% and 79%, respectively, in favour of the cis isomer (cis/trans = 72:28 and 61:39, respectively). The use of dichloromethane as a solvent in the reaction of 428 with 195a and 211a resulted in 22% (cis/trans = 75:25) and 65% (cis/trans = 83:17) yields, respectively (Scheme 185).106

The boron trifluoride–diethyl ether complex mediated reaction of allyltrimethylsilane with resin-bound racemic piperidine 431 gave racemic 2,4-trans isomers 432 in 71–86% yields after they were cleaved from the resin (Scheme 186). Piperidine 431, where R² = Ph, was treated with CH₃=CH(C)(CH3)TMS to afford the corresponding racemic 2,4-trans adduct exclusively in 76% yield.108

N-tert-Butyloxycarbonyl-6-acetoxypiperidine 433 reacted with propargyltrimethylsilane under boron trifluoride–diethyl ether complex catalysis to afford the allene 434 in 62% yield, in favour of the cis isomer (cis/trans = 80:20) (Scheme 187).109

Scheme 185

Scheme 186

Scheme 187

The reaction of bN-Boc piperidine 435 with a silyl dienol ether in the presence of trimethylsilyl triflate yielded exclusively the 2,3-trans isomer of adduct 436 in 86% yield (Scheme 188).109

The N-acyl piperidines 437a,b were treated with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether complex to give exclusively the corresponding 2,3-trans adducts 438a and 438b in 95% and 97% yields, respectively (Scheme 189).110

Treatment of the N-Fmoc piperidine 439 with silicon nucleophiles in the presence of boron trifluoride–diethyl ether complex provided the products 440 and 441 in a
range of yields (78–96%), with good 2,6-cis selectivity. The reaction of 439 with CH$_2$=CHCH(TMS)(CH$_2$)$_2$Me afforded the corresponding 2,6-cis adduct exclusively (Scheme 190).\textsuperscript{111}

3.3.2.1.2 Aromatic Nucleophiles

The treatment of polymer-bound racemic piperidine 431 with furan in the presence of camphorsulfonic acid provided the racemic 2-furyl/piperidine adduct 442 exclusively in 54% yield (Scheme 191).\textsuperscript{108}

3.3.2.1.3 Organostannanes

Treatment of racemic piperidine 428 with allenyltributylstannane in the presence of boron trifluoride–diethyl ether complex afforded product 443 in 67% yield, in favour of the 2,4-cis isomer (Scheme 192).\textsuperscript{106}

The reaction of the N-Boc piperidine 444 with allyltributylstannane in the presence of boron trifluoride–diethyl ether complex gave products 445 and 446 and one other isomer in a ratio of 89:7:4, respectively, and in combined yield of 72% (Scheme 193). The third isomer was suggested to be the result of partial epimerisation of the ste reocentre in the N-acyliminium ion intermediate.\textsuperscript{112}

3.3.2.1.4 Organometallic Reagents

The N-acyliminium ion 447, generated in situ from the corresponding carbamate by electrochemical oxidation, reacted with Grignard reagents in diethyl ether to afford the 2-substituted piperidine products 448 in 50–57% yields (Scheme 194).\textsuperscript{38}

Piperidine 412 reacted with an in situ generated zinc alkynylide to give the corresponding propargylic adduct 449 in 40% yield (Scheme 195).\textsuperscript{52}

The polymer-bound racemic piperidine 431 was treated with diethylzinc in the presence of boron trifluoride–
diethyl ether complex to give the racemic 2,4-trans isomer 450 exclusively in 14% yield (Scheme 196).\(^\text{108}\)

The reaction of piperidines 439 with diethylzinc in the presence of boron trifluoride–diethyl ether complex yielded products 451 and 452 in 63% and 27% yields, respectively (Scheme 197, equation 1). Treatment of 453, a diastereomer of piperidine 439, with diethylzinc under the same reaction conditions afforded products 454 and 455 in yields of 40% and 27%, respectively (Scheme 197, equation 2).\(^\text{111}\)

### 3.3.2.1.5 Carbonyl Compounds

The reaction of N-tert-butyloxycarbonyl-2-ethoxypiperidine (416a) with an N,O-silylketene acetal, itself prepared in situ by treatment of N-propionyloxazolidine-2-one 367 with trimethylsilyl triflate and triethylamine, led to the formation of 2-substituted piperidines 456 and 457 in 36% combined yield (456/457 = 67:33) (Scheme 198).\(^\text{98}\)

Treatment of the 2-methoxypiperidines 458a,b with the titanium enolate of 381a led to the formation of 459a and 459b in 62% and 58% yields, respectively (Scheme 199), whereas treatment of the N-Boc analogue of piperidine 458 with titanium enolate of 381a under the same reaction conditions did not give the desired product.\(^\text{113}\)
The titanium enolates of 373a–d reacted with the N-acyl piperidines 416a–c to afford the diastereomeric products 460 and 461 in 60–73% yields (Scheme 200).98

Scheme 200

In the same study the piperidines 416a–c reacted with the titanium enolates of 378a,b to give the corresponding products 462 and 463 in 60–73% yields (Scheme 201).98

Scheme 201

3.3.2.1.6 Alkyl Radicals

The N-acyliminium ion 447 was treated with heptyl iodide in the presence of hexabutyldistannane to give the 2-heptyl-N-acylpiperidine derivative 464 in 35% yield (Scheme 202).142

Scheme 202

3.3.2.1.7 Alkenes

Treatment of piperidine 439 with methylenecyclohexane under catalysis by tin(IV) bromide yielded the 2,6-cis adduct 465 and the 2,6-trans adduct 466 in 80% and 10% yields, respectively (Scheme 203).111

Scheme 203

Treatment of N-Chz-protected 2-methoxypiperidine 416b with cyclopentenone or cyclohexenone and dimethyl sulfide in the presence of trimethylsilyl triflate led to the formation of products 468 in 75–90% yields. The use of a chiral sulfide 467 resulted in 49–88% yields and enantioselectivities of 94–98% ee (Scheme 204).114

Scheme 204

3.3.2.1.8 Active Methylene Compounds

The indium(III) chloride catalysed reaction of piperidine 412 with acetylacetone (R¹ = Me, R² = OEt), acetylacetone (R¹ = R² = Me), and diethyl malonate (R¹ = R² = OEt) provided the products 469 in 53%, 38%, and 53% yields, respectively (Scheme 205).82a The use of indium(IV) chloride in sodium dodecyl sulfate and water has also been described for these reactions.82b
The N-acylpiperidines 470 reacted with 1,3-dicarbonyl compounds in the presence of copper(II) triflate and bisoxazoline ligand 471 to give products 472 in yields ranging from 16% to 78%. The highest enantioselectivity (97% ee) was obtained from the reaction of piperidine 470 \((R^1 = 4-\text{MeOC}_6\text{H}_4)\) and di(4-chlorophenyl)malonate (Scheme 206).\(^{115}\)

\[
\text{R}^1 = 4-\text{MeOC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, \\
\text{MeO, PhO, Ph}
\]

\[
\text{R}^2 = \text{Me, Et, } \text{but, Ph, } 4-\text{MeC}_6\text{H}_4, \\
4-\text{MeC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4 \\
4-\text{FOH}, 3-\text{ClC}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4
\]

The reaction of piperidine 473 with diene 474 in the presence of boron trifluoride–diethyl ether complex afforded cycloadduct 475 in 53% yield (Scheme 207, equation 1). Treatment of piperidines 476a and 476b with diene 477 in the presence of scandium(III) triflate afforded the corresponding cycloadducts 478a and 478b in 60% and 41% yields, respectively. Cycloadduct 478b was obtained in 68% yield from the reaction of 476a with 477 under catalysis by boron trifluoride–diethyl ether complex (Scheme 207, equation 2).\(^{116}\)

The boron trifluoride–diethyl ether complex catalysed reaction of 3-methoxy-1,4-dimethylpiperazine-2,5-dione (482a) with allyltrimethylsilane provided allylated product 483 in 68% yield, whereas 482b with allyltrimethylsilane under the same reaction conditions provided allylated product 483 and product 484 in 66% and 33% yields, respectively. Treatment of 482c with allyltrimethylsilane under the same reaction conditions gave exclusively product 484 in 76% yield (Scheme 209).\(^{116,118}\)

---

**Scheme 205**

**Scheme 206**

**Scheme 207**

**Scheme 208**
3.3.5 Reactions of N,O-Acetal Oxathiazinane N-Sulfonyliminium Ions with Nucleophiles

3.3.5.1 Organometallic Reagents

The reactions of N,O-acetal oxathiazinane 488 and related heterocycles with alkynylzinc reagents gave adducts 489 in high yields and high diastereoselectivities (Scheme 212).\(^\text{129}\)

\[
\begin{align*}
\text{R} & \quad \text{ZnCl} \\
\text{BF}_3\text{OEt}_2 & \quad \text{THF, 40 °C} \\
\text{488} & \quad \text{489} \quad 71-92\% \\
\end{align*}
\]

Scheme 212

3.4 Seven-Membered-Ring N-Acyliminium Ions

3.4.1 Reactions with Silicon-Based Nucleophiles

Treatment of the N-acyl-2-ethoxyazepines 490a–c with 2-silyloxyfurans 491a,b in the presence of trimethylsilyl triflate afforded products 492, 493, and 494 in 46–83% yields (Scheme 213). The reactions of azepines 490a–c with 491a in the presence of trimethylsilyl triflate afforded products 492 and 493 in ratios of 93:7, 85:15, and 80:20, respectively, while the reactions with 491b yielded products 492, 493, and 494 in ratios of 13:45:42, 6:52:42, and 30:70:0, respectively. The regiosomer 494 was not obtained from the reaction of 490a–c with 491a.\(^\text{84}\)

\[
\begin{align*}
\text{R}^1 & \quad \text{TMSOTI (10 mol%)} \\
\text{CH}_2\text{Cl}_2 & \quad -78 ^\circ \text{C} \\
\text{490a} & \quad \text{490b} & \quad \text{490c} \quad \text{491a} & \quad \text{491b} \\
\text{R}^2 & \quad \text{OTMS} & \quad \text{R}^3 & \quad \text{TBS} \\
\end{align*}
\]

Scheme 213

3.4.2 Cycloaddition Reactions

Azipine 495 reacted with diene 474 in the presence of boron trifluoride–diethyl ether complex to give cycloadduct 496 in 78% yield (Scheme 214).\(^\text{116}\)

\[
\begin{align*}
\text{495} & \quad \text{474} \quad \text{496} \quad 78\% \\
\end{align*}
\]

Scheme 214

Synthesis 2009, No. 4, 513–541 © Thieme Stuttgart - New York
3.5 Bicyclic N-Acyliminium Ions

3.5.1 Reactions with Nucleophiles

3.5.1.1 Silicon-Based Nucleophiles

Treatment of phthalimide 497 with silicon nucleophiles under triisopropylsilyl triflate catalysis afforded the desired products 498 in 45–89% yields (Scheme 215). In a similar study the phthalimide 497 reacted with CH$_3$=C(OTIPS)CeCH (2 equiv) in the presence of bis(trifluoromethane)sulfonimide (0.3 mol%) at room temperature under solvent-free conditions to give the corresponding a-substituted product in 82% yield.

In the same study, the triisopropylsilyl triflate catalysed reactions of phthalimides 499 with 260 gave the products 500 and 501 in 45–76% yields and 13–17% yields, respectively (Scheme 216). Silicon nucleophiles reacted with phthalimide 502 in the presence of bismuth(III) triflate in acetonitrile to provide product 503 in yields of 64–84%. Lower yields were obtained when dichloromethane was used as a solvent (56–66%) (Scheme 217).

In the same study, chiral phthalimide 504 reacted with alkyltrimethylsilane under bismuth(III) triflate catalysis to give product 505 in a trans/cis ratio of 75:25, and in 97% yield (Scheme 218).

Treatment of bicyclic imide 506 with sodium borohydride and then triethylsilane in the presence of trifluoroacetic acid afforded products 507 and 508 in 86% yield, in a 507/508 product ratio of 45:55 (Scheme 219).

Isoquinoline derivative 509 reacted with silicon nucleophiles in an ionic liquid, BMI$\cdot$InCl$_3$, to give the corre-
The reaction of 511 with allyltrimethylsilane in the presence of titanium(IV) chloride afforded the desired α-allyl product 512 in 91% yield, as a single isomer. The stereochemistry of the product was suggested to be the result of exo-face attack on the intermediate N-acyliminium ion (Scheme 221).\textsuperscript{21}

The ring-opening reaction of tricyclic lactam 513a with allyltrimethylsilane in the presence of titanium(IV) chloride, boron trifluoride–diethyl ether complex afforded product 520 as a single isomer in 77% yield. Treatment of 520 with lithium triethylborohydride and then allyltrimethylsilane under the same reaction conditions yielded the dialkylation product 521 as a single isomer in 76% yield (Scheme 222).\textsuperscript{123}

In a similar study, the boron trifluoride–diethyl ether complex catalysed reactions of bispidine 522 with silicon nucleophiles yielded products 523 in yields of 70–90% (Scheme 226).\textsuperscript{105}

### 3.5.1.2 Organometallic Reagents

The addition reactions of in situ generated zinc alkynylides to isoquinoline derivative 509 gave the corre-
The reaction of allylmagnesium bromide with a mixture of the α-methoxy and α-chloro benzamides 525 under boron trifluoride–diethyl ether complex catalysis afforded the exo-allylated product 526 in 68% yield and also led to the removal of the N-benzoyl group (Scheme 228).\textsuperscript{121}

Treatment of the α-methoxy lactam 527 with an organocupper reagent, generated in situ from the corresponding Grignard reagent and copper(II) bromide–dimethyl sulfide complex, led to the formation of an 88:12 mixture of products 528 and 529 in 87% yield (Scheme 229).\textsuperscript{124}

Treatment of 530 with 4-methoxybenzylmagnesium chloride under titanium(IV) chloride catalysis provided products 531 and 532 in a ratio of 55:45 and in 87% yield (Scheme 230).\textsuperscript{125}

In the same study, compound 533 was treated with sodium cyanoborohydride in acetic acid to give the desired product 534 as a single isomer in 69% yield (Scheme 231).\textsuperscript{124}

The α-methoxy bispidine 535 underwent reaction with Grignard reagents to afford the corresponding α-substituted bispidines 536 in 61–89% yields (Scheme 232).\textsuperscript{126}

Treatment of Grignard and zinc reagents with the chiral isoquinoline derivative 537 in the presence of Ph$_3$C$^+\text{BF}_4^-$ led to the formation of diastereomeric products 538 and 539 in 65–98% yields (Scheme 233).\textsuperscript{127}

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>522</td>
<td>-OTMS</td>
<td>90*</td>
</tr>
<tr>
<td>523</td>
<td>-CN</td>
<td>90*</td>
</tr>
<tr>
<td>524</td>
<td>-Me</td>
<td>69%</td>
</tr>
</tbody>
</table>

* TIC$_4$ was used.
Treatment of quinoline with acyl chlorides and then organosilicon reagents gave products 540 in yields of 60–93% (Scheme 234).119

Scheme 234

Phthalimide 541 was treated with alkenylalanes, themselves generated by the hydrozirconation of alkynes and transmetallation to trimethylaluminum, to give products 542 in yields of 43–81% (Scheme 235).128

Scheme 235

3.5.1.3 Enamines

Cyclic enaminoketones 543 reacted with N-acyliminium ion salts of 3,4-dihydroquinoline to provide the adducts 544 in 31–78% yields (Scheme 236).129

Scheme 236

3.5.2 Cycloaddition Reactions

The [4+2]-cycloaddition reaction of phthalimide 545 with alkenes in the presence of boron trifluoride–diethyl ether complex led to the formation of cycloadducts 546 and 547 in yields of 45–94% as mixtures of cis and trans products in different ratios (Scheme 237).130
3.6 Other Systems

3.6.1 Silicon-Based Nucleophiles

The addition reaction of silicon nucleophiles to α-hydroxy lactam 548 in the presence of boron trifluoride–diethyl ether complex or titanium(IV) chloride yielded the α-substituted products 549 in yields of 69–95% (Scheme 238).\(^{131}\)

![Scheme 238](image)

4 Stereochemical Outcomes

A recent paper by Woerpel\(^{132}\) on the stereochemical outcomes of the additions of nucleophiles to five-membered oxocarbenium ion intermediates are of relevance to our discussion here on the reactions of related five-membered-ring iminium ion intermediates. Woerpel has shown that the allylation reaction of dihydrofuran derivative 550 was cis selective (Scheme 239).

![Scheme 239](image)

This stereochemical outcome was consistent with nucleophilic attack on the oxocarbenium ion envelope conformation A from the ‘inside’ rather than on conformation B. Attack from the ‘inside’ gives rise to a more stable staggered product rather than an eclipsed product. Addition to the pseudo-equatorial conformation A is favoured over B due to stabilisation of the developing \(\sigma^a\) orbital at C-2 by the pseudo-axial \(\sigma_{C-H}\) orbital at C-3 (Cieplak effect).\(^{133}\) The \(\sigma_{C-H}\) bond is a better electron donor (more electron-rich) than the \(\sigma_{C-OBn}\) bond (Scheme 240).

A similar analysis on related five-membered-ring cyclic iminium ion intermediates is further complicated by the extra exocyclic or endocyclic carbonyl group, which further flattens the envelope conformation in the latter system. The N-substituent and its conformational preferences must also be considered in the latter. From a survey of the reactions in Section 3.2.1, it is clear that the nature of the O-substituent (OAc, OBn, OTBS), the N-substituent (NH, NBr, NPMB, N-allyl), the nucleophile and the Lewis acid can affect the diastereoselectivity and 4,5-cis to 4,5-trans selectivity. The examples that highlight the difference between a 4-OAc and 4-OTBS substituent in the N-unsubstituted case are shown in Scheme 241.

![Scheme 241](image)

Both reactions are highly diastereoselective; however, they show opposite trans/cis selectivity. The OAc derivative favours the 4,5-trans adduct while the OTBS derivative favours the 4,5-cis adduct. Thus, the OTBS derivative behaves similarly to the dihydrofuran 548 (Scheme 239) in its cis selectivity (Scheme 241). Indeed, the reactive envelope conformation C with the OTBS group (R\(^2\) = TBS) in the favourable pseudo-equatorial orientation (Cieplak effect), can be invoked to explain this cis selectivity. The trans selectivity in the case of the OAc derivative can be rationalised by the neighbouring-group participation of the OAc group to give the bridged bicyclic cationic intermediate E, S\(_N^2\)-like attack on this intermediate would provide the trans adduct (Scheme 242).
In the case of the allylation reaction of the related N-substituted pyrrolidinones,24 the same reverse-sense trans/cis selectivity is observed between 4-OAc and 4-OTBS derivatives; however, the diastereoselectivity is considerably reduced (Scheme 243). Clearly the N-substituent is responsible for this erosion of diastereoselectivity. The influence of the N-substituent in the reactions of N-heterocyclic compounds has been well documented.134,135

This trans/cis selectivity is also dependent upon the nucleophile, as illustrated in Scheme 244, in which the 4-OAc and 4-OTBS derivatives both favour formation of the trans adduct. It is possible that these reactions are under thermodynamic control.

Titanium enolates are highly trans selective on 4-OTBS pyrrolidinone derivatives (Scheme 115). The addition of boronic acids to 4-OBn substituted pyrrolidinones are also trans selective (Schemes 111 and 112).

The reaction of 3,4-disubstituted pyrrolidinones 552 (R1 ≠ Ac) often gave 4,5-cis adducts (R2 = H) with high diastereoselectivities (Schemes 92, 93, 101, 102, and 103). 5,5-Disubstituted derivatives (R2 ≠ Ac, R4 ≠ H) gave products from nucleophilic addition cis to the C-4 OR3 group (Schemes 89, 94, and 105). This can be attributed to the effect of the C-4 OR3 group (Cieplak effect). In the cases where the C-3 and C-4 groups are acetate, a neighbouring-group effect by the C-3 acetate has been suggested to explain the 4,5-cis selectivity (Scheme 245).79

In the case of the aminals 229, reduction with triethylsilane and boron trifluoride–diethyl ether complex gave the 3,5-cis adducts (Scheme 246).
attacking. In conformation F, 1,3-allylic strain may project the N-benzyl group to the β-face of the iminium ion thus more effectively blocking the face to nucleophilic attack.\textsuperscript{65}

From a survey of reactions in Section 3.2 on N-acylpyrrolidines, it is clear that 2,3-\textit{trans} products are normally favoured in the case where the 3-substituent is I (Schemes 131 and 162), NHCO₂R (Scheme 131), alkyl (Scheme 147), aryl (Scheme 147) or allyl (Scheme 134). The exceptions are when the 3-substituent is OH or N₃, wherein \textit{cis} products are formed almost exclusively (Schemes 146 and 131, respectively). When the 3-substituent is I or NHCO₂R, neighbouring-group participation can be used to explain the \textit{trans} selectivity (compare with Scheme 241). When the C-3 substituent is OH, formation of a boronate intermediate can be invoked to explain the high \textit{cis} selectivity as reported in Scheme 146. When the C-3 substituent is alkyl or N₃, steric and stereoelectronic arguments can be used to account for the stereoselectivities (Scheme 247).

Because the hyperconjugative donating ability of a \(\sigma_{C-H}\) bond is similar to that of a \(\sigma_{C-C}\) bond, there would be little difference in electronic stabilisation of the transition states involving attack from the ‘inside’ on the pseudo-equatorial or pseudo-axial conformations H (X = alkyl) or I (Y = alkyl). Attack on conformation H, however, would result in unfavourable \textit{gauche} butane interactions between the Nu and the X group, and thus attack would be expected to occur on compound I to give the \textit{trans} product. When the C-3 substituent is N₃, then attack on conformation H would be favoured stereoelectronically since the C-3 \(\sigma_{C-N₃}\) bond is a much stronger electron donor than the \(\sigma_{C-N₃}\) bond. Steric considerations are not important with the relatively smaller N₃ group.

Iminium ions generated from 4-substituted N-acylpyrrolidines give 2,4-\textit{cis} products (Schemes 129 and 133). A reactive conformation analogous to F (Scheme 246) can explain the stereochemical outcome.

In general, reactions on the corresponding six-membered ring N-acyliminium ion analogues have been less studied and often proceed with poorer diastereoselectivity. The stereochemical outcomes of the major products can often be rationalised as arising from axial attacks on a half-chair conformation.\textsuperscript{134a,135}

5 Conclusions

The intermolecular addition reactions of N-acyliminium ions have been a major area of investigation by synthetic chemists over the past eight years. New methods to generate these cationic intermediates have been developed, including the use of new Lewis acid catalysts, polymer-supported precursors and electrochemical methods. The latter method has been successfully extended to peptide systems and can be used to prepare N-acyliminium ions in the absence of a nucleophile.

The reactions of N-acyliminium ions include the addition of nucleophiles, especially silicon-based ones, cycloaddition reactions, free-radical additions and nucleophilic aromatic substitution reactions. These latter reactions can be more selectively and efficiently performed using a micro-mixer. The applications of these methods to the synthesis of peptides, natural products and new pharmaceutical drugs will continue to grow over the next decade.

Acknowledgment

We thank the Australian Research Council for supporting our research in this area.

References

(135) Huang, P.-Q. Synlett 2006, 1133.