Synthesis and Ring-Opening Reactions of Bicyclic Alkene-Fused Isoxazolines

by

Jaipal Reddy Nagireddy

A Thesis

Presented to

The University of Guelph

In partial fulfillment of requirements

for the degree of

Doctor of Philosophy

in

Chemistry

Guelph, Ontario, Canada

© Jaipal Reddy Nagireddy, December, 2014
ABSTRACT

Synthesis and Ring-Opening Reactions of Bicyclic Alkene-Fused Isoxazolines

Jaipal Reddy Nagireddy
University of Guelph, 2014

Advisor:
Prof. William Tam

This thesis is an investigation of 1,3-dipolar cycloaddition reactions of nitrile oxides with symmetrical and unsymmetrical bicyclic alkenes, and their subsequent isoxazoline ring opening reactions. Although a large number of 1,3-dipolar cycloaddition reactions between nitrile oxides and bicyclic alkenes have been reported, most of these are currently limited to carbobicyclic alkenes. Introduction of a heteroatom in the bicyclic ring offers differences in the reactivity and selectivity of cycloaddition reactions. Introduction of a substituent at the bridgehead carbon of the bicycloalkene makes the molecule unsymmetrical. The implications of the reduction of symmetry in C1-substituted heterobicyclic rings open the door to regioselectivity studies for these cycloaddition reactions.

The stereo- and regiochemical aspects of 1,3-dipolar cycloaddition reactions with acetonitrile oxide and benzonitrile oxide were examined on a wide variety of symmetrical and unsymmetrical oxabicyclic and azabicyclic alkenes. The cycloadditions were found to be completely stereoselective producing only the exo adducts in moderate to excellent yields. In the majority of the cycloaddition reactions, both of the possible regioisomers were produced in varying ratios that depended on electronic and steric effects of the C1 substituent.

After having generated numerous isoxazoline derivatives, various metal-catalyzed (Mo, Pd, Zn, Fe and Ni) cleavage conditions were investigated, with successful N-O
bond cleavage of isoxazoline rings achieved using Raney-Ni/AlCl₃. An N-O bond cleavage, followed by an imine hydrolysis led to the formation of a variety of novel β-hydroxyketone products with moderate to excellent yields.

In the early part of this project, a simple and scalable procedure for the preparation of 2-bromofuran was developed. 2-Bromofuran was found to be useful for preparing a series of 2-aryl furans using the Suzuki cross coupling reaction with arylboronic acids. Similarly 2-alkyl furans were prepared using an iron catalyzed cross coupling reaction between 2-bromofuran and alkyl Grignard reagents. The 2-substituted furans were used for the preparation of various C¹-substituted oxabicyclic alkenes via the Diels-Alder cycloaddition strategy.
Acknowledgements

First and foremost, I would like to thank my supervisor, Prof. William Tam, who has provided me with the opportunity to pursue my goals. I am highly grateful to Prof. Tam for his encouragement, motivation and guidance for all these years. I owe special thanks to Prof. Tam for his numerous meeting appointments on weekends.

I would like to express my gratitude to my advisory committee members Prof. Mike Chong of University of Waterloo, Prof. Adrian Schwan, Prof. Michael Denk and Prof. France-Isabelle Auzanneau, of University of Guelph for their contributions to my experiences as a Ph.D. candidate. I would like to thank my external examiner Dr. Malik Slassi, President & Chief Scientific Officer of Fluorinov Pharma Inc. for agreeing to participate in my dissertation. I would also like to thank Prof. Wojciech Gabryelski, the chair of the examination committee and Prof. Richard Manderville of University of Guelph for being on my defense examination committee.

I would like to express my sincere thanks to Mr. Darren Hall, Mr. Jason Fischer, Dr. Steve Horne, and Dr. Gamini Weeratunga for their encouragement at Apotex Pharmachem Inc. I would like to offer my special thanks to Dr. Bhaskar Guntoori and Dr. Keshava Murthy for inspiring me to pursue PhD studies. I would like to thank Dr. Farzad Mirzaei for his encouragement and support at Vibrant Pharma Inc.

I would also like to thank all the past and present members of the Tam group. I would like to thank my friend Raheem for always being there in each and every step of my graduate studies and making this fabulous task possible. I would also like to thank Karine, Gavin, Nicole and Woo for their support and enlightening conversations. I would
also like to thank Michelle, Jordon, Neil, Ben, Paul and Jamie for their friendly
discussions and help during my research.

I owe a special thanks to Paula Estey and Emily Carlson for not only proofreading
my thesis but also providing very valuable suggestions for improvement. I sincerely
appreciate their time and efforts in shaping my thesis.

I would like to thank my parents, all my friends and family members who have
tolerated my absence during studies. Most significantly, I appreciate and thank my wife
Nalini and my daughter Harika for their support, understanding and sacrifices during the
course of my graduate studies.
Table of Contents

List of Contents vi
List of Schemes x
List of Figures xiv
List of Tables xv
Abbreviations and Acronyms xvi
Appendix List xx

Table of Contents

Chapter 1 Introduction and Background 1

1.1 Cycloaddition Reactions 2
1.2 Cycloadditions with Bicyclic Alkenes 3
1.3 1,3-Dipolar Cycloadditions 5
  1.3.1 Basic Aspects 5
  1.3.2 1,3-Dipolar Cycloadditions of Nitrile Oxides 12
  1.3.3 Regio- and Stereochemical Aspects of Nitrile Oxide 1,3-Dipolar Cycloadditions 15
  1.3.4 Nitrile Oxide Cycloadditions of Bicyclic Alkenes 20
1.4 Tam Group’s Research on Cycloaddition Reactions of Bicyclic Alkenes 27
  1.4.1 [2+2] Cycloaddition 27
  1.4.2 Rhodium Catalyzed Cyclodimerization 33
  1.4.3 1,3-Dipolar Cycloaddition 34
  1.4.4 Rhodium Catalyzed Cyclopropanation 37
1.5 Ring-Opening Reactions ofIsoxazolines 37
  1.5.1 β-Hydroxycarbonyls Through N-O Bond Cleavage of Isoxazolines 38
    1.5.1.1 Nickel Catalyzed Cleavage 38
    1.5.1.2 Palladium Catalyzed Cleavage 39
    1.5.1.3 Titanium Catalyzed Cleavage 40
    1.5.1.4 Samarium Iodide Catalyzed Cleavage 41
    1.5.1.5 Iron Catalyzed Cleavage 41
    1.5.1.6 Oxidative Cleavage 42
    1.5.1.7 Metal Carbonyl Catalyzed Cleavage 43
  1.5.2 Retro-aldo Products from Metal Carbonyl Induced Cleavage 44
1.5.3 γ-Aminoalcohols Through N-O Bond Cleavage 44
1.5.4 Oximes Through C-O Bond Cleavage with Inorganic Bases 45
1.5.5 β-Hydroxynitriles Through N-O Bond Cleavage with Organic Bases 45
| 1.6 | Synthetic Applications of Nitrile Oxide Cycloadditions Followed by Ring-Opening Reactions of Isoxazolines | 46 |
| 1.7 | Research Goals | 49 |

Chapter 2 Synthesis of Substituted Furans and Bicyclic Alkenes 52

| 2.1 | Introduction | 53 |
| 2.2 | Synthesis of 2-Substituted Furans | 53 |
| 2.2.1 | Preparation of 2-Bromofuran | 53 |
| 2.2.2 | Background | 54 |
| 2.2.3 | Results and Discussion | 55 |
| 2.3 | Synthesis of 2-Aryl Furans | 55 |
| 2.3.1 | Background | 55 |
| 2.3.2 | Pd Catalyzed Suzuki Cross Coupling Reactions | 56 |
| 2.3.3 | General Mechanism of Suzuki Cross Coupling Reaction | 57 |
| 2.3.4 | Results and Discussions | 58 |
| 2.3.5 | Pd Catalyst Screening Study | 63 |
| 2.3.6 | Results and Discussions | 64 |
| 2.4 | Synthesis of 2-Alkyl Furans | 67 |
| 2.4.1 | Background | 67 |
| 2.4.2 | Alkyl-Aryl Cross Coupling | 68 |
| 2.4.3 | Iron Catalyzed Cross Coupling | 69 |
| 2.4.4 | Mechanism of the Iron Catalyzed Cross Coupling | 69 |
| 2.4.5 | The Tam Group’s Previous Work on Iron Catalyzed Cross Coupling | 72 |
| 2.4.6 | Results and Discussions | 73 |
| 2.5 | Synthesis of C1-Substituted Oxanorbornenes | 79 |
| 2.5.1 | Background | 79 |
| 2.5.2 | Results of Reactions Between 2-Substituted Furans with Maleic Anhydride | 80 |
| 2.5.3 | Results of Reactions Between 2-Substituted Furans with N-Phenylmaleimide | 82 |
| 2.6 | Synthesis of C1-Substituted Oxabenzonorbornadienes | 85 |
| 2.6.1 | Background | 85 |
| 2.6.2 | Results and Discussions | 86 |

Chapter 3 1,3-Dipolar Cycloadditions between Bicyclic Alkenes and Nitrile Oxides 94

| 3.1 | Introduction | 95 |
| 3.2 | Proposed Methodology | 98 |
| 3.3 | Stereochemical Considerations | 99 |
| 3.4 | Results and Discussion | 101 |
| 3.4.1 | Cycloadditions with Symmetrical Bicyclic Alkenes | 101 |
| 3.4.1.1 | 1,3-Dipolar Cycloadditions of Symmetrical 7-Oxabenzonorbornadienes | 101 |
3.4.1.2 1,3-Dipolar Cycloadditions of Symmetrical 7-Azabenzonorbornadienes
3.4.1.3 1,3-Dipolar Cycloaddition of 5,6-Bis-methoxymethyl-7-oxabicyclo[2.2.1]hept-2-ene

3.4.2 Cycloadditions with Unsymmetrical Bicyclic Alkenes
3.4.2.1 1,3-Dipolar Cycloaddition of C1-Substituted-7-oxabenzonorbornadienes
3.4.2.2 1,3-Dipolar Cycloadditions of C1-Substituted N-Phenylmaleimide Fused Oxanorbornenes
3.4.2.3 1,3-Dipolar Cycloaddition of N-Acyl-2-oxa-3-azanorborn-5-enes

3.5 Conclusions

Chapter 4 Cleavage of Bicyclic Alkene-fused 2-Isoxazolines
4.1 Introduction
4.2 Development of Cleavage Methodology for 2-Isoxazolines
4.3 Molybdenum-Mediated Cleavage of 2-Isoxazolines
4.3.1 Tam Group Research on Molybdenum-Mediated Cleavage Reactions of 2-isoxazolines
4.3.2 Results and Discussion on Molybdenum-Mediated Cleavage
4.4 Palladium-Mediated Cleavage of 2-Isoxazolines
4.5 Zinc-Mediated Cleavage Reactions of 2-Isoxazolines
4.6 Fe-NH₄Cl-Mediated Cleavage of 2-Isoxazolines
4.7 Nickel-Mediated Cleavage of 2-Isoxazolines
4.7.1 Results and Discussion on Nickel-Mediated Cleavage
4.7.2 Cleavage of 2-Isoxazolines Derived from Symmetrical 7-Oxabenzonorbornadienes
4.7.3 Cleavage of 3-Methyl-2-isoxazolines Derived from C1-Substituted 7-Oxabenzonorbornadienes
4.7.4 Cleavage of 3-Methyl-2-isoxazolines Derived from C1-Substituted 7-Oxanorbornenes
4.7.5 Cleavage of 3-Methyl-2-isoxazolines Derived from Symmetrical 7-Azabenzonorbornadienes
List of Schemes

Scheme 1.1  Selected examples of norbornadiene/norbornene cycloaddition reactions. 4
Scheme 1.2  Representation of allyl/propargyl type 1,3-dipoles. 6
Scheme 1.3  Examples of common allyl/propargyl type 1,3-dipoles. 7
Scheme 1.4  Huisgen-proposed concerted mechanism for 1,3-dipolar cycloaddition. 8
Scheme 1.5  Firestone-proposed step-wise mechanism for 1,3-dipolar cycloaddition. 8
Scheme 1.6  Regiochemical considerations based on orbital coefficient magnitudes. 11
Scheme 1.7  1,3-Dipolar cycloaddition of nitrile oxide with alkenes/alkynes. 13
Scheme 1.8  Resonance structures of nitrile oxides. 13
Scheme 1.9  Preparation of nitrile oxides from aldehydes. 14
Scheme 1.10 Preparation of nitrile oxides from nitroalkanes using Mukaiyama method. 14
Scheme 1.11 Preparation of nitrile oxides from nitroalkanes using Hassner’s method. 15
Scheme 1.12 Possible regioisomers from 1,3-DCA of nitrile oxides with monosubstituted olefins. 16
Scheme 1.13 Possible regioisomers from 1,3-DCA of nitrile oxides with 1,2-disubstituted olefins. 16
Scheme 1.14 Possible regio- and stereoisomers from 1,3-DCA of nitrile oxides with 1,2-disubstituted is and trans olefins. 17
Scheme 1.15 1,3-DCA of chiral nitrile oxide 1-64 with cis 1,2-disubstituted olefin. 18
Scheme 1.16 1,3-DCA of chiral nitrile oxide 1-67 with cis 1,2-disubstituted olefin. 18
Scheme 1.17 1,3-DCA of nitrile oxides with chiral olefin 1-71. 19
Scheme 1.18 1,3-DCA of nitrile oxide 1-75 with chiral olefin 1-74. 19
Scheme 1.19 1,3-DCA of olefins with chiral auxiliary. 20
Scheme 1.20 Nitrile oxide 1,3-DCA of norbornadienes 1-86. 21
Scheme 1.21 Nitrile oxide 1,3-DCA of bicyclic alkenes 1-89 to 1-91. 22
Scheme 1.22 Nitrile oxide 1,3-DCA of bicyclic alkene 1-98. 23
Scheme 1.23 Nitrile oxide 1,3-DCA of bicyclic alkenes 1-102. 24
Scheme 1.24 Nitrile oxide 1,3-DCA of bicyclic alkenes 1-106. 25
Scheme 1.25 Nitrile oxide 1,3-DCA of bicyclic alkenes 1-109. 25
Scheme 1.26  Nitrile oxide 1,3-DCA of bicyclic alkenes 1-112.
Scheme 1.27  Nitrile oxide 1,3-DCA of bicyclic alkene 1-115.
Scheme 1.28  Nitrile oxide 1,3-DCA of bicyclic alkenes 1-119.
Scheme 1.29  Ru-catalyzed [2+2] cycloaddition of 7-substituted norbornadienes.
Scheme 1.30  Ru-catalyzed [2+2] cycloaddition of 2,3-disubstituted norbornadienes.
Scheme 1.31  Ru-catalyzed [2+2] cycloaddition of norbornadiene with alkynes.
Scheme 1.32  Ru-catalyzed [2+2] cycloaddition of 2-substituted norbornadienes.
Scheme 1.33  Ru-catalyzed [2+2] cycloaddition of 2-substituted norbornenes.
Scheme 1.34  Ru-catalyzed [2+2] cycloaddition of C1-substituted 7-oxanorbornadienes 1-139.
Scheme 1.35  Ru-catalyzed [2+2] cycloaddition of norbornene/norbornadiene with chiral propargylic alcohol derivatives.
Scheme 1.36  Ru-catalyzed [2+2] cycloaddition of bicyclic alkenes with alkynes attached with chiral auxiliaries.
Scheme 1.37  Rh-catalyzed cyclodimerization of oxabenzonorbornadienes.
Scheme 1.38  Rh-catalyzed isomerization of C1-substituted
Scheme 1.39  Intramolecular 1,3-DCA of bicyclic alkene tethered nitrile oxides.
Scheme 1.40  Intramolecular 1,3-DCA of bicyclic alkene tethered nitrones.
Scheme 1.41  1,3-DCA of norbornadiene with nitrile oxides.
Scheme 1.42  1,3-DCA of 2-substituted-2-norbornenes with nitrile oxides.
Scheme 1.43  1,3-DCA of 2-substituted-5-norbornenes with nitrile oxides.
Scheme 1.44  1,3-DCA of C1-substituted norbornene 1-167 with nitrile oxide.
Scheme 1.45  Ru catalyzed cyclopropanation of oxabenzonorbornadienes.
Scheme 1.46  Raney Ni/H2 catalyzed cleavage of 2-isoxazolines.
Scheme 1.47  Raney Ni/AlCl3 catalyzed cleavage of 2-isoxazolines.
Scheme 1.48  Raney Ni/boric acid catalyzed cleavage of 2-isoxazolines.
Scheme 1.49  Palladium catalyzed cleavage of 2-isoxazolines.
Scheme 1.50  Ti3+ catalyzed cleavage of 2-isoxazolines.
Scheme 1.51  Ti4+ catalyzed cleavage of 2-isoxazolines.
Scheme 1.52  Samarium iodide catalyzed cleavage of 2-isoxazolines.
Scheme 1.53  Fe/NH4Cl catalyzed cleavage of 2-isoxazolines.

xi
Scheme 1.54  Cleavage of 2-isoxazolines with ozone.  
Scheme 1.55  Peracid Cleavage of 2-isoxazolines.  
Scheme 1.56  Mo(CO)₆ catalyzed cleavage of 2-isoxazolines.  
Scheme 1.57  Fe(CO)₅ catalyzed cleavage of 2-isoxazolines.  
Scheme 1.58  Mo(CO)₆/Fe(CO)₉/Fe(CO)₅ catalyzed cleavage of 2-isoxazolines 1-204.  
Scheme 1.59  Inorganic base catalyzed cleavage of 2-isoxazolines.  
Scheme 1.60  Organic base catalyzed cleavage of 2-isoxazolines.  
Scheme 1.61  Application of 1,3-DCA of nitrile oxide towards the synthesis of Acivicin.  
Scheme 1.62  Application of 1,3-DCA of nitrile oxide towards the synthesis of VGX-1027.  
Scheme 1.63  Application of 1,3-DCA of nitrile oxide followed by 2-isoxazoline cleavage towards the synthesis of Bacrophelide B.  
Scheme 1.64  Application of 1,3-DCA of nitrile oxide followed by 2-isoxazoline cleavage towards synthesis of (+)-Brefeldin A.  
Scheme 1.65  Application of 1,3-DCA of nitrile oxide followed by 2-isoxazoline cleavage towards synthesis of (±)-Vinigrrol.  
Scheme 2.1  Preparation of 2-bromofuran.  
Scheme 2.2  General mechanism for Suzuki cross coupling reaction.  
Scheme 2.3  Synthesis of 2-alkylfurans using Suzuki cross coupling reaction.  
Scheme 2.4  Synthesis of 2-alkylfurans from 2-lithiated furans.  
Scheme 2.5  Pd-I₂-catalyzed cycloisomerization of (Z)-2-en-4-yn-1-ols to 2-alkylfurans.  
Scheme 2.6  Catalytic cycle for Fe-catalyzed cross-coupling reaction based on proposal that Fe(I) as an active catalyst.  
Scheme 2.7  Catalytic cycle for Fe-catalyzed cross-coupling reaction based on proposal that Fe(-II) as active catalyst.  
Scheme 2.8  Fe-catalyzed cross-coupling reaction of bicyclic alkenyl triflates with Grignard reagents.  
Scheme 3.1  Possible cycloadducts from 1,3-dipolar cycloaddition of bicyclic alkenes with nitrile oxides.  
Scheme 3.2  Cycloaddition-cleavage approach of bicyclic alkenes.  
Scheme 3.3  Proposed methodology for 1,3-dipolar cycloaddition of bicyclic alkenes with nitrile oxides.  
Scheme 3.4  Results of 1,3-dipolar cycloaddition of substituted norbornadienes with nitrile oxide.  
Scheme 3.5  Possible cycloadducts from 1,3-dipolar cycloaddition of symmetrical bicyclic alkenes with nitrile oxides.  
Scheme 3.6  1,3-Dipolar cycloaddition of bicyclic alkenes 3-3.
Scheme 3.7 Relative charge densities on C$^2$ and C$^3$ of oxabenzonorbornadiene 3-4 and the preferred approach of nitrile oxide to afford major regioisomer 3-23.

Scheme 4.1 Cycloaddition-cleavage approach of bicyclic alkenes.

Scheme 4.2 Expected Mo(CO)$_6$ mediated cleavage pathways for 2-isoxazoline 4-1 based on previously reported results from Tam group.

Scheme 4.3 Mo(CO)$_6$ mediated cleavage of 2-isoxazoline fused in bicyclic rings.

Scheme 4.4 Mo(CO)$_6$ mediated cleavage of 2-isoxazolines generated from intramolecular nitrile oxide cycloadditions.

Scheme 4.5 Mo(CO)$_6$ mediated cleavage mechanism proposed by Tam group.

Scheme 4.6 Mo(CO)$_6$ mediated cleavage of 2-isoxazolines 4-20a.

Scheme 4.7 Mo mediated cleavage of 2-isoxazolines 4-9aa, 4-9ab.

Scheme 4.8 Pd-C mediated cleavage of 2-isoxazolines 4-9aa, 4-9ab.

Scheme 4.9 Zn mediated cleavage of 2-isoxazoline 4-9aa.

Scheme 4.10 Fe-NH$_4$Cl mediated cleavage of 2-isoxazoline 4-9aa.

Scheme 4.11 Raney Ni/AlCl$_3$ mediated cleavage of 3-methyl-2-isoxazoline 4-27aa.

Scheme 4.12 Raney Ni/AlCl$_3$ mediated cleavage of 3-phenyl-2-isoxazoline 4-9ab.

Scheme 4.13 Raney Ni/AlCl$_3$ mediated cleavage of 2-isoxazoline 4-30.

Scheme 5.1 Preparation of 2-aryl furans by Suzuki cross-coupling protocol (top) and 2-alkyl furans by iron cross-coupling protocol (bottom).

Scheme 5.2 Preparation of C$^1$-substituted oxabicyclic alkenes.

Scheme 5.3 1,3-DCA reactions of nitrile oxides with symmetrical bicyclic alkenes.

Scheme 5.4 1,3-DCA reactions of nitrile oxides with unsymmetrical bicyclic alkenes.

Scheme 5.5 Investigation for the cleavage of 2-isoxazoline ring fused to bicyclic framework.

Scheme 5.6 Cleavage of 2-isoxazolines with Raney-Ni/AlCl$_3$.

Scheme 5.7 Proposed metal catalyzed enantioselective 1,3-DCA reaction.

Scheme 5.8 Application of 1,3-amino alcohols in asymmetric 1,3-DCA reactions.

Scheme 5.9 Application of chiral ligands derived from 1,3-amino alcohols in asymmetric 1,3-DCA reactions.
List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Structure of norbornadiene (1-1a) and norbornene (1-2a).</td>
<td>3</td>
</tr>
<tr>
<td>1.2</td>
<td>Representative bicyclic alkene structures used for various cycloaddition reactions in the literature.</td>
<td>5</td>
</tr>
<tr>
<td>1.3</td>
<td>Types of 1,3-dipolar cycloadditions based on HOMO-LUMO interactions of dipoles and dipolarophiles.</td>
<td>10</td>
</tr>
<tr>
<td>1.4</td>
<td>1,3-dipole, and dipolarophile orbital energy representation with Lewis acid coordination.</td>
<td>12</td>
</tr>
<tr>
<td>1.5</td>
<td>Houk’s models for possible transition states of 1,3-DCA with chiral olefins.</td>
<td>19</td>
</tr>
<tr>
<td>1.6</td>
<td>Houk’s models for possible transition state of 1,3-DCA with chiral olefins with oxygen at allylic position.</td>
<td>20</td>
</tr>
<tr>
<td>1.7</td>
<td>Representation of σ-π, π-π interactions in 2-substituted norbornenes.</td>
<td>30</td>
</tr>
<tr>
<td>2.1</td>
<td>Homocoupled products obtained during Fe-catalyzed cross coupling.</td>
<td>78</td>
</tr>
<tr>
<td>2.2</td>
<td>Known C1-substituted oxabenzonorbornadienes.</td>
<td>85</td>
</tr>
<tr>
<td>3.1</td>
<td>Bicyclic alkenes used for 1,3-dipolar cycloaddition reactions with nitrile oxides.</td>
<td>97</td>
</tr>
<tr>
<td>3.2</td>
<td>Assignment of stereochemistry of cycloadducts 3-20aa-3-20fb.</td>
<td>105</td>
</tr>
<tr>
<td>3.3</td>
<td>Assignment of stereochemistry of cycloadducts 9aa-9cb.</td>
<td>108</td>
</tr>
<tr>
<td>3.4</td>
<td>Assignment of regiochemistry of cycloadducts 3-23aa to 3-24gb.</td>
<td>115</td>
</tr>
<tr>
<td>3.5</td>
<td>By-product from 1,3-dipolar cycloaddition of 3-5c.</td>
<td>119</td>
</tr>
<tr>
<td>3.6</td>
<td>Assignment of stereo and regiochemistry of cycloadducts 3-25a, 3-25b and 3-25e.</td>
<td>119</td>
</tr>
<tr>
<td>3.7</td>
<td>Assignment of stereo and regiochemistry of cycloadducts 3-27aa to 3-21bb.</td>
<td>122</td>
</tr>
<tr>
<td>4.1</td>
<td>Representative 2-isoaxazolines for cleavage reactions.</td>
<td>133</td>
</tr>
</tbody>
</table>
List of Tables

<p>| Table 2.1 | Synthesis of 2-aryl furans using Pd-C catalyzed Suzuki cross coupling reactions between 2-bromofuran and arylboronic acids. | 60 |
| Table 2.2 | Synthesis of 2-aryl furans using PdCl₂(Ph₃P)₂ catalyzed Suzuki cross coupling reactions between 2-bromofuran and arylboronic acids. | 61 |
| Table 2.3 | Screening of different Pd-Catalysts. | 65 |
| Table 2.4 | Optimization of Fe catalyzed reaction conditions for the synthesis of 2-12t. | 74 |
| Table 2.5 | Fe catalyzed cross coupling with various Grignard reagents. | 76 |
| Table 2.6 | DA reactions of 2-substituted furans with maleic anhydride. | 81 |
| Table 2.7 | DA reactions of 2-substituted furans with N-phenylmaleimide. | 83 |
| Table 2.8 | Synthesis of C¹-substituted oxabenzonorbornadienes. | 89 |
| Table 3.1 | 1,3-Dipolar cycloaddition with symmetrical 7-oxabenzonorbornadienes. | 102 |
| Table 3.2 | 1,3-Dipolar cycloadditions of symmetrical 7-azabenzenornbornadienes. | 107 |
| Table 3.3 | 1,3-Dipolar cycloaddition with C¹-substituted 7-oxabenzonorbornadienes. | 111 |
| Table 3.4 | 1,3-Dipolar cycloadditions of C¹-substituted N-phenylmaleimide fused oxanorbornenes. | 117 |
| Table 3.5 | Results of 1,3-dipolar cycloaddition with N-Acyl-2-oxa-3-azanorborn-5-enes. | 121 |
| Table 3.6 | Confirmation of regiochemistry of cycloadducts 27bb and 28bb by comparing ¹H NMRs to previously reported data. | 124 |
| Table 3.7 | Confirmation of regiochemistry of cycloadducts 27bb and 28bb by comparing ¹³C NMRs to previously reported data. | 125 |
| Table 3.8 | Assignment of regiochemistry of cycloadducts 3-27aa to 3-28ba based on confirmed ¹H data of regioisomers 3-27bb and 3-28bb. | 126 |
| Table 3.9 | Assignment of regiochemistry of cycloadducts 3-27aa to 3-28ba based on confirmed ¹³C data of regioisomers 3-27bb and 3-28bb. Cleavage of the 3-methyl-2-isoxazolines derived from | 127 |
| Table 4.1 | Cycloaddition between acetonitrile oxide and 7-oxabenzonorbornadienes. Cleavage of the 3-methyl-2-isoxazolines derived from | 144 |
| Table 4.2 | Cycloaddition between acetonitrile oxide and C¹ substituted 7-oxabenzonorbornadienes. | 146 |
| Table 4.3 | Cleavage of 2-isoxazolines derived from cycloaddition between acetonitrile oxide and 7-oxanorbornenes. | 149 |
| Table 4.4 | Cleavage of 2-isoxazolines derived from cycloaddition between acetonitrile oxide and 7-azabenzonorbornadienes. | 150 |</p>
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3-DCA</td>
<td>1,3-dipolar cycloaddition</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetone</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>ACN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>BHT</td>
<td>butylated hydroxytoluene</td>
</tr>
<tr>
<td>BOC anhydride</td>
<td>di-tert-butyl dicarbonate</td>
</tr>
<tr>
<td>br s</td>
<td>broad singlet (¹H NMR) or broad strong (IR)</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>CARs</td>
<td>cycloaddition reactions</td>
</tr>
<tr>
<td>C-C</td>
<td>carbon-carbon</td>
</tr>
<tr>
<td>C-O</td>
<td>carbon-oxygen</td>
</tr>
<tr>
<td>COD</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>Cp*</td>
<td>1,2,3,4,5-pentamethylcyclopentadienide</td>
</tr>
<tr>
<td>d</td>
<td>doublet (¹H NMR) or day</td>
</tr>
<tr>
<td>DA</td>
<td>Diels-Alder</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
</tbody>
</table>
DMA  dimethylacetamide
DMAD  dimethyl acetylenedicarboxylate
DMAP  4-dimethylaminopyridine
DME  1,2-dimethoxyethane
DMF  N,N-dimethylformamide
DMSO  dimethyl sulfoxide
DMPU  1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dppf  1,1'-bis(diphenylphosphino)ferrocene
dppm  bis(diphenylphosphino)methane
dppp  1,3-bis(diphenylphosphino)propane
DIBAL  diisobutylaluminium hydride
ee  enantiomeric excess
equiv.  equivalents
EtOAc  ethyl acetate
Et$_3$N  triethylamine
EtMgBr  ethylmagnesium bromide
FMO  frontier molecular orbital
FVT  flash vacuum thermolysis
GC  gas chromatography
h  hour(s)
Hex  hexyl
HOMO  highest occupied molecular orbital
HRMS  high-resolution mass spectroscopy
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>kcal</td>
<td>kilocalories</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (¹H NMR) or medium (IR)</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>mol</td>
<td>mole</td>
</tr>
<tr>
<td>NBD</td>
<td>norbornadiene</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NBN</td>
<td>norbornene</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methylpyrrolidone</td>
</tr>
<tr>
<td>N-O</td>
<td>nitrogen-oxygen</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMP</td>
<td>1,2,2,6,6-pentamethylpiperidine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>RBF</td>
<td>round-bottomed flask</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>rDA</td>
<td>retro-Diels-Alder</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet ($^1$H NMR) or strong (IR)</td>
</tr>
<tr>
<td>sat'd</td>
<td>saturated</td>
</tr>
<tr>
<td>$S_N2$</td>
<td>Substitution nucleophilic bimolecular</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>$^t$Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBSCl</td>
<td>tert-butyldimethylsilyl chloride</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>Ti($^t$OPr)$_4$</td>
<td>titanium(IV) isopropoxide</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>trimethylsilyl</td>
</tr>
<tr>
<td>TMSCl</td>
<td>trimethylsilyl chloride</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>w</td>
<td>weak (IR)</td>
</tr>
<tr>
<td>Compound #</td>
<td>List of Spectra</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2-40b</td>
<td>$^1$H NMR of $\text{exo-1-ethyl-4,10-dioxatricyclo[5.2.1.0]dec-8-ene-3,5-dione}$</td>
</tr>
<tr>
<td>2-40b</td>
<td>$^{13}$C NMR of $\text{exo-1-ethyl-4,10-dioxatricyclo[5.2.1.0]dec-8-ene-3,5-dione}$</td>
</tr>
<tr>
<td>2-43b</td>
<td>$^1$H NMR of $\text{exo-1-ethyl-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0]decahydronaphtho[2,3-d]isoxazole}$</td>
</tr>
<tr>
<td>2-43b</td>
<td>$^{13}$C NMR of $\text{exo-1-ethyl-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0]decahydronaphtho[2,3-d]isoxazole}$</td>
</tr>
<tr>
<td>3-20da</td>
<td>$^1$H NMR of $\text{3,5,8-trimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole}$</td>
</tr>
<tr>
<td>3-20da</td>
<td>$^{13}$C NMR of $\text{3,5,8-trimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole}$</td>
</tr>
<tr>
<td>3-22a</td>
<td>$^1$H NMR of $\text{8,9-bis-methoxymethyl-5-methyl-3,10-dioxa-4-azatricyclo[5.2.1.0]dec-4-ene}$</td>
</tr>
<tr>
<td>3-22a</td>
<td>$^{13}$C NMR of $\text{8,9-bis-methoxymethyl-5-methyl-3,10-dioxa-4-azatricyclo[5.2.1.0]dec-4-ene}$</td>
</tr>
<tr>
<td>3-23ea</td>
<td>$^1$H NMR of $\text{methyl-3-methyl-3a,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazole-9(4H)-carboxylate}$</td>
</tr>
<tr>
<td>3-23ea</td>
<td>$^{13}$C NMR of $\text{methyl-3-methyl-3a,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazole-9(4H)-carboxylate}$</td>
</tr>
<tr>
<td>3-23ga</td>
<td>$^1$H NMR of $\text{5,8-dimethoxy-3,9-dimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole}$</td>
</tr>
<tr>
<td>3-23ga</td>
<td>$^{13}$C NMR of $\text{5,8-dimethoxy-3,9-dimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole}$</td>
</tr>
<tr>
<td>3-23ga</td>
<td>Molecular structure of $\text{5,8-dimethoxy-3,9-dimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole}$ from X-Ray Diffraction analysis</td>
</tr>
<tr>
<td>3-25a</td>
<td>$^1$H NMR of $\text{3,8-dimethyl-6-phenyl-3a,4,4a,7a,8a-hexahydro-5H-4,8-epoxysisoxazolo[4,5-f]isoxindole-5,7(6H)-dione}$</td>
</tr>
<tr>
<td>3-25a</td>
<td>$^{13}$C NMR of $\text{3,8-dimethyl-6-phenyl-3a,4,4a,7a,8a-hexahydro-5H-4,8-epoxysisoxazolo[4,5-f]isoxindole-5,7(6H)-dione}$</td>
</tr>
<tr>
<td>3-27ba</td>
<td>$^1$H NMR of $\text{(5-methyl-3,8-dioxo-4,9-diazatricyclo[5.2.1.0]dec-4-en-9-yl)-phenyl-methanone}$</td>
</tr>
<tr>
<td>3-27ba</td>
<td>$^{13}$C NMR of $\text{(5-methyl-3,8-dioxo-4,9-diazatricyclo[5.2.1.0]dec-4-en-9-yl)-phenyl-methanone}$</td>
</tr>
<tr>
<td>3-28ba</td>
<td>$^1$H NMR of $\text{(5-methyl-3,9-dioxo-4,8-diazatricyclo[5.2.1.0]dec-4-en-8-yl)-phenyl-methanone}$</td>
</tr>
<tr>
<td>3-28ba</td>
<td>$^{13}$C NMR of $\text{(5-methyl-3,9-dioxo-4,8-diazatricyclo[5.2.1.0]dec-4-en-8-yl)-phenyl-methanone}$</td>
</tr>
<tr>
<td>3-28ba</td>
<td>Molecular Structure of $\text{(5-methyl-3,9-dioxo-4,8-diazatricyclo[5.2.1.0]dec-4-en-8-yl)-phenyl-methanone}$ from X-Ray Diffraction analysis</td>
</tr>
</tbody>
</table>
4-27da  $^1$H NMR of 1-(3-hydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one  236
4-27da  $^{13}$C NMR of 1-(3-hydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one  237
4-33g  $^1$H NMR of 1-(3-hydroxy-5,8-dimethoxy-4-methyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one  238
4-33g  $^{13}$C NMR of 1-(3-hydroxy-5,8-dimethoxy-4-methyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one  239
4-33g  Molecular Structure of 1-(3-hydroxy-5,8-dimethoxy-4-methyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one from X-Ray Diffraction analysis  240
Chapter 1

Introduction and Background
1.1 **Cycloaddition Reactions**

Inspired by nature’s creations, organic chemists have been developing synthetic methods and strategies for the total synthesis of extremely complex molecules. As many natural products such as taxol\(^1\) and halichondrins\(^2\) have demonstrated their efficacy to treat diseases, medicinal chemists from academic and pharmaceutical industries continue their efforts to solve nature’s puzzles. Development of a concise, economical synthesis of the target molecule with low ecological impact has become a principal priority for chemists. For this reason, reduction in the number of synthetic steps, minimization of by-products and maximization of efficiency are some of the more relevant challenges. One of the best ways to address these challenges relies on the development of methods that allow maximum synthetic efficiency. Cycloaddition reactions (CARs), by virtue of allowing the regio- and stereoselective construction of new rings by a simple addition of two or more molecules, occupy a leading position among the tools available to the synthetic organic chemist that best meet the above requirements.

CARs represent the formation of a diverse array of ring structures by either intermolecular or intramolecular cyclization. The process of cycloaddition is one of the most powerful and versatile methods to create a wide variety of complex molecules.\(^3\) Two of the most well-known CARs are the Diels-Alder reaction\(^4\), and the 1,3-dipolar cycloaddition reaction.\(^5\) 1,3-dipolar cycloaddition (1,3-DCA) reactions have found extensive use as a high-yielding and efficient, regio- and stereo-controlled method for the synthesis of many different heterocyclic compounds.\(^6\) Other CARs include the [2+2] cycloadditions of activated alkenes to form cyclobutanes,\(^7\) the reaction of allyl cations
with dienes to give seven membered rings\textsuperscript{8} and thermal\textsuperscript{9} or photochemical\textsuperscript{10} cycloadditions, which afford a variety of other ring sizes.

1.2 Cycloadditions with Bicyclic Alkenes

Bicyclic alkenes have unique geometry and inherent angle strain that serve as excellent templates for studying various CARs and their applications towards the synthesis of complex and highly substituted ring systems.\textsuperscript{11} Bicyclo[2.2.1]hepta-2,5-diene (norbornadiene) (NBD), is one of the most commonly studied bicyclic alkenes (Fig.1). The two double bonds of NBD are homoconjugated, which means a unique “through-space” interaction between the two double bonds is operative.\textsuperscript{12} Reactions of norbornadiene follow a pattern that is typically observed in cycloaddition reactions of bridged bicyclic molecules, where reactions occur preferentially on the more accessible \textit{exo} face, although some examples include formation of both \textit{endo} and \textit{exo} products.\textsuperscript{13}

![Figure 1.1. Structure of norbornadiene (1-1a) and norbornene (1-2a).](image)

The presence of homoconjugation between the two non-neighbouring carbon-carbon double bonds of NBD has also been found by investigating the photoelectron spectrum.\textsuperscript{14} Homoconjugation, defined in this case as the phenomenon of interactions of the \(\pi\)-orbitals through space, occurs in this type of system due to the proximity of the alkene functionalities. This through space interaction creates the opportunity to undergo reactions involving both alkenes such as \([2+2+2]\) homo-Diels-Alder cycloaddition with
alkenes and alkynes as reaction partners\textsuperscript{15} and photochemical isomerisation into the corresponding quadricyclanes.\textsuperscript{16}

There have been numerous CARs developed for bicyclic alkenes by methods involving thermal or photochemical stimuli and Lewis acid or transition-metal catalyzed reactions. Selected examples for norbornadiene and norbornene cycloaddition reactions are shown in Scheme 1.1. In the case of the norbornadiene core, cycloaddition paths (d)-(f) involve both double bonds to generate cycloadducts.

\begin{center}
\textbf{Scheme 1.1. Selected examples of norbornadiene/norbornene cycloaddition reactions.}
\end{center}
Some of the most common examples of bicyclic alkene structures used in cycloaddition reactions are shown below in Figure 1.2.

![Bicyclic Alkene Structures](image)

**Figure 1.2.** Representative bicyclic alkene structures used for various cycloaddition reactions in the literature.

1.3 1,3-Dipolar Cycloadditions

1.3.1 Basic Aspects

According to the Woodward – Hoffmann rules, 1,3-dipolar cycloaddition (1,3-DCA) is a symmetry allowed process under thermal conditions.\(^\text{9b, 17}\) 1,3-DCA reactions are isoelectronic with Diels-Alder reactions. Both of these 1,3-DCA and Diels-Alder reactions are \([4\pi+2\pi]\) cycloaddition reactions that proceed through a \(6\pi\)-electron transition state with a \(4\pi\)-electron component and a \(2\pi\)-electron component. 1,3-Dipoles are the \(4\pi\)-electron component in 1,3-DCA reaction and exist as zwitterionic three atom units which consist of at least one heteroatom. Alkenes or alkynes are typically employed...
as the $2\pi$-electron component, usually described as the dipolarophile, and are comprised of two atoms. The 1,3-dipolar cycloaddition reaction has become one of the most powerful methods for creating five-membered heterocycles.\textsuperscript{18}

1,3-Dipoles can be classified as either allyl anion type or propargyl/allenyl anion type according to their structure as shown in \textbf{Scheme 1.2}. Allyl type 1,3-dipoles are geometrically bent and isoelectronic with allyl anions. The propargyl/allenyl type 1,3-dipoles are linear and isoelectronic with propargyl/allenyl anions.

\begin{center}
\begin{tikzpicture}

\node (a) at (0,0) {\textbf{Allyl Type}};
\node (b) at (0,-2) {\textbf{Propargyl/Allenyl Type}};
\node (c) at (1,0) {\textbf{1-20}};
\node (d) at (1,-2) {\textbf{1-22}};
\node (e) at (2,0) {\textbf{1-21}};
\node (f) at (2,-2) {\textbf{1-23}};
\node (g) at (0.5,0) {\textbf{1-20}};
\node (h) at (0.5,-2) {\textbf{1-22}};
\node (i) at (1.5,0) {\textbf{1-21}};
\node (j) at (1.5,-2) {\textbf{1-23}};

\draw[->,thick,red] (a) -- (b);
\draw[<-,thick,red] (c) -- (d);
\draw[->,thick,red] (e) -- (f);
\draw[<-,thick,red] (g) -- (h);
\draw[->,thick,red] (i) -- (j);
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.2. Representation of allyl/propargyl type 1,3-dipoles.}

Commonly used allyl anion type 1,3-dipoles are nitrones, azomethine imines, azomethine ylides, azimines, azoxy compounds, nitro compounds, carbonyl ylides, carbonyl imines, carbonyl oxides, nitrosoimines, nitrosoxide and ozone. Familiar propargyl/allenyl type 1,3-dipoles are nitrile ylides, nitrile imines, nitrile oxides, diazoalkanes, azides and nitrous oxide (\textbf{Scheme 1.3}).\textsuperscript{19}
The 1,3-DCA reaction mechanism has been studied methodically and these reactions are largely considered to occur through a concerted transition state.\textsuperscript{20} A very nice synopsis of the mechanistic considerations of 1,3-dipolar cycloadditions has appeared in the literature.\textsuperscript{21} It has been detailed that the solvent polarity has very little effect on the rate of the cycloaddition reactions, and the reactions occur with a high degree of stereospecificity and regiospecificity. The main debate relating to the mechanism of 1,3-dipolar cycloaddition reactions has rested on the fact of whether the two new $\sigma$-bonds that are formed in the reaction are created one at a time or simultaneously. Arguments have been put forth in favour of both the step-wise reaction mechanism and the concerted mechanism.

Using molecular orbital theory, Huisgen proposed a concerted model for the transition state of the 1,3-DCA reactions, in which the $4\pi$ electron system present in 1,3-dipoles interacts with the $\pi$-bond of the dipolarophile (Scheme 1.4).\textsuperscript{6a, 19, 22}
Scheme 1.4. Huisgen proposed concerted mechanism for 1,3-dipolar cycloaddition.

Alternatively, Firestone proposed a step-wise mechanism for 1,3-DCA reactions via diradical intermediates.\textsuperscript{23} The diradical intermediate formed by the 1,3-dipole and the dipolarophile reacting to form one $\sigma$-bond as a diradical structure 1-29. The diradical intermediate then collapses to close the ring to form the second new $\sigma$-bond resulting in the final products (Scheme 1.5).

Scheme 1.5. Firestone-proposed step-wise mechanism for 1,3-dipolar cycloaddition.

The high degree of stereospecificity observed in many 1,3-dipolar cycloaddition reactions is often considered to be compelling evidence for concertedness of the reaction.\textsuperscript{6i, 19, 22} If diradical intermediates were being formed during the reaction (Scheme 1.5), the barrier to rotation about the bond ‘a’ requires a minimum of 2.3 kcal. mol$^{-1}$ higher than the barrier to cyclization.\textsuperscript{24} Barrier to rotation of bond ‘a’ for a simple primary, secondary, and tertiary alkyl radicals are 0-1.2 kcal. mol$^{-1}$.\textsuperscript{24b} means practically
there is no barrier to the predominant cycloaddition pathway. This evidence supporting the concerted mechanism makes it the most likely pathway for 1,3-DCA reactions.\textsuperscript{24}

The frontier molecular orbital (FMO) theory states that chemical reactions are governed by the interaction between the highest occupied and lowest unoccupied MOs (HOMO and LUMO, respectively) of the reactant molecules.\textsuperscript{25} 1,3-DCA reactions as dictated by FMO theory, occurs with the interaction of the HOMO\textsubscript{1,3-dipole} – LUMO\textsubscript{dipolarophile} or the LUMO\textsubscript{1,3-dipole} – HOMO\textsubscript{dipolarophile}.\textsuperscript{6e} Sustmann classified the 1,3-DCA reactions based on the character of the HOMO – LUMO interactions (Figure 1.3).\textsuperscript{26} The Group I reactions involve the HOMO\textsubscript{1,3-dipole} – LUMO\textsubscript{dipolarophile} interaction, also called normal electron demand reactions. Various ylides are electron rich species with high-lying HOMO’s and LUMO’s and preferentially react with electron deficient dipolarophiles due to the narrow energy gap between HOMO\textsubscript{1,3-dipole} – LUMO\textsubscript{dipolarophile}. Group III reactions are governed by LUMO\textsubscript{1,3-dipole} – HOMO\textsubscript{dipolarophile} interactions, which is known as inverse electron demand. Electrophilic 1,3-dipoles, such as nitrous oxide and ozone are in the Group-III category as their low-lying HOMO’s and LUMO’s allow them to preferentially react with electron rich dipolarophiles due to the narrow gap between LUMO\textsubscript{1,3-dipole} – HOMO\textsubscript{dipolarophile}. As for the Group II reactions where the energies of the frontier molecular orbitals of two reactants are similar, both molecular orbital interactions are possible allowing the cycloadditions to proceed either through the HOMO\textsubscript{1,3-dipole} – LUMO\textsubscript{dipolarophile} or through the LUMO\textsubscript{1,3-dipole} – HOMO\textsubscript{dipolarophile} interactions. Nitrile and azomethine imines and oxides react rapidly with both electron-rich and electron-deficient dipolarophile species.
Regiochemical orientations during the 1,3-DCA reactions are established by the rule of preferential facing, which indicates that both the large and small coefficients of the terminal atoms of the 1,3-dipole and dipolarophile are involved (Scheme 1.6). The coefficient magnitudes of HOMO orbitals of 1,3 dipoles have larger values for the terminus “z” than the terminus “x”. Control of regioselectivity by the dipole HOMO will lead to products with the substituent remote from the “z” terminus (4-substituted heterocycle) for monosubstituted, conjugated, and electron-deficient dipolarophiles (larger coefficient unsubstituted carbon in the LUMO) and to products with the substituent near the “z” terminus (5-substituted heterocycle) for electron-rich dipolarophiles (larger LUMO coefficient at substituted carbon). Since the largest coefficient of dipole LUMO orbitals is on the atom “x” and all dipolarophiles have the largest HOMO coefficient on the unsubstituted carbon, control of the LUMO dipole will lead to the predominant product with the substituent near the “z” termini (5-substituted heterocycle). However, application of this theory can lead to incorrect regiochemical predictions, in particular when steric or electrostatic effects are involved.
Scheme 1.6. Regiochemical considerations based on orbital coefficient magnitudes.

1,3-DCA reactions occur under thermal conditions over a wide range of temperatures, depending on the nature of the 1,3-dipole and dipolarophile. These 1,3-DCA reactions often require the presence of a catalyst which forms complexes with the reactant molecules. From the FMO standpoint, selective coordination of the Lewis acid to the dipolarophile accelerates the Group I reactions by lowering the dipolarophile orbital energy thereby decreasing the energy difference (ΔE) between the HOMO\text{dipole} and LUMO\text{dipolarophile}. The Lewis acid coordination to the dipole leads to inhibition of the reaction, while coordination to both reactants has little effect on the reaction rate. In the case for Group III reactions, coordination of the Lewis acid to the dipole lowers the energy of the dipole orbitals and decreases the energy difference (ΔE) between HOMO\text{dipolarophile} and LUMO\text{dipole} (Figure 1.4). For Group II reactions use of Lewis acids favours the occurrence of the process if the catalyst is selectively coordinated to the dipole or to the dipolarophile. Coordination to both reactants may have no net effect.
1,3-DCA reactions can occur by either intermolecular or intramolecular fashions depending on where the 1,3-dipole is attached. The reactions occur either in the presence or the absence of a catalyst. Many aspects of intramolecular reactions are similar to those of intermolecular reactions. However, due to the proximity of the reacting groups the regio- and stereoselectivity can differ significantly.

Due to the concertedness of 1,3-DCA reactions these reactions are among the most powerful tools for the stereospecific creation of new chiral centers in organic molecules. When 1,2-disubstituted alkenes are involved in cycloaddition reactions with 1,3-dipoles, two new chiral centers can be formed in a stereospecific manner due to the syn attack of the dipole on the double bond. If the alkene or the 1,3-dipole contains a chiral center(s), the approach toward one of the faces of the alkene or the 1,3-dipole can be discriminated, leading to a diastereoselective reaction. This type of selectivity is referred to as diastereofacial selectivity and is identified by diastereomeric excess (de).

### 1.3.2 1,3-Dipolar Cycloadditions of Nitrile Oxides

1,3-Dipolar cycloaddition of nitrile oxides with alkenes/alkynes is the general method for synthesis of isoxazolines/isoxazoles (Scheme 1.7). The parent nitrile oxide,
fulminic acid (formonitrile oxide, H-C\(\equiv\)N-O) has been used to prepare many derivatives over the last two centuries. The first cycloaddition reaction between nitrile oxides and olefins was recorded by the Weygand group.\(^{27}\) Huisgen later categorized the nitrile oxides as being members of a broader class of 1,3 dipoles that were capable of undergoing \([3+2]\) cycloaddition reactions.\(^{28}\)

\[ \text{R-C\(\equiv\)N-O} + \text{Y-X} \rightarrow \text{N-O-X} + \text{Y-R-C-N-O} \]

**Scheme 1.7. 1,3-Dipolar cycloaddition of nitrile oxide with alkenes/alkynes.**

Although nitrilium betaine R-C\(\equiv\)N-O is the most commonly used resonance structure for representing nitrile oxides, other important resonance hybrid structures are useful to explain the behaviour of these dipoles (Scheme 1.8). Resonance structures 1-37a and 1-37b are the only possible full octet structures, which are most influential in determining the electronic structures of the dipoles. Structures 1-37c and 1-37d are sextet formulas, which represent the tendency of the 1,3-dipolar cycloaddition of these dipoles. Neutral structure 1-37e represents the carbene behaviour of dipole and structures 1-37f and 1-37g are part of a full valence bond description.

**Scheme 1.8. Resonance structures of nitrile oxides.**

In general, nitrile oxides are unstable dipoles that are commonly prepared \textit{in situ} in the presence of a dipolarophile. The most widely used methods for generating nitrile oxides are (1) dehydrohalogenation of hydroxamoyl chlorides (Scheme 1.9) and (2)
dehydration of nitroalkanes (Scheme 1.10). In dehydrohalogenation the respective aldehydes are conveniently converted to aldoximes (1-41) with hydroxylamine and then aldoximes are reacted with halogenating reagents such as chlorine,\textsuperscript{29} NOCl,\textsuperscript{30} N-chlorosuccinimide (NCS),\textsuperscript{31} or N-bromosuccinimide (NBS)\textsuperscript{32} to form hydroxamoyl halides (1-42). Treatment of hydroxamoyl halides with a tertiary amine base (commonly triethylamine) results in the generation of the corresponding nitrile oxides.\textsuperscript{33}

\begin{align*}
&\text{H} = \text{NOH} \quad \text{Cl}_2, \text{NOCl} \quad \text{or NBS or NCS} \quad \text{Et}_3\text{N} \quad \text{R-C=N-O} \\
&\text{1-41} \quad \text{1-42} \quad \text{1-37}
\end{align*}

**Scheme 1.9. Preparation of nitrile oxides from aldehydes.**

In the dehydration method, the treatment of primary nitroalkanes with phenyl isocyanate and triethylamine introduced by Mukaiyama is the most commonly used method to generate the nitrile oxides.\textsuperscript{34}

\begin{align*}
&R \text{NO}_2 \quad \text{Et}_3\text{N} \quad \text{R-N}=\text{O} \quad \text{HNEt}_3 \quad \text{O=C=Ph} \quad \text{Et}_3\text{N} \quad \text{R-C=N-O} \\
&\text{1-43} \quad \text{1-44} \quad \text{1-45} \quad \text{1-46} \quad \text{1-47} \quad \text{1-48} \quad \text{1-37}
\end{align*}

**Scheme 1.10. Preparation of nitrile oxides from nitroalkanes using Mukaiyama method.**

Shimizu used ethyl chloroformate in combination with triethylamine for dehydration of nitroalkanes, but this method requires higher temperatures and sometimes leads to lower yields.\textsuperscript{35} Hassner developed a new method for dehydration of nitroalkanes
using 4-dimethylaminopyridine (DMAP) and di-tert-butyl dicarbonate (BOC anhydride), providing milder reaction conditions and is the most useful method for nitrile oxide generation (Scheme 1.11).\textsuperscript{36}

\begin{center}
\includegraphics[width=\textwidth]{nitrile_oxide_generation.png}
\end{center}

Scheme 1.11. Preparation of nitrile oxides from nitroalkanes using Hassner’s method.

1.3.3 Regio and Stereochemical Aspects of Nitrile Oxide 1,3-Dipolar Cycloadditions

1,3-DCA reactions of nitrile oxides with substituted olefins offer the potential to generate two regioisomers that are 4-substituted and 5-substituted isoxazolines. Reactions with monosubstituted olefins occur with almost complete regioselectivity giving 5-substituted isoxazolines (Scheme 1.12).\textsuperscript{37}
Scheme 1.12. Possible regioisomers from 1,3-DCA of nitrile oxides with monosubstituted olefins.

Nitrile oxides with 1,2-disubstituted olefins normally give a mixture of regioisomers and the ratio of isomers is governed by electronic and steric factors as described earlier in Section 1.3.1 (Scheme 1.13).$^{37d, 38}$

Scheme 1.13. Possible regioisomers from 1,3-DCA of nitrile oxides with 1,2-disubstituted olefins.

In the case of 1,1-disubstituted alkenes, the obtained cycloaddition products occur with the oxygen atom from the nitrile oxide attached to the most crowded carbon atom of the dipolarophile (which is the more substituted carbon at the 5-position of the heterocycle).$^{39}$ For trisubstituted alkenes, the most substituted carbon will end up at the 5-position of the heterocycle$^{40}$ while donor substituted alkenes are an exception resulting in the opposite isomers.$^{41}$

Due to the concertedness of the 1,3-DCA reactions, these reactions occur in a stereospecific manner. The reaction of nitrile oxides with 1,2-disubstituted alkenes generates two new stereocenters in a stereospecific manner due to the syn attack of the dipole on the double bond. For example, in the cycloaddition of nitrile oxide with cis-
alkene four products are possible. Out of these four products, 1-59a is regioisomer to 1-60a and 1-59b is regioisomer to 1-60b. Also 1-59a is stereoisomer to 1-59b and 1-60a is stereoisomer of 1-60b. A similar scenario occurs with the trans-alkene (Scheme 1.14).

Scheme 1.14. Possible regio and stereoisomers from 1,3-DCA of nitrile oxides with 1,2-disubstituted cis and trans olefins.

The introduction of a chiral center to one of the reactants (either the alkene or the 1,3-dipole) results in a discrimination of one of the faces of the alkene, leading to a diastereoselective reaction. Chiral nitrile oxides have been used in 1,3-DCA since 1970; however, only a limited number of reports exist. In the first report by Tronchet, reaction of a chiral glucoside-derived nitrile oxide did not give the desired facial selectivity, yet subsequent reports have shown improved facial selection. Thomas et al. achieved modest...
diastereoselectivity using chiral nitrile oxides 1-64 with \textit{cis}-1,2-disubstituted alkenes (Scheme 1.15). \footnote{19}

\begin{center}
\begin{tikzpicture}
\tikz[baseline=-0.65ex]
\node[above,align=left,font=\footnotesize]{1-64} + \node[above,align=left,font=\footnotesize]{1-65} \implies \node[above,align=left,font=\footnotesize]{1-66};
\draw[->,thick] (1-64) -- (1-66); \node[below,align=left,font=\footnotesize]{R= H: 49\% de}; \node[below,align=left,font=\footnotesize]{R=Me: 30\% de};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.15. 1,3-DCA of chiral nitrile oxide 1-64 with \textit{cis} 1,2-disubstituted olefin.}

Nitrile oxide 1-67, derived from glyceraldehydes, showed improved diastereoselectivity with 1,2-disubstituted alkenes while achieving the best selectivity with \textit{cis}-1,2-disubstituted alkenes. Improved selectivity with 1,2-disubstituted alkenes over monosubstituted alkenes could be due to the proximity of a newly formed chiral center to the original chiral centre (Scheme 1.16). \footnote{20}

\begin{center}
\begin{tikzpicture}
\tikz[baseline=-0.65ex]
\node[above,align=left,font=\footnotesize]{1-67} + \node[above,align=left,font=\footnotesize]{1-68} \implies \node[above,align=left,font=\footnotesize]{1-69};
\draw[->,thick] (1-67) -- (1-69); \node[below,align=left,font=\footnotesize]{49\% de};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.16. 1,3-DCA of chiral nitrile oxide 1-67 with \textit{cis} 1,2-disubstituted olefin.}

Nitrile oxide cycloadditions to chiral olefins have been actively reported since the 1980s. CycloadDITION to the monosubstituted alkenes preferentially occurs on the less sterically shielded face of the alkene and stereoselectivity improves as the size of the R group attached to the chiral centre is increased (Scheme 1.17). \footnote{21}
Scheme 1.3-DCA of nitrile oxides with chiral olefin 1-71.

Kozikowski also demonstrated that the reaction occurs on the less hindered side of the alkene derived from glyceraldehyde with nitrile oxide providing 86% de (Scheme 1.18).\(^{46}\)

Scheme 1.18. 1,3-DCA of nitrile oxide 1-75 with chiral olefin 1-74.

Houk proposed transition state models based on the addition results of nitrile oxides with chiral allyl ethers that account for the observed stereoselectivities.\(^ {45, 47}\)

Figure 1.5. Houk’s models for possible transition states of 1,3-DCA with chiral olefins.

According to Houk’s model (Figure 1.5), the major product arises from transition state 1-77 and the minor product is proposed to arise from transition state 1-78. In transition state 1-77 which is responsible for the major product, the largest group (L) occupies the anti position relative to nitrile oxide, the medium group (M) the inside
position, and the smallest group (S) occupy the outside position. Allylic alkoxy and siloxy groups tend to prefer the inside position due to the secondary orbital interactions. However, the hydroxyl group favours the outside over the inside position with transition state 1-79 (Figure 1.6), due to hydrogen bonding of the nitrile oxide oxygen atom to the hydroxy group giving syn product as major diastereomer.

![Figure 1.6. Houk’s models for possible transition state of 1,3-DCA with chiral olefins with oxygen at allylic position.](image)

Chiral auxiliaries are used to induce the diastereoselectivity in the nitrile oxide cycloadditions with achiral alkenes. Acrylates containing camphor derived chiral auxiliary gave moderate to good diastereoselectivity (Scheme 1.19).

![Scheme 1.19. 1,3-DCA of olefins with chiral auxiliary.](image)

### 1.3.4 Nitrile Oxide Cycloadditions of Bicyclic Alkenes

As discussed earlier, 1,3-DCA reactions of norbornenes are known to follow the “exo rule” resulting in exo-adducts. However cycloaddition reactions of norbornadiene with benzonitrile oxide have resulted in the formation of small amounts of
endo-adducts along with major exo-adducts. The Taniguchi group confirmed the formation of minor quantities of endo-adducts along with exo-adducts in 1,3-DCA reactions of norbornadienes with nitrile oxides (Scheme 1.20). The formation of endo-adducts in the case of norbornadiene but not with norbornenes can be explained based on Inagaki’s proposal that \( \pi \)-electron distribution of norbornene extends more to the exo-face (due the interaction of a \( \pi \)-orbital and a methano bridge orbital or the back side of the anti C-H bond orbital at \( C^7 \) position). In case of norbornadiene, due to homoconjugation present on the endo-face of the molecule, the \( \pi \)-electron distribution extends towards the endo-face. As a result, the difference in the \( \pi \)-electron distribution between exo- and endo-faces of the norbornadiene is smaller than that of norbornene and causes the formation of endo-adducts in the cycloaditions of electron-accepting 1,3-dipoles to norbornadienes.

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{Cl} \\
\text{N} \quad \text{O} \quad \text{OH} & \quad \text{Et}_3\text{N} \\
\text{THF} & \quad 0-5 \, ^\circ \text{C} \\
\text{1-84} & \quad \text{1-85} \\
\end{align*}
\]

**Scheme 1.20. Nitrile oxide 1,3-DCA of norbornadienes 1-86.**

The Taniguchi group has shown that the polarity of non-aromatic solvents has an effect on exo/endo product ratios. As the solvent polarity (measured by the Dimroth-Reichardt parameter) is increased, the rate of the formation of endo adduct is increased. It was hypothesized that as solvent polarity (\( E_r \)) is increased, the free energy of solvation becomes smaller. The dipole moment of the endo-form in the transition is greater than the exo-form and an increasing \( E_r \) value of the solvent results in a larger decrease in the free
energy of solvation for the endo-form in the transition state relative to the exo-form. Therefore, as the E_v value of the solvent increases, the rate of the formation of the endo adduct increases.

Taniguchi’s research group subjected bicycloalkenes 1-89, 1-90 and 1-91 (Scheme 1.21) to 1,3-DCA reaction. Endo selectivity was observed for bicycloalkene 1-89 while exo selectivity was observed with 1-90. In the 1,3-DCA of 1-91, a mixture of exo and endo adducts were formed with the exo adduct as the major product. These results were rationalized based on the orbital mixing rules as described previously. The HOMO of the C^5-C^6 double bond extends more to the endo-face and in 1-89, similarly HOMO of the C^8-C^9 double bond of compound 1-90 extends more to the exo-face. For compound 1-91 similar explanation to norbornene could be used to explain the predominant exo product (Scheme 1.21).

\begin{align*}
\text{R}_1 &= \text{CO}_2\text{Me} \\
\text{R}_2 &= \text{Ph, PhCO}
\end{align*}

\begin{align*}
\text{exo:endo} &= 87:17
\end{align*}

Scheme 1.21. Nitrile oxide 1,3-DCA of bicyclic alkenes 1-89 to 1-91.
The 1,3-DCA reaction of bicycloalkene 1-98 with various nitrile oxides demonstrates excellent chemo- and stereoselectivities (Scheme 1.22). These cycloadditions gave exclusively exo products and the exo selectivity has been explained based on the orbital mixing rule of norbornene the HOMO norbornene extends more towards exo face than the endo face as discussed previously. The chemo-selectivity observed (only C⁶=C⁷ participated in cycloaddition) could be due to a combination of factors since (a) both double bonds are influenced by the electron donating character of the N atom (based on chemical shifts of 4-H and 7-H), (b) interaction of HOMO of the C⁶=C⁷ double bond with the methano-bridge orbital is assumed to be greater than the HOMO of the C³=C⁴ double bond with the methano-bridge orbital and (c) the bulky N-substituent (phenyl sulfonyl group) may hinder the approach of the dipole towards the C³=C⁴ double bond. Regioselectivity (cycloadduct as major product) is due the fact that these dipoles are electron-accepting dipoles, which indicates these cycloadditions are LUMO-controlled reactions (interactions between HOMO of olefin and LUMO of the dipole are assumed). Chemical shifts of the protons on C⁶=C⁷ (6-H: 6.14 ppm, 7-H: 5.1-5.5 ppm) indicates that the C⁶=C⁷ double bond is polarized due to the electron donating character of the nitrogen and this polarization of the double bond is responsible for regioselectivity.

Scheme 1.22. Nitrile oxide 1,3-DCA of bicyclic alkene 1-98.
The Plumet group has studied the 1,3-DCA using acetonitrile oxide and benzonitrile oxide, with substituted oxanorbornene systems 1-102.\(^{56}\) Reactions of \(C^2\) substituted oxanorbornenes gave corresponding \(exo\) adducts exclusively with excellent yields. In all the cases, mixtures of regioisomers were formed. The highest regioselectivity was observed in cycloadditions of acetonitrile oxide with a cyanoacetoxy derivative, and afforded a 75:25 mixture of cycloadducts 1-104 and 1-105, respectively (Scheme 1.23).

\[ \text{Scheme 1.23. Nitrile oxide 1,3-DCA of bicyclic alkenes 1-102.} \]

Introduction of a halogen atom at position 5 of the 7-oxanorbornene dramatically changes the observed regioselectivity. The cycloaddition of 1-106 with acetonitrile oxide and mesityl nitrile oxide proceeds with high selectivity such that the oxygen of the nitrile oxide becomes bonded to the more hindered terminus of the double bond. Thus, the reaction of compounds 1-106 affords only adducts 1-107 except substrate 1-106c gave mixtures of regioisomers 1-107c and 1-108c. The reduced regioselectivity for the reaction of 1-106c could be explained by the factor that the homodonating character of the ethylenedioxy group destabilizes the transition state to form cycloadduct 1-107c (Scheme 1.24).\(^{56a}\)
from the cycloaddition on bicyclic alkenes.

\[
\text{acetonitrile oxide}
\]

hindered terminus of the double bond high selectivity such that the oxygen of the nitrile oxide becomes bonded to the more hindered terminus of the double bond. Substrates 1-109a and 1-109b afforded only corresponding adduct 1-111 with mesityl nitrile oxide but substrate 1-109c with acetonitrile oxide gave corresponding mixtures of regioisomers 1-110 and 1-111 (Scheme 1.25).

Scheme 1.24. Nitrile oxide 1,3-DCA of bicyclic alkenes 1-106.

Cycloaddition reactions of substrates with a halogen atom at position 6 of the 7-oxanorbornene 1-109 with mesityl nitrile oxide and acetonitrile oxide proceeded with high selectivity such that the oxygen of the nitrile oxide becomes bonded to the more hindered terminus of the double bond. Substrates 1-109a and 1-109b afforded only corresponding adduct 1-111 with mesityl nitrile oxide but substrate 1-109c with acetonitrile oxide gave corresponding mixtures of regioisomers 1-110 and 1-111 (Scheme 1.25).

Scheme 1.25. Nitrile oxide 1,3-DCA of bicyclic alkenes 1-109.

The Namboothiri group demonstrated the substituent effect on 1,3-dipolar cycloaddition on bicyclic alkenes. The approach of the dipole takes place exclusively from the \textit{exo}-face of the dicyclopentadiene moiety providing a mixture of regioisomers in an approximately 55:45 ratio. On the other hand, nitrile oxide cycloaddition to
dimethyldicyclopentadiene dicarboxylate (Thiele’s ester) exhibits complete regioselectivity as well, providing a single isomer in good yield. The influence of remote substituents on the regioselectivity has also been investigated using 8-hydroxy and 1-keto derivatives of dicyclopentadiene (Scheme 1.26).

Scheme 1.26. Nitrile oxide 1,3-DCA of bicyclic alkenes 1-112.

The N-benzyl-2-azanorborn-5-ene system 1-115 was subjected to 1,3-dipolar cycloaddition reaction by Quadrelli et al. and resulted in the formation of a mixture of regioisomers (Scheme 1.27). The slight regiochemical preference of cycloadduct 1-117 over 1-118 was attributed to the polarization of the double bond caused by the electronegative nitrogen at the allylic position.

Scheme 1.27. Nitrile oxide 1,3-DCA of bicyclic alkene 1-115.
N-Acyl-2-oxa-3-azanorborn-5-enes 1-119 have been studied for 1,3-dipolar cycloadditions with aryl nitrile oxides. These substrates also generated exclusively exo isomers (Scheme 1.28).\textsuperscript{59} In all cases, mixture of regioisomers were formed, and the slight regiochemical preference of cycloadduct 1-121 over 1-122 could be due to the polarization of the double bond caused by the electronegative nitrogen substitution at the allylic position.

Scheme 1.28. Nitrile oxide 1,3-DCA of bicyclic alkenes 1-119.

1.4 Tam Group’s Research on Cycloaddition Reactions of Bicyclic Alkenes

The Tam group has made extensive contributions to the research on cycloaddition reactions involving bicyclic alkenes. The cycloaddition reactions that have been studied include [2+2] cycloaddition,\textsuperscript{60} cyclodimerization\textsuperscript{61} and 1,3-dipolar cycloaddition reactions.\textsuperscript{62}

1.4.1 [2+2] Cycloaddition

The [2+2] cycloaddition reaction is a convenient method for the construction of four membered ring systems. The [2+2] cycloaddition between bicyclic alkenes and an unsaturated reaction partner is a thermally forbidden process by the Woodward–Hoffman rules,\textsuperscript{17b} yet it is a photochemically allowed process and it can be achieved by Lewis acid or transition metal catalysis. The [2+2] cycloaddition reactions of bicycloalkenes with
alkynes to form fused cyclobutene rings have been extensively explored using various transition metal catalysts.  

The electronic effects of 7-substituted norbornadienes were examined in the Ru-catalyzed [2+2] cycloaddition with ethyl 3-phenylpropiolactone 1-123 (Scheme 1.29). Out of the four possible isomeric products, only the anti-exo cycloadduct 1-125 was formed as a single regio- and stereoisomer. From these results, it is observed that as electronegativity of the Y substituent in 1-123 is increased, the reactivity of the alkene was reduced. The electron withdrawing Y group reduces the electron density on the reacting anti-π bond thereby reducing reactivity.

Scheme 1.29. Ru-catalyzed [2+2] cycloaddition of 7-substituted norbornadienes.

The 2,3-disubstituted norbornadienes (1-126) in Ru-catalyzed [2+2] cycloaddition reactions proceeded in a completely chemoselective manner, on the unsubstituted double bond (Scheme 1.30). Electron poor alkenes, due to electron withdrawing groups have showed lower reactivity.

Scheme 1.30. Ru-catalyzed [2+2] cycloaddition of 2,3-disubstituted norbornadienes.
Expanding the scope of the ruthenium-catalyzed [2+2] cycloaddition reaction to study the reactivity of alkyne components revealed that more electron deficient alkynes are more reactive relative to unactivated alkenes (Scheme 1.31).<sup>66</sup> Sterics are also a contributing factor, since as the degree of substitution at the propargylic position is increased, the reactivity of the alkyne decreases significantly.

![Scheme 1.31. Ru-catalyzed [2+2] cycloaddition of norbornadiene with alkynes.](image)

During the regioselectivity studies of [2+2] cycloaddition reactions on unsymmetrical bicyclic alkenes, Ru-catalyzed cycloaddition between 2-substituted norbornadiene 1-132 with alkyne 1-133 produced cycloadducts with moderate regioselectivities with 1-134 as the major product and 1-135 as the minor product (Scheme 1.32).<sup>65</sup>

![Scheme 1.32. Ru-catalyzed [2+2] cycloaddition of 2-substituted norbornadienes.](image)
2-Substituted norbornenes 1-136 offer more complexity than their norbornadiene counterparts due to the possibility of both exo and endo substituents as well as the exocyclic double bonds. In these cases, two regioisomers were formed: major product 1-137 with the ester group anti to the 2-substituent and minor product 1-138 the ester group syn to the 2-substituent (Scheme 1.33).67

\[
\begin{align*}
\text{X} & \quad \text{Y} \\
\text{OAc} & \quad \text{H} \\
\text{H} & \quad \text{OAc} \\
\text{OBn} & \quad \text{H} \\
\text{H} & \quad \text{OBn} \\
\text{X},\text{Y} = \text{O} \text{ (ketone)}
\end{align*}
\]

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Ratio of 1-137:1-138</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAc</td>
<td>H</td>
<td>4:1</td>
</tr>
<tr>
<td>H</td>
<td>OAc</td>
<td>1.4:1</td>
</tr>
<tr>
<td>OBn</td>
<td>H</td>
<td>3:1</td>
</tr>
<tr>
<td>H</td>
<td>OBn</td>
<td>1.2:1</td>
</tr>
<tr>
<td>X,Y = O (ketone)</td>
<td>7.5:1</td>
<td></td>
</tr>
</tbody>
</table>


Exo substituents gave better regioselectivity than the endo substituents, which is attributed to the backside of the \(\sigma^*\)-bond (from the Y substituent) interacting with the \(\pi\)-orbitals of the double bond. With endo substituents, the backside of the \(\sigma\)-bond is in the exo face of the molecule and is unable to interact with the \(\pi\)-system, leading to much lower selectivity. 2-Substituted norbornenes with exocyclic double bonds (1-136e) are more effective than exo substituents in providing selectivity due to greater overlap of the \(\pi\)-system in the endo face of the bicyclic compounds compared to \(\sigma\)-\(\pi\) interactions of the \(\text{sp}^3\) carbon exo substituents (Figure 1.7).

Figure 1.7. Representation of \(\sigma\)-\(\pi\), \(\pi\)-\(\pi\) interactions in 2-substituted norbornenes.
Ru-catalyzed [2+2] cycloadditions between various C1-substituted 7-oxanorbornadienes 1-139 with unsymmetrical alkynes produced cycloadducts 1-141 and 1-142 in moderate to good yields (Scheme 1.34).60b

Scheme 1.34. Ru-catalyzed [2+2] cycloaddition of C1-substituted 7-oxanorbornadienes 1-139.

A methyl ester in the C1 position of the oxabenzonorbornadiene provided the best regioselectivity of the alkenes studied. On the other hand a methyl group at C1 did not affect the electronics or steric s of the alkene appreciably inducing no selectivity in the reaction. Of the alkynes employed in the study, the sulfone provided both the greatest yield and regioselectivity, forming 1-141 in a 110:1 ratio over 1-142.

Asymmetric versions of the Ru-catalyzed [2+2] cycloaddition were explored by the Tam research group. Cycloaddition reactions on symmetrical bicycloalkenes 1-2a/1-3a with chiral propargylic alcohol derivatives 1-143 gave good to moderate diastereoselectivity and giving 1-144 as the major product (Scheme 1.35).68

Introducing chiral auxiliaries (Xc) such as acyl carbamates and acyl sultams on the alkyne induced asymmetry into the cycloaddition. Acyl carbamates were found to effect poor diastereoselectivity and the sultam was highly diastereoselective resulting in 65-98.8% de with a variety of bicyclic alkenes (Scheme 1.36).\textsuperscript{60a} Diastereoselective cycloaddition utilizing chiral cyclic ynamides resulted in a low to moderate level of asymmetric induction.\textsuperscript{69}

Scheme 1.36. Ru-catalyzed [2+2] cycloaddition of bicyclic alkenes with alkynes attached with chiral auxiliaries.
1.4.2 Rhodium Catalyzed Cyclodimerization

The Tam research group accidentally discovered a cyclodimerization process during isomerization studies of bicyclic alkenes. Oxabenzonorbornadienes upon treatment with \([\text{RhCl(cod)}]_2\) lead to the formation of naphtha[1,2-b] furan ring system.\(^{61}\) Simultaneously, a similar transformation was also reported independently by the Hayashi group using a rhodium catalyst (Scheme 1.37).\(^{70}\)

![Scheme 1.37. Rh-catalyzed cyclodimerization of oxabenzonorbornadienes.](image)

Upon screening a number of different rhodium catalysts, silver salts, solvents and phosphine ligands, it was found that \([\text{RhCl(cod)}]_2\) in the presence of AgBF\(_4\) and BINAP in DCE are the best conditions for performing this transformation. Chiral BINAP ligands are able to achieve high enantioselectivity (as high as 98% ee), while maintaining high chemical yield. Various substituents such as Me, OMe, Br, F on the aromatic ring were compatible in producing good to excellent enantioselectivities.

Interestingly, C\(^{1}\)-substituted oxabicycles did not undergo cyclodimerization under similar conditions; the starting materials were either isomerized to the corresponding naphthol 1-153, or remained unreacted (Scheme 1.38).\(^{61}\)
Scheme 1.38. Rh-catalyzed isomerization of C¹-substituted oxabenzonorbornadienes.

1.4.3 1,3-Dipolar Cycloaddition

The Tam research group is actively involved in investigating 1,3-DCA reactions of bicyclic alkenes with nitrile oxides and nitrones. The first examples of the intramolecular 1,3-dipolar cycloadditions of norbornadiene-tethered nitrile oxides were demonstrated. These cycloadditions can yield multiple regio- and stereoisomers, yet they have been shown to proceed in a highly regio- and stereoselective manner, giving the exo cycloadducts in good yields.⁶²a,⁶²b Reactions with bicyclic alkenes 1-154 proceeded well with all carbon, oxygen and sulphur containing tethers while greatest yields were achieved with the carbon tether. The 1,3-DCA reaction of 1-154 tolerated three- and four-atom tethers, providing cycloadducts with five- and six-membered rings. As the length of the tether increased, the rate of the desired reaction decreased, as side reactions could occur more readily. The cycloaddition reaction proceeded with various substituents in the C³ position including alkyl and heteroatom moieties (Scheme 1.39).

Scheme 1.39. Intramolecular 1,3-DCA of bicyclic alkene tethered nitrile oxides.
The intramolecular 1,3-DCA reactions of norbornadiene-tethered nitrones have been investigated using norbornadiene framework. Although eight possible cycloadducts could be formed in the cycloadditions, in most cases, single regio- and stereoisomers were formed. Similar to intramolecular nitrile oxide cycloadditions, these cycloadditions were found to be highly regio- and stereoselective, giving the exo cycloadducts in moderate to good yields (Scheme 1.40).

![Scheme 1.40. Intramolecular 1,3-DCA of bicyclic alkene tethered nitrones.](image)

The intermolecular 1,3-DCA reactions of the corresponding bicyclic alkenes with the nitrile oxides (generated from the corresponding nitroalkanes using the Hassner method (BOC)₂O/DMAP) occurred at room temperature with moderate stereoselectivity (exo vs endo) (Scheme 1.41).

![Scheme 1.41. 1,3-DCA of norbornadiene with nitrile oxides.](image)

The cycloadditions of norbornene and 2-substituted-2-norbornenes were found to be completely regio- and stereoselective, giving single regio- and stereoisomers in good...
yields. Only the regioisomers with the oxygen of the nitrile oxide attached to $C^2$ of the norbornene were produced in the case of 2-substituted-2-norbornenes (Scheme 1.42).

![Scheme 1.42. 1,3-DCA of 2-substituted-2-norbornenes with nitrile oxides.](image)

1,3-Dipolar cycloaddition of exo-2-substituted-5-norbornenes and endo-2-substituted-5-norbornenes with benzonitrile oxide were completely stereoselective, giving only exo cycloadducts. Although chemical yields were good, low regioselectivities were observed (Scheme 1.43).

![Scheme 1.43. 1,3-DCA of 2-substituted-5-norbornenes with nitrile oxides.](image)

1,3-Dipolar cycloaddition of the $C^1$-substituted norbornene system has been explored. In this case also, the reaction is completely stereoselective giving the exo cycloadduct. Two regioisomers were formed in the ratio of 80:20 with 87% overall yield. The major isomer was found to be the one with the oxygen atom of the nitrile oxide being attached to $C^2$ of the norbornene (Scheme 1.44).
1.4.4 Rhodium Catalyzed Cyclopropanation

During the ruthenium-catalyzed [2+2] cycloaddition of propargylic alcohols with oxabenzonorbornadiene the Tam research group observed the cyclopropanation product (1-171) instead of the expected [2+2] cycloadduct (Scheme 1.45). Interestingly, chiral propargylic alcohols would undergo the expected [2+2] cycloaddition reaction with a selection of bicyclic alkenes with a carbon atom in the 7-position. But when the oxabenzonorbornadiene was used with a secondary propargylic alcohol under the same reaction conditions, a meso cyclopropane was formed as the major product 1-171. The formation of this product was found to be highly stereoselective, producing a single exo cyclopropane adduct.\(^\text{72}\)

1.5 Ring-Opening Reactions of Isoxazolines

2-Isoxazolines serve as excellent precursors for the preparation of β-hydroxycarbonyls, β-hydroxyimines, β-hydroxynitriles, γ-aminoalcohols and β-
aminoenones through N-O bond cleavage. In addition, oximes can be formed by C-O bond cleavage and carbonyl derivatives via retro-aldol cleavage. Numerous other products are obtained by the rearrangement of 2-isoxazolines. Often these ring-opening products are formed in a diastereoselective or stereoselective manner.

1.5.1 β-Hydroxy carbonyls Through N-O Bond Cleavage of Isoxazolines

N-O bond cleavage of 2-isoxazolines provides a powerful alternative to classic carbonyl addition methods for the preparation of stereochemically well-defined aldol adducts. Reductive methods using Ni, Pd, Ti and oxidative methods using ozone, bromine, peracids and metal carbonyls such as Mo(CO)$_6$, Fe(CO)$_5$ and Fe/NH$_4$Cl offer the β-hydroxycarbonyls from the N-O bond cleavage of the 2-isoxazolines.

1.5.1.1 Nickel Catalyzed Cleavage

Wollenberg demonstrated the reductive cleavage of 2-isoxazoline 1-172 by hydrogenolysis using Raney-nickel in acetic acid to give β-hydroxyketone 1-173 with high yields (Scheme 1.46). Mixtures of cis and trans isomers were formed due to the epimerization at the β-hydroxyimine intermediate stage via the tautomeric enamine form.$^{73}$

\[
\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\xrightarrow{1. \text{ Raney Ni, H}_2, \text{ HOAc}}
\begin{array}{c}
\text{O} \\
\text{OH}
\end{array}
\]

Scheme 1.46. Raney Ni/H$_2$ catalyzed cleavage of 2-isoxazolines.

The epimerization problem was addressed by Kozikowski by employing a strong mineral acid such as HCl or Lewis acid (AlCl$_3$) in the reaction medium. By using these modified conditions Kozikowski’s group reported efficient transformation of a variety of
substituted 2-isoxazolines \(1-174\) into \(\beta\)-hydroxyketones \(1-175\) with excellent yields (Scheme 1.47).\(^{74}\)

\[
\begin{align*}
\text{Raney Ni/AlCl}_3 & \quad \text{(4 eq.)} \\
\text{MeOH:Water} & \quad 5:1
\end{align*}
\]

\[
\begin{align*}

\text{Scheme 1.47. Raney Ni/AlCl}_3 \text{ catalyzed cleavage of 2-isoxazolines.}

\text{Additives such as an acetate buffer (NaOAc/AcOH), phosphate buffer (NaH}_2\text{PO}_4/\text{Na}_2\text{HPO}_4), \text{trimethyl borate, and boric acid in the reaction medium improves the stereochemical outcome of the ring opening reactions of Ni catalyzed reactions.}^{75} \text{ A series of 2-isoxazolines } 1-176 \text{ were subjected to Ni catalyzed cleavage conditions to obtain } \beta\text{-hydroxyketones } 1-177 \text{ in excellent yields (Scheme 1.48).}^{75b}

\text{Scheme 1.48. Raney Ni/boric acid catalyzed cleavage of 2-isoxazolines.}

1.5.1.2 Palladium Catalyzed Cleavage

\text{N-O bond cleavage of 2-isoxazolines in the presence of Pd/C leads to the formation of } \beta\text{-hydroxyketones}^{76} \text{ or } \gamma\text{-aminoalcohols.}^{77} \text{ 2-Isoxazolines substituted with phenyl and alkyl groups on the } C^3 \text{ and } C^5 \text{ position tend to form } \gamma\text{-aminoalcohols. C-O bond cleavage is prominent when electron withdrawing groups such as carboxyl or carbonyl are on the } C^3 \text{ position, and an aromatic group is on the } C^5 \text{ position to form}
oximes. When the C³ position is substituted with aromatic or alkyl groups and there is no aromatic substitution at the C⁵ position, then normal N-O cleavage occurs. Lindlar’s catalyst in aqueous methanol containing acetic acid was found to give β-hydroxyketones 1-179 from various olefin-containing isoxazolines 1-178 with excellent yields (Scheme 1.49).  

![Scheme 1.49. Palladium catalyzed cleavage of 2-isoxazolines.](image)

1.5.1.3 Titanium Catalyzed Cleavage

Ring opening of 2-isoxazolines using Ti³⁺ to form β-hydroxycarbonyls through N-O bond cleavage is well documented (Scheme 1.50).  

![Scheme 1.50. Ti³⁺ catalyzed cleavage of 2-isoxazolines.](image)

Titanium (IV) isopropoxide in the presence of ethylmagnesium bromide reacts with 2-isoxazolines to cause the formation of the corresponding β-hydroxyketones through N-O bond cleavage. It was found that in the absence of ethylmagnesium bromide or titanium (IV) isopropoxide, the cleavage of the isoxazoline ring was not observed. It has been demonstrated that equimolar quantities of titanium (IV) isopropoxide and
ethylmagnesium bromide leads to the formation of titanium(III) isopropoxide and this titanium(III) species caused homolytic cleavage of the N-O bond of 2-isoxazolines to the corresponding β-hydroxyketones with good yields (Scheme 1.51).\(^\text{82}\)

![Scheme 1.51. Ti⁴⁺ catalyzed cleavage of 2-isoxazolines.](image)

**1.5.1.4 Samarium Iodide Catalyzed Cleavage**

Samarium iodide in the presence of triethylamine offers the chemoselective cleavage of isoxazolines to form β-hydroxyketones with excellent yields (Scheme 1.52).\(^\text{83}\) It was noticed that in the absence of triethylamine the β-elimination of the hydroxy group was observed.

![Scheme 1.52. Samarium iodide catalyzed cleavage of 2-isoxazolines.](image)

**1.5.1.5 Iron Catalyzed Cleavage**

The Chen group reported a very facile, economical, efficient and chemoselective method for the cleavage of 2-isoxazolines 1-186 using iron and ammonium chloride on a wide range of substituted 2-isoxazolines to prepare β-hydroxyketones 1-187 (Scheme 1.53).\(^\text{84}\)
Scheme 1.53. Fe/NH₄Cl catalyzed cleavage of 2-isoxazolines.

1.5.1.6 Oxidative Cleavage

Ring opening of 2-isoxazolines using oxidative methods are required in cases where the reductive methods are not suitable due to the incompatible functional groups or epimerization issues. Kozikowski developed oxidative methods for N-O bond cleavage of 2-isoxazolines using ozone, bromine and peracids. An ozonolytic method for the cleavage of 2-isoxazolines using ozone/oxygen gave $\beta$-hydroxyketones with moderate to good yields (Scheme 1.54).

Scheme 1.54. Cleavage of 2-isoxazolines with ozone.

Kozikowski utilized bromine for the opening of the N-O bond of a 2-isoxazoline ring followed by $\alpha$-bromination of $\beta$-hydroxyketone to form $\alpha$-bromoketal. Peracids such as 3-chloroperoxybenzoic acid, peroxymethoxyacetic acid, or 3,5-dinitroperoxybenzoic acid were utilized to form $\beta$-hydroxyketones. In the case of peroxymethoxyacetic acid, the Baeyer-Villiger oxidation product of the $\beta$-hydroxyketones was obtained (Scheme 1.55).
**Scheme 1.55. Peracid cleavage of 2-isoxazolines.**

### 1.5.1.7 Metal Carbonyl Catalyzed Cleavage

Ring opening of 2-isoxazolines using metal carbonyls is a complementary methodology to the existing reductive hydrogenolysis methods with Raney-Ni and palladium. The metal carbonyl induced cleavage reaction conditions are mild and chemoselective. There are numerous reports in the literature for the smooth transformation of various 2-isoxazolines to the corresponding \( \beta \)-hydroxyketones using \( \text{Mo(CO)}_6 \).\textsuperscript{87} N-O bond cleavage reactions of 3,5-disubstituted isoxazolines 1-193 using \( \text{Mo(CO)}_6 \) gives \( \beta \)-hydroxyketones under aqueous conditions but under anhydrous conditions retro-aldol cleavage products were observed (**Scheme 1.56**).\textsuperscript{88}

**Scheme 1.56. \text{Mo(CO)}_6 \text{ catalyzed cleavage of 2-isoxazolines.}**

Thermal and photochemical ring opening of 2-isoxazolines in the presence of \( \text{Fe(CO)}_3 \) revealed that the 3,5-disubstituted-2-isoxazole 1-200 gives products via retro-
aldol pathway from N-O and C^4-C^5 bond cleavage. In cases, where 2-isoxazolines without substituent on the C^5 position gives β-hydroxy and β-methoxyketones as major products as a result of N-O bond cleavage (Scheme 1.57).^{89}

Scheme 1.57. Fe(CO)_5 catalyzed cleavage of 2-isoxazolines.

1.5.2 Retro-Aldol Products from Metal Carbonyl Induced Cleavage

As mentioned in the previous section, metal carbonyl induced ring opening of 2-isoxazolines substrates with substitution on C^5 position under anhydrous conditions leads to retro-aldol products. Fused 2-isoxazolines under thermolysis reaction conditions using [Fe_2(CO)_9] or Mo(CO)_6 undergo N-O cleavage followed by C^4 – C^5 bond cleavage to give retro-aldol products (Scheme 1.58).^{87a, 89-90}

Scheme 1.58. Mo(CO)_6/Fe(CO)_5/Fe(CO)_5 catalyzed cleavage of 2-isoxazolines 1-204.

1.5.3 γ-Aminoaicyclools Through N-O Bond Cleavage

Conversion of isoxazolines to γ-aminoaicyclools has been achieved using LiAlH_4, Ni-borohydrides, H_2/Pd, Na-Hg/H_2O, Na/ethanol, Na_BuOH, Me_2S-BH_3, NaAlH_2(OCH_2CH_2OCH_3)_2. LiAlH_4 reduction was found to be superior compared to other reagents resulting in higher stereoselectivity and yields for the preparation of γ-
aminoalcohols, while delivering the hydride from the sterically less hindered side gives
the major diastereomer as syn products.\textsuperscript{91}

1.5.4 Oximes Through C-O Bond Cleavage with Inorganic Bases

There are many successful examples using inorganic bases resulting in the ring
opening of 3-substituted isoxazolines to give oximes. For example ring opening reactions
on isoxazoline 1-207 with Pd/C-H\textsubscript{2} or Raney-Ni-H\textsubscript{2} were unsuccessful but using the
bases EtONa and LiAlH\textsubscript{4} the oxime 1-208 was afforded in good yield (Scheme 1.59).\textsuperscript{92}

\begin{center}
\begin{tikzcd}
1-207 \rightarrow \begin{array}{c}
\text{EtONa or} \\
\text{LiAlH}_4 \\
\end{array} \rightarrow 1-208 \\
\text{Yield: 85-93\%}
\end{tikzcd}
\end{center}

Scheme 1.59. Inorganic base catalyzed cleavage of 2-isoxazolines.

1.5.5 β-Hydroxynitriles Through N-O Bond Cleavage with Organic Bases

A proton on a 3-unsubstituted 2-isoxazoline can potentially be removed using
bases resulting in N-O bond cleavage to generate the corresponding β-hydroxynitrile
compounds. There have been numerous examples using organic bases such as
triethylamine and Grignard reagents for the smooth transformation of 3-unsubstituted 2-
isoxazolines to give β-hydroxynitriles (Scheme 1.60).\textsuperscript{93}

\begin{center}
\begin{tikzcd}
1-209 \rightarrow \begin{array}{c}
\text{Et}_3\text{N} \\
\end{array} \rightarrow 1-210
\end{tikzcd}
\end{center}

Scheme 1.60. Organic base catalyzed cleavage of 2-isoxazolines.
1.6 Synthetic Applications of Nitrile Oxide Cycloadditions Followed by Ring-Opening Reactions of Isoxazolines

2-Isoxazolines have attracted significant attention due to their high biological activity. 2-Isoxazolines have been reported to possess a variety of significant and diverse pharmacological activities such as anti-inflammatory,\textsuperscript{94} anti-depressant,\textsuperscript{95} anti-tuberculosis,\textsuperscript{96} anti-Candida,\textsuperscript{97} anticancer,\textsuperscript{98} anti-bacterial,\textsuperscript{99} anti-viral,\textsuperscript{100} α7 nicotinic acetylcholine antagonists,\textsuperscript{101} glycoprotein IIb/IIIa antagonists,\textsuperscript{102} blood coagulation (Xa) inhibitors,\textsuperscript{103} MIF (macrophage migration inhibitory factor) inhibitory activity.\textsuperscript{104} As discussed in Section 1.5, 2-isoxazolines can yield access to various functional groups such as γ-aminoalcohols, β-hydroxyketones, and β-hydroxynitriles. Typically 2-isoxazolines rings are generated in the molecules using the 1,3-DCA reaction. By specifically designed nitrile oxide and alkene reagents with appropriate substitutions the 2-isoxazoline unit as well as the desired functional groups can be easily incorporated into the target molecule. Acivicin is an example of a drug based on a 2-isoxazoline core that displays significant activity against a number of tumours and is generated by a 1,3-DCA reaction (Scheme 1.61).\textsuperscript{98d}

\[
\begin{align*}
\text{HO}_2\text{C} & \quad \text{Cl} \\
\text{NPh} & \quad \text{OH} \\
\text{1-211} & \quad \text{1-212} \\
\end{align*}
\]

\[
\text{10.8\% yield over 2 steps} \\
\text{Acivicin} \\
\text{1-213}
\]

\textbf{Scheme 1.61.} Application of 1,3-DCA of nitrile oxide towards the synthesis of Acivicin.

VGX-1027 is another 2-isoxazoline based drug developed by VGX Pharmaceuticals for inflammatory diseases. VGX-1027 has demonstrated preclinical efficacy against various inflammatory diseases including rheumatoid arthritis (RA) and
type 1 diabetes (T1D) (Scheme 1.62).\textsuperscript{105} VGX-1027 has completed a phase I single-ascending dose, double-blind study in healthy volunteers in which the compound was generally well-tolerated. Its main mechanism of action is the inhibition of NF-κB and the early transient inhibition of P38 MAP kinase signalling pathways.

![Chemical reaction scheme](image)

Scheme 1.62. Application of 1,3-DCA of nitrile oxide towards the synthesis of VGX-1027.

Many examples can be found in the literature using the 1,3-DCA strategy to make 2-isoxazolines and opening of the 2-isoxazoline ring to get the desired functional groups for the synthesis of natural products. For instance, intramolecular 1,3-DCA followed by \( \text{Mo(CO)}_6 \) catalyzed isoxazoline ring opening were key steps during the total synthesis of (+)-Macrosphelide B 1-220 (Scheme 1.63).\textsuperscript{106}

![Chemical reaction scheme](image)

Scheme 1.63. Application of 1,3-DCA of nitrile oxide followed by 2-isoxazoline cleavage towards the synthesis of Macrosphelide B.
In another example, intramolecular 1,3-DCA followed by a Mo(CO)$_6$ catalyzed isoxazoline ring opening was used by Kim and coworkers for the synthesis of macrolide 1-223 which is the precursor to the fungal metabolite (+)-Brefeldin A 1-224 (Scheme 1.64).

![Diagram of chemical reactions](image)

**Scheme 1.64. Application of 1,3-DCA of nitrile oxide followed by 2-isoxazoline cleavage towards synthesis of (+)-Brefeldin A.**

Total synthesis of Vinigrol 1-231 was achieved by utilizing intermolecular 1,3-DCA and ring opening of 2-isoxazoline 1-228 with LiAlH$_4$ to afford the $\gamma$-aminoalcohol 1-229. A regio- and chemoselective 1,3-dipolar cycloaddition of *in situ* generated bromo nitrile oxide was utilized to generate the 2-isoxazoline. After several transformations, the 2-isoxazoline was cleaved with a large excess of LiAlH$_4$ to afford the $\gamma$-aminoalcohol which was converted to formamide 1-230 then converted to Vinigrol over several steps with good overall yield (Scheme 1.65).

48
1.7 Research Goals

Many examples of 1,3-DCA reactions between nitrile oxides and bicyclic alkenes are reported in the literature offering high yields with excellent regio- and stereoselectivities. However, to our surprise there exist only a limited number of reports regarding 1,3-DCA reactions involving oxabicyclic and azabicyclic alkenes with nitrile oxides. The 1,3-DCA of nitrile oxides with unsymmetrical bicyclic alkene substrates is not fully understood, which is represented by limited publications in the literature. From the preceding sections, it is obvious that bicyclic alkenes can produce an array of different products depending on the method of generation of the nitrile oxide and by varying the reaction conditions. Therefore, it is the goal of this research project to expand the scope of nitrile oxide 1,3-dipolar cycloadditions through the synthesis of symmetrical and unsymmetrical oxabicyclic and azabicyclic alkenes. By introducing a substituent at the bridgehead carbon of the bicyclic alkene the number of possible products will
increase due to the possibility of formation of different regioisomers during 1,3-DCA reactions.

As previously mentioned, the Tam group has studied various aspects of [2+2] cycloaddition and 1,3-dipolar cycloaddition reactions of bicyclic alkenes. It was found that using unsymmetrical bicyclic alkenes resulted in a preference in the formation of one regioisomer over another, depending on the steric and electronic nature of the substituents. These results can be used to predict the major isomers that will be formed in the cycloadditions with unsymmetrical bicyclic alkenes.

The results of this study will provide regioisomeric data that is useful for predicting future research results, and understanding the reaction mechanism of nitrile oxide 1,3-DCA reactions. By having a comprehensive understanding of the mechanism of the 1,3-DCA reactions involving unsymmetrical bicyclic alkenes, reaction conditions targeting high regio- and stereoselectivity can be planned. This research project will then allow the development of methodologies towards the synthesis of natural products resulting in the generation of effective and efficient synthetic routes to drugs. Due to the diverse pharmacological activity and high efficacy this is a highly desirable area of research.

This project will examine the regioselectivity of 1,3-DCA reactions, as well as the development of a broad cleavage method for the N-O bond in 2-isoxazolines. As mentioned previously, numerous methods for cleavage of 2-isoxazolines have been developed, yet a cleavage procedure suitable to a broad range of substrates has not yet been achieved. Currently, there are few studies available in the literature designed for cleavage of 2-isoxazolines fused to oxabicyclic and azabicyclic rings systems. This
research project will help develop a cleavage methodology suitable for 2-isoxazolines fused to oxabicyclic and azabicyclic rings. This cleavage method would allow for the preparation of novel oxabicyclic and azabicyclic compounds with important functionalities such as β-hydroxyketone and γ-aminoalcohol. This procedure to reach β-hydroxyketone and γ-aminoalcohol functionalities will allow facile synthesis of natural products and desired complex molecules.
Chapter 2

Synthesis of Substituted Furans and Bicyclic Alkenes
2.1 Introduction

In order to begin the current investigation of 1,3-dipolar cycloaddition reactions, we planned to examine regio- and stereoselectivities on cycloaddition reactions using unsymmetrical bicyclic alkenes with various substitutions. C1-substituted bicyclic alkenes are not commercially available; therefore, their synthesis is warranted. We decided to prepare a variety of C1-substituted bicyclic alkenes that incorporate furan. Most of the aryl and alkyl substituted furans that were necessary for this project are not commercially available. This chapter outlines the synthesis of 2-substituted furans using metal catalyzed cross coupling methodologies and C1-substituted oxabicyclic alkenes using Diels-Alder cycloaddition reactions.

2.2 Synthesis of 2-Substituted Furans

Substituted furan ring systems are found to be the main component of many organic compounds that have exhibited a vast array of biological activity.\textsuperscript{109} The ability of substituted furans to easily undergo Diels-Alder cycloadditions presents an invitation for the construction of valuable intermediates for a variety of heterocyclic organic compounds.\textsuperscript{110} Some 2-substituted furans are commercially available (such as R = Me, \textsuperscript{1}Bu, COOMe etc.), yet 2-substituted furans with R = alkyl, cycloalkyl and substituted aryl groups are either not reported in the literature or are not readily available from commercial suppliers. Therefore the development of a suitable methodology for the preparation of 2-substituted furans was necessary.

2.2.1 Preparation of 2-Bromofuran

In order to develop a procedure for the synthesis of 2-substituted furans we first required a 2-halofuran, which could undergo a coupling reaction with alkyl, arylboronic
acids/Grignard reagents leading to the desired 2-substituted furan products. We envisioned that 2-bromofuran would be suitable for this purpose and could lead to a variety of 2-substituted furans in good yields. Therefore, we began to develop a scalable method to prepare 2-bromofuran 2-2 with simple reaction conditions and cheap reagents.

2.2.2 Background

The most common method in the literature for the synthesis of 2-bromofuran is by bromination of furan.\textsuperscript{111} Brominating agents such as hexabromocyclopentadiene,\textsuperscript{111b} dioxane dibromide\textsuperscript{111d} and microwave assisted bromination using 2,4,4,6-tetrabromo-2,5-cyclohexadienone\textsuperscript{111g} are not suitable for large scale reactions due to the corrosiveness of the reagents. The methods developed by Brandsma using EtLi/Br\textsubscript{2},\textsuperscript{111d} and Br\textsubscript{2}/DMF\textsuperscript{122b} conditions are effective and provided 2-bromofuran in 70-80% yield; however, we and others\textsuperscript{111g} found that these methods are difficult to work with because the isolation of the product is troublesome.

We initially followed Brandsma’s procedure for bromination of furan using Br\textsubscript{2} in DMF. We encountered difficulties in the isolation of 2-bromofuran similar to those mentioned by Gupta et al. in isolation of 2-bromofuran.\textsuperscript{111g} The isolation step was modified using direct steam distillation of the reaction mixture to isolate 2-bromofuran in good yields (50-55 %). Using Br\textsubscript{2}/DMF, it was found that the addition of Br\textsubscript{2} to DMF is highly exothermic, and it is very difficult to control the reaction temperature in the large scale reaction (20-30 g). Furthermore, due to its corrosive nature, handling elemental bromine is not easy. Therefore, we decided to pursue an alternative method to synthesize 2-bromofuran.
2.2.3 Results and Discussion

We developed a novel procedure for the bromination of furan, which offers a simplified work-up and isolation for large-scale preparation (20-200 g scale) using safe, inexpensive and readily available reagents. The results have been published in the literature.\textsuperscript{112} The described preparation does not require extractive workup procedures or chromatographic purifications (Scheme 2.1).

![Scheme 2.1. Preparation of 2-bromofuran.](image)

N-Bromosuccinimide (NBS) was chosen as a brominating agent because it is readily available and easy to handle and the addition of NBS to DMF is not exothermic. The bromination of furan was done by controlled addition of NBS-DMF solution at room temperature followed by stirring the reaction mixture at room temperature overnight. Direct steam distillation of the reaction mixture resulted in isolation of 2-bromofuran in 65-75\% yields.

In conclusion, we have investigated a new, simple, straightforward and scalable procedure for the preparation of 2-bromofuran using NBS in DMF.

2.3 Synthesis of 2-Aryl Furans

2.3.1 Background

The most commonly used methods for the synthesis of 2-arylfurans involve generating aryl radicals (diazotization of aromatic amines with alkyl nitrites\textsuperscript{113}, decomposition of N-nitrosoacetanilides,\textsuperscript{114} (phenylazo)triphenylmethane\textsuperscript{115} or aromatic diazonium salts\textsuperscript{116}) in the presence of furan. Alternative methods involving multi-step
synthesis are photochemically induced cyclization of acetylenic ketones,\textsuperscript{117} acid-catalyzed cyclization of 3-tosylpropanal ethylene acetal,\textsuperscript{118} degradation of 3,4-diazacyclopentadienone derivatives,\textsuperscript{119} and acid-catalyzed cyclization of 4-hydroxy-1-phenyl-but-2-en-1-one.\textsuperscript{120} Transition metal catalyzed cross-coupling methods have been reported using 2-halofuran with Grignard reagents,\textsuperscript{121} 2-lithiofuran or 2-furylzinc chloride with aryl halides.\textsuperscript{122} Many of these methods have limitations due to low yields, multi-step synthesis, and sensitive/unstable reagents. The development of transition metal catalyzed cross-coupling methods using stable reagents such as boronic acids and 2-halofuran would be useful as it can be applied to synthesize a variety of 2-arylfuran derivatives.

### 2.3.2 Pd Catalyzed Suzuki Cross-coupling Reactions

The Suzuki-Miyaura reaction is the Pd-catalyzed cross-coupling of an organoboron reagent and an organohalide or sulfonate.\textsuperscript{123} Since its discovery,\textsuperscript{124} the Suzuki-Miyaura reaction has become one of the most powerful and synthetically valuable methods for carbon-carbon bond formation.\textsuperscript{125} The key advantages of the Suzuki-Miyaura reaction stems from a variety of factors, such as mild reaction conditions, and commercial availability of a wide range of boronic acids. Boronic acids are relatively non-hazardous reagents and their stability towards heat and water as well as their tolerance to a wide range of functional groups offers coupling to a broad range of organohalides. These desirable features make the Suzuki-Miyaura reaction an important tool for the synthesis of highly functionalized molecules in medicinal chemistry as well as in the large-scale synthesis of pharmaceuticals\textsuperscript{126} and fine chemicals.\textsuperscript{127} Despite considerable effort in developing more active catalysts for the Suzuki-Miyaura reaction over the past two decades, some limitations still remain. For example, simple aryl halides
and aryl boronic acids are successful coupling partners, whereas reactions involving their heteroaryl analogues are less straightforward. Therefore, the development of a universal method for the cross-coupling of heteroaryl substrates would be highly advantageous.

2.3.3 General Mechanism of Suzuki-Miyaura Cross-coupling Reaction

The most commonly used palladium catalysts are Pd(Ph₃P)₄, PdCl₂(dppf)₂, PdCl₂(Ph₃P)₂ and Pd(OAc)₂ with Ph₃P or other phosphine ligands with aryl, alkenyl, benzyl and allyl halides and triflates. The Suzuki-Miyaura reaction proceeds through three key steps; (1) oxidative addition of organo halide or sulfonate to a low-valent metal complex, (2) transmetalation with the organoboron component, and (3) reductive elimination to give the cross-coupling product and metal complex that goes on to the next catalytic cycle (Scheme 2.2). Oxidative addition of the organic halide to the Pd (0) complex results in the stable trans-σ-organopalladium halide complex, 2-4. Typically, the process of oxidative addition is the rate determining step in the catalytic cycle. Oxidative addition can be enhanced if the aryl halide, trflate or sulfonates are activated by the presence of electron withdrawing groups. The relative rate of the oxidative addition of electrophiles is in the order of I > Br > OTf > Cl. A base is required for Suzuki-Miyaura reactions to proceed. Stronger bases such as NaOH, NaOMe are good for reactions occurring in a THF-water system, while weaker bases such as K₂CO₃ and K₃PO₄ work well with a DMF-water system. It is known that the base is involved in 2 steps; the halide ligand exchange with hydroxide on organopalladium halide complex (RPd^{II}X to more reactive RPd^{II}OH), and binding to the organoboron species forming borate complexes (2-7). The borate complexes undergo transmetalation with the organopalladium hydroxide
center to yield diorganopalladium species (2-9). The diorganopalladium species exists in trans form then undergoes isomerization to the corresponding cis complex followed by reductive elimination of organic partners leading to C-C bond formation producing the cross coupled product (2-10), while simultaneously regenerating the palladium (0) catalyst.

Scheme 2.2. General mechanism for Suzuki cross coupling reaction.

2.3.4 Results and Discussions

This project was started with the intention of preparing the 2-aryl furans to utilize them as starting materials for synthesis of C1-substituted bicycloalkenes. In the initial experiments we tried reactions between furan-2-boronic acid and iodobenzene using PdCl2(dppf)2 as catalyst, DMF as a solvent and K2CO3 as a base at 80 °C over 4 hours. The reaction gave the desired product with 86% isolated yield when performed on a small
scale. However, when the exact reaction conditions were repeated on a 10 fold scale, we did not observe the product formation. We believe that furan-2-boronic acid is unstable and therefore it would be appropriate to develop a cross-coupling method using more stable boronic acids. We altered our strategy to use arylboronic acids and 2-halofurans for cross-coupling reactions. Since we had developed an efficient methodology for the synthesis of 2-bromofuran (Section 2.2.3), we realized that it could be a key intermediate for the preparation of a wide range of 2-aryl furans by palladium-catalyzed Suzuki cross-coupling reactions with various aryl boronic acids. Having 2-bromofuran in hand, we tried a cross-coupling reaction between phenylboronic acid and 2-bromofuran using literature conditions reported by Bussolari. Under these conditions, reactions were performed at room temperature over 2-4 hours using Pd(OAc)$_2$ as a catalyst, water as a solvent, K$_2$CO$_3$ as a base and $^n$Bu$_4$NBr as a phase transfer catalyst. Bussolari et al. reported 45% yield, yet we obtained only 28-30% isolated yields using these reaction conditions. As part of our investigation in search of a suitable catalyst for the preparation of 2-arylfurans, we tried a cross-coupling reaction between 2-bromofuran and phenylboronic acid using Pd-C as a catalyst in combination with triphenylphosphine as a ligand, Na$_2$CO$_3$ as a base and toluene-water as the solvent at reflux. We achieved yields up to 90% using the Pd-C/Ph$_3$P catalyst system with phenylboronic acid and therefore, we attempted the cross-coupling reaction of 2-bromofuran to other substituted phenylboronic acids using the aforementioned reaction conditions. In coupling of 2-bromofuran with 2-methoxyphenylboronic acid under these conditions, only 35% yield was achieved. The Pd-C/Ph$_3$P catalyst system was not as effective with 2-methoxyphenylboronic acid as for simple phenylboronic acid (Table 2.1).
Table 2.1. Synthesis of 2-aryl furans using Pd-C catalyzed Suzuki cross coupling reactions between 2-bromofuran and aryl boronic acids.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl boronic acid</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C6H5B(OH)2</td>
<td>2-11a</td>
<td>2-12a 90</td>
</tr>
<tr>
<td>2</td>
<td>C6H5B(OH)2OMe</td>
<td>2-11g</td>
<td>2-12g 35</td>
</tr>
</tbody>
</table>

<sup>a</sup>isolated yields after column chromatography.

Our next attempt utilized PdCl₂(Ph₃P)₂ as a catalyst, K₂CO₃ as a base in DMF-water at 80 °C. The reaction proceeded smoothly and provided 2-phenylfuran with 62% isolated yield. We extended these same reaction conditions to coupling reactions between 2-bromofuran and a series of substituted phenylboronic acids (Scheme 2.3). As summarized in Table 2.2, the Suzuki-Miyaura coupling reactions of 2-bromofuran worked well (56-80% yield) with boronic acids containing both electron-donating groups attached to the Ar ring (Ar = CH₃, entries 2, 3, 4; Ar = OCH₃, entries 5, 6, 7; Ar = Et, entry 11), as well as with electron-withdrawing groups attached to the Ar ring (Ar = Cl, entries 8, 9, 10; Ar = Ac, entry 12). The position of the substituent on the Ar ring (ortho, meta, or para) showed little effect on the yields of the Suzuki coupling reactions.
(compare entries 2 to 4; entries 5 to 7; and entries 8 to 10). In general, all the palladium-catalyzed Suzuki coupling reactions of 2-bromofuran occurred smoothly, giving moderate to good yields of the 2-arylfurans 2-12.

Table 2.2. Synthesis of 2-aryl furans using PdCl₂(Ph₃P)₂ catalyzed Suzuki cross coupling reactions between 2-bromofuran and aryl boronic acids.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl boronic acid</th>
<th>Product</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅B(OH)₂</td>
<td>2-11a</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-12a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅B(OH)₂</td>
<td>2-11b</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>H₃C</td>
<td>2-12b</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅B(OH)₂</td>
<td>2-11c</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td>2-12c</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>C₆H₅B(OH)₂</td>
<td>2-11d</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td>2-12d</td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>Aryl boronic acid</td>
<td>Product</td>
<td>Yield (%)a</td>
</tr>
<tr>
<td>-------</td>
<td>------------------</td>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>5</td>
<td><img src="image1" alt="Aryl boronic acid" /></td>
<td><img src="image2" alt="Product" /></td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td><img src="image3" alt="Aryl boronic acid" /></td>
<td><img src="image4" alt="Product" /></td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td><img src="image5" alt="Aryl boronic acid" /></td>
<td><img src="image6" alt="Product" /></td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td><img src="image7" alt="Aryl boronic acid" /></td>
<td><img src="image8" alt="Product" /></td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Aryl boronic acid" /></td>
<td><img src="image10" alt="Product" /></td>
<td>67</td>
</tr>
<tr>
<td>10</td>
<td><img src="image11" alt="Aryl boronic acid" /></td>
<td><img src="image12" alt="Product" /></td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td><img src="image13" alt="Aryl boronic acid" /></td>
<td><img src="image14" alt="Product" /></td>
<td>56</td>
</tr>
<tr>
<td>Entry</td>
<td>Aryl boronic acid</td>
<td>Product</td>
<td>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>-------</td>
<td>------------------</td>
<td>---------</td>
<td>----------------------</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Aryl boronic acid 2-11l" /></td>
<td><img src="image" alt="Product 2-12l" /></td>
<td>59</td>
</tr>
<tr>
<td>13</td>
<td><img src="image" alt="Aryl boronic acid 2-11m" /></td>
<td><img src="image" alt="Product 2-12m" /></td>
<td>77</td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="Aryl boronic acid 2-11n" /></td>
<td><img src="image" alt="Product 2-12n" /></td>
<td>85</td>
</tr>
</tbody>
</table>

<sup>a</sup> isolated yields after column chromatography.

### 2.3.5 Pd Catalyst Screening Study

It has been demonstrated that in Suzuki-Miyaura coupling reactions, the combination of palladium catalysts with various phosphine ligands results in excellent yields and high efficiency. However, most of the phosphine ligands are expensive and many of them are air sensitive, which places significant limitations on their synthetic applications. The development of new and efficient phosphine-free palladium catalyst systems remains a desire for organic chemists. In order to find an efficient Pd catalyst for cross-coupling reactions between 2-bromofuran and arylboronic acids, we planned to explore coupling reactions with various Pd catalysts in a common reaction system (consistent solvent, base, and temperature). For this purpose, we selected four...
commercially available Pd (0) and Pd (II) catalysts Pd(OAc)$_2$, PdCl$_2$(Ph$_3$P)$_2$, Pd(Ph$_3$P)$_4$, and 5% Pd/C and screened their effectiveness for the coupling reaction (Table 2.3).

### 2.3.6 Results and Discussions

2-Bromofuran was reacted with various aryl boronic acids in the presence of palladium catalysts (Pd(OAc)$_2$, PdCl$_2$(Ph$_3$P)$_2$, Pd(Ph$_3$P)$_4$, and 5% Pd/C using K$_2$CO$_3$ as a base in DMF-water at 80 °C. Yields of less than 50% were obtained in all cases when Pd(OAc)$_2$ was used. PdCl$_2$(Ph$_3$P)$_2$ and Pd(Ph$_3$P)$_4$ functioned as effective catalysts with Pd(Ph$_3$P)$_4$ providing slightly higher yields in most cases except for the coupling of 3-MeO-C$_6$H$_4$, 2-MeO-C$_6$H$_4$, and 4-biphenyl groups (Table 2.3, entries 6,7,13). Interestingly, when Pd/C was used as a catalyst, the cross coupling reactions afforded products in 67-73% yields for phenyl, 4-Cl-C$_6$H$_4$, and 1-naphthyl groups (entries 1,8,14). The highest yield for the coupling of phenylboronic acid was provided with Pd/C at 73%. It is worth noting that Pd/C in combination with Ph$_3$P as a ligand gave superior yields in toluene-water system (90%, 35% with phenylboronic acid and 2-methoxyphenylboronic acid, respectively) relative to Pd-C without Ph$_3$P in DMF-water conditions (73%, 9% respectively with phenylboronic acid and 2-methoxyphenylboronic acid, respectively).
Table 2.3. Screening of different Pd-catalysts.

\[
\begin{array}{c}
\text{Entry} & \text{Boronic Acid} & \text{Yield (%)}^{b} \text{ using different Pd catalysts} \\
\hline
 & & \text{Pd(OAc)}_{2} & \text{PdCl}_{2}(\text{Ph}_{3}\text{P})_{2} & \text{Pd}(\text{Ph}_{3}\text{P})_{4} & \text{Pd/C} \\
1 & \text{2-11a} & 21 & 62 & 71 & 73 \\
2 & \text{2-11b} & 24 & 80 & 97 & 38 \\
3 & \text{2-11c} & 19 & 78 & 95 & 40 \\
4 & \text{2-11d} & 12 & 56 & 77 & 11 \\
5 & \text{2-11e} & 36 & 57 & 77 & 40 \\
6 & \text{2-11f} & 48 & 72 & 53 & 41 \\
\end{array}
\]
<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic Acid</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt; using different Pd catalysts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>7</td>
<td>2-11f</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>2-11g</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>2-11h</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>2-11i</td>
<td>2.8</td>
</tr>
<tr>
<td>11</td>
<td>2-11j</td>
<td>38</td>
</tr>
<tr>
<td>12</td>
<td>2-11k</td>
<td>40</td>
</tr>
<tr>
<td>Entry</td>
<td>Boronic Acid</td>
<td>Yield (%)&lt;sup&gt;b&lt;/sup&gt; using different Pd catalysts</td>
</tr>
<tr>
<td>-------</td>
<td>-------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>13</td>
<td><img src="image1.png" alt="Image" /></td>
<td>32</td>
</tr>
<tr>
<td>14</td>
<td><img src="image2.png" alt="Image" /></td>
<td>36</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 2 mol% of the Pd catalyst was used with 2.5 eq. of base with 2:1 DMF:water.

<sup>b</sup> Isolated yields after column chromatography.

To expand the scope of this Pd-catalyzed reaction, Suzuki coupling between 2-bromofuran and 1° or 2° alkylboronic acids 2-13 was attempted (Scheme 2.3). Unfortunately, none of the reactions were successful, and did not afford any coupling products 2-14. Thus, this Pd catalyzed Suzuki coupling reaction methodology would only be useful for the preparation of 2- Aryl substituted furans 2-12.

\[ \text{2-2} + \text{2-13} \xrightarrow{\text{Pd catalysts}} \text{2-14} \]

Scheme 2.3. Synthesis of 2-alkylfurans using Suzuki cross coupling reaction.

2.4 Synthesis of 2-Alkyl Furans

2.4.1 Background

It was surprising that there have been only limited methods published regarding the preparation of 2-alkyl substituted furans. Levi et al. and Suzuki et al. demonstrated
synthesis of 2-alkylfurans by the coupling of 2-lithiated furan and the corresponding organoboranes followed by subsequent treatment with NCS or iodine (Scheme 2.4).\textsuperscript{134}

\[
\text{Scheme 2.4. Synthesis of 2-alkylfurans from 2-lithiated furans.}
\]

\[
\begin{align*}
\text{PdI}_2 \text{-catalyzed cycloisomerization of (Z)-2-en-4-yn-1-ols under neutral condition leading to substituted furans in high yields was disclosed by Gabriele et al. (Scheme 2.5).} \text{\textsuperscript{135}} \\
\text{This methodology was improved by Yin et al.\textsuperscript{136} by utilizing Au (I) and Au (III) catalysts. However, these methods are limited to the synthesis of 2-substituted furans containing a methylene group directly bonded to the C\textsuperscript{2} position of the furan.}
\end{align*}
\]

\[
\text{Scheme 2.5. PdI}_2\text{-catalyzed cycloisomerization of (Z)-2-en-4-yn-1-ols to 2-alkylfurans.}
\]

2.4.2 Alkyl-Aryl Cross Coupling

Our attempts to expand the scope of the Pd-catalyzed Suzuki coupling reaction with 1\textdegree{} or 2\textdegree{} alkyl boronic acids was found to be unsuccessful, and did not afford any coupling products. Thus, the Pd-catalyzed Suzuki coupling reaction method would only allow the production of 2-substituted furans with R = aryl groups. As an alternative for preparing a series of 2-alkyl furans by a single step process from 2-bromofuran, we envisaged an alkyl–aryl cross coupling using an iron catalyst and Grignard reagents as an alkyl nucleophile.
2.4.3 Iron Catalyzed Cross Coupling Reaction

Iron catalysis has gained popularity over the years as these catalysts are less expensive than Pd and Ni, possess a higher stability in variety of reaction conditions and have a lower toxicity making iron an ideal choice for cross-coupling reactions. In 1945, Kharasch and co-workers reported the first Fe-catalyzed alkenylation of Grignard reagents.\textsuperscript{137} Kochi and co-workers improved upon Kharasch’s methods and studied the mechanism of the reaction in 1971, but the yields of the reactions were still low and not convenient for preparative applications.\textsuperscript{138} More recently, in 1998, Cahiez reported that the use of NMP or DMPU as a co-solvent greatly improved the yields of Fe-catalyzed alkenylations of Grignard reagents, and alkenyl chlorides, bromides and iodides as well as alkenyl phosphates allowing these reactions to be used successfully on larger scales.\textsuperscript{139} In 2004, Fürstner extended Cahiez’s conditions to include alkenyl triflates as successful substrates in Fe-catalyzed alkenylations of Grignard reagents.\textsuperscript{140}

2.4.4 Mechanism of the Iron Catalyzed Cross Coupling Reaction

Similar to other cross-coupling mechanisms, the first step of the iron catalyzed cross-coupling mechanism is the oxidative addition of ArX to an in situ generated active Fe catalyst species followed by transmetalation with RMgX to generate the intermediate species Ar-Fe-X, which undergoes reductive elimination to afford the cross-coupling product while regenerating the active catalyst species. These steps are outlined in Scheme 2.6 below.

There have been various proposals regarding the catalytic cycle of iron during the cross-coupling reaction. Based on the experimental evidence\textsuperscript{141} Kochi proposed that the active catalyst species is Fe(I), which is formed by the reduction of Fe(III) with 2 eq. of
Grignard reagent. The active Fe(I) species is oxidized to Fe(III) during oxidative addition, and is reduced to Fe(I) during reductive elimination.

Scheme 2.6. Catalytic cycle for Fe-catalyzed cross-coupling reaction based on proposal that Fe(I) as an active catalyst.

Alternatively, Fürstner\textsuperscript{142} and co-workers proposed that the active catalytic species consists of iron with a formal oxidation state of -2 (Fe(-II)(MgX)\textsubscript{2}), which is generated from the reaction of pre-catalyst with 4 equivalents of the Grignard reagent. This proposal is demonstrated in Scheme 2.7. Oxidative addition of the iron complex (Fe(-II)(MgX)\textsubscript{2}) to ArX gives an Fe(0) complex 2-29. This complex then undergoes transmetallation with the organomagnesium reaction partner (RMgX) to give an iron complex that now has two organic groups attached to it. Subsequent reductive elimination forms the cross-coupling product and the Fe(-II) catalytic species.
Scheme 2.7. Catalytic cycle for Fe-catalyzed cross-coupling reaction based on proposal that Fe(-II) as active catalyst.

Bogdanovic and co-workers have also established that the catalyst FeCl₂ is reduced in situ by four equivalents of Grignard reagent to form an iron(-II) complex of formal composition \([\text{Fe}(\text{MgX})_2]\) during the cross coupling reaction of Grignard reagents containing β-hydrogens. More recently, Fürstner proposed two different active species for Grignard reagents with and without β-hydrogens based on experimental observations of the reactions with EtMgBr and MeMgBr in iron cross-coupling reactions. The active species in reactions of Grignard reagents with β-hydrogens is Fe(-II)(MgX)₂ and catalytic cycle is as depicted in Scheme 2.7 and the active species for Grignard reagents without β-hydrogens is the Fe(II) complex \((\text{R}_4\text{Fe}(\text{MgX})_2)\) which reacts with \(\text{R'X}\) to give the coupling product \((\text{R-R'})\).
2.4.5 The Tam Group’s Previous Work on Iron Catalyzed Cross Coupling

Previously, the Tam research group investigated Fe catalyzed coupling reactions with bicyclic alkenyl triflates using various alkyl and aryl Grignard reagents, providing an efficient route for the synthesis of 2-substituted bicyclic alkenes (Scheme 2.8).^{145}

Scheme 2.8. Fe-catalyzed cross-coupling reaction of bicyclic alkenyl triflates with Grignard reagents.

Iron-catalyzed cross-coupling reactions of bicyclic alkenyl triflate with various alkyl and aryl Grignard reagents were explored with different Fe catalysts and solvent systems at different temperatures. A wide range of solvents were tested for the bicyclic alkenne triflate/CyMgCl/Fe(acac)$_3$ reaction comprising of ether, amide, and amine based solvents. The results showed that THF, NMP, DMPU and THF/NMP (1:3) produced the desired product with >80% yield. The solvent systems THF/NMP (1:3) and DMPU were found to give the highest yields (88%) of the desired product 2-34. Iron catalysts FeCl$_3$, Fe(acac)$_3$, Fe(dpm)$_3$, Fe(dbm)$_3$ etc, provided the product in moderate to good yields. However, the commercially available and air-stable Fe(acac)$_3$ afforded the highest yield of 88% and proved to be a suitable catalyst choice.

The effect of different Grignard halides on the iron-catalyzed coupling reaction was revealed when the halide of the Grignard reagent was changed from Cl to Br to I. Changing the halide to Br and I resulted in a decrease in the yield of the desired coupling product and an increase in the yield of the undesired reduction product. Reaction
temperature was also observed to have a significant role on the product formation. The coupling reactions produced higher yields at -25 to -40 °C whereas at above 0 °C the decomposition of the triflate starting material resulted in lower yields.

2.4.6 Results and Discussions

We began our investigation on the reaction conditions of this Fe-catalyzed coupling reaction using 2-bromofuran and cyclohexylmagnesium chloride (Table 2.4). The yields were determined by GC using benzophenone as an internal standard. The study investigated the effects of varying the solvent, iron catalysts, reaction temperatures, reaction time, and equivalency of the Grignard reagent to optimize the reaction conditions. Amide, phosphoramide, and urea-based solvents provided the highest yields (Table 2.4, entries 1-8), whereas ether, amine, or pyridine-based solvents provided minimal to no product (entries 9-12). The solvents DMPU and DMA provided the highest yield of coupling product at 60% (entries 1,8).

Of the five iron catalysts screened, Fe(acac)₃ provided the highest yield (entry 1). The bulkier malonate derived iron catalysts, Fe(dbm)₃ or Fe(dpm)₃ produced only 30% and 22% yields, respectively (entry 15,16). FeCl₃ provided the second highest yield of 40% where as the hydrate of FeF₃ provided no observed coupling product (entries 13,14). Low yields were also obtained for Fe(Salen)Cl of 5% (entry 17). Reaction times of 15, 30, 60, and 120 minutes were screened with 120 minutes showing the highest yield (entries 1,18, 19, 20), and prolonged reaction times beyond 120 minutes did not improve these yields. Variation of reaction temperature at 0, -25, and -40 °C (entries 1, 21, 22) showed that the highest yield was obtained at -25 °C.
2.4. Optimization of Fe catalyzed reaction conditions for the synthesis of 2-12t.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Fe catalyst</th>
<th>Time (min)</th>
<th>Temp (°C)</th>
<th>Yield (%)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMPU</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>THF:DMPU (3:1)</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>NMP</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>THF:NMP (3:1)</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>DMEU:THF (3:1)</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>THF + 1 eq. HMPA</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>DMA</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>Et₃N</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>17</td>
</tr>
<tr>
<td>11</td>
<td>TMEDA</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>3</td>
</tr>
<tr>
<td>12</td>
<td>Pyridine</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-25</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>DMPU</td>
<td>FeCl₃</td>
<td>120</td>
<td>-25</td>
<td>40</td>
</tr>
<tr>
<td>14</td>
<td>DMPU</td>
<td>FeF₃H₂O</td>
<td>120</td>
<td>-25</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>DMPU</td>
<td>Fe(dbm)₃</td>
<td>120</td>
<td>-25</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>DMPU</td>
<td>Fe(dpm)₃</td>
<td>120</td>
<td>-25</td>
<td>22</td>
</tr>
<tr>
<td>17</td>
<td>DMPU</td>
<td>Fe(Salen)Cl</td>
<td>120</td>
<td>-25</td>
<td>5</td>
</tr>
<tr>
<td>18</td>
<td>DMPU</td>
<td>Fe(acac)₃</td>
<td>15</td>
<td>-25</td>
<td>6</td>
</tr>
<tr>
<td>19</td>
<td>DMPU</td>
<td>Fe(acac)₃</td>
<td>30</td>
<td>-25</td>
<td>41</td>
</tr>
<tr>
<td>20</td>
<td>DMPU</td>
<td>Fe(acac)₃</td>
<td>60</td>
<td>-25</td>
<td>45</td>
</tr>
<tr>
<td>21</td>
<td>DMPU</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>22</td>
<td>DMPU</td>
<td>Fe(acac)₃</td>
<td>120</td>
<td>-40</td>
<td>55</td>
</tr>
</tbody>
</table>

² GC yields with internal standard of benzophenone.
Having achieved the optimized reaction conditions, Grignard reagents with various R groups were investigated to expand the scope of the reactions. The results of Fe-catalyzed coupling reactions of 2-bromofuran with alkyl Grignard reagents have been published in the literature.\textsuperscript{146} Primary and secondary alkyl Grignard reagents, including small to medium–sized ring cycloalkyl groups (3–7 carbon rings) provided moderate to low yields (35–55\%) of 2-substituted furans \textbf{2-12o-v} (Table 2.5 entries 1-8). For smaller sized alkyl groups of less than five carbons, isolation of the product proved to be difficult due to their volatility. Aryl groups were successfully coupled with 2-bromofuran; however, low yields were observed (4-26\%, entries 10-18) with the lowest yields of 5-6\% obtained for phenyl, 2-methyl, 2-methoxy and the 4-fluoro substituted aryl groups (entries 10, 13, 16 and 18). Higher yields of 20-26\% were obtained for 4- and 3-methyl and methoxy substituted aryl groups (entries 11, 12, 14 and 15). Low yields of 15\% of 2-benzylfuran were obtained (entry 9). No coupling product was observed from the reactions with phenylethynylmagnesium chloride, or \textit{tert}-butylmagnesium chloride and thus this coupling methodology may not extend to halide substituted aryl, sp-hybridized, or tertiary alkyl Grignard reagents although further studies would be necessary to confirm these results. The variation of the halide within the Grignard reagents from chloride to bromide did not offer significant improvement in yields.
Table 2.5. Fe catalyzed cross coupling with various Grignard reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>X</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cyclopropyl</td>
<td>Br</td>
<td><img src="image" alt="2-12o" /></td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu</td>
<td>Cl</td>
<td><img src="image" alt="2-12p" /></td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>s-Bu</td>
<td>Cl</td>
<td><img src="image" alt="2-12q" /></td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>Cyclobutyl</td>
<td>Cl</td>
<td><img src="image" alt="2-12r" /></td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>Cyclopentyl</td>
<td>Cl</td>
<td><img src="image" alt="2-12s" /></td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>Cyclohexyl</td>
<td>Cl</td>
<td><img src="image" alt="2-12t" /></td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>Cycloheptyl</td>
<td>Br</td>
<td><img src="image" alt="2-12u" /></td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>Dodecyl</td>
<td>Cl</td>
<td><img src="image" alt="2-12v" /></td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>Cl</td>
<td><img src="image" alt="2-12w" /></td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>Br</td>
<td><img src="image" alt="2-12a" /></td>
<td>5</td>
</tr>
<tr>
<td>No.</td>
<td>Substituent</td>
<td>Yield (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4-CH₃-C₆H₄</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3-CH₃-C₆H₄</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2-CH₃-C₆H₄</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>4-CH₃O-C₆H₄</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>3-CH₃O-C₆H₄</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>2-CH₃O-C₆H₄</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>4-Biphenyl</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>4-F-C₆H₄</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Isolated yield after column chromatography.*
While many of the coupling reactions described above were successful, a by-product was also being produced in all the reactions. The unreacted 2-bromofuran was being converted to bifuran 2-37. The bifuran was likely formed as a result of magnesium halide exchange to provide a 2-furylmagnesium halide compound, which could undergo further unwanted homo-coupling with 2-bromofuran. The dimer of the Grignard reagent 2-38, was also observed in all cases. Both of these compounds often co-elute during column chromatography and have similar boiling points to the desired coupled product, which complicated isolation of the target product, often requiring quantification by NMR.

![2-37](image1)

**Figure 2.1. Homocoupled products obtained during Fe-catalyzed cross coupling.**

In conclusion, our efforts have led to the synthesis of a variety of 2-aryl and 2-alkyl furans by palladium and iron catalyzed coupling methodologies. Iron catalyzed coupling of 2-bromofuran with Grignard reagents (primary and secondary) provided the corresponding 2-alkyl furans in low to moderate yields. This coupling methodology has allowed access to 2-alkyl furans through a general methodology while previously reported syntheses for secondary 2-alkyl furans required more difficult methods. 2-Aryl furans were also attainable by this coupling methodology, albeit at unappreciable low yields. The limitations of this reaction were shown to be that tertiary alkyl or alkynyl Grignard reagents are not amenable coupling partners. These successfully synthesized furans will be crucial intermediates in the synthesis of a variety of C1-substituted Diels-Alder cycloadducts by treatment with the appropriate dienophile, which will be discussed in the following sections.
2.5 **Synthesis of C\textsuperscript{1}-Substituted Oxanorbornenes**

The synthesis of a variety of C\textsuperscript{1}-substituted oxabicyclobutenes will allow us to explore the regio- and stereoselectivity of the 1,3-dipolar cycloaddition reactions. As we have chosen the oxanorbornene skeleton as the basic bicyclic alkene to study, the ease of synthesis and high yielding reactions is important to allow us to create a variety of C\textsuperscript{1}-substituted oxanorbornenes. The simplest method for construction of the oxanorbornene skeleton is a Diels-Alder reaction between a 2-substituted furan and an appropriate dienophile. The yields of Diels-Alder reactions involving furan are typically highly sensitive to substitution on both the diene and dienophile. In particular, substitution on the furan ring greatly affects the chemical reactivity during the cycloaddition reaction. There have been several reports available for synthesis of C\textsuperscript{1}-substituted 7-oxanorbornenes using [4+2] Diels-Alder cycloaddition between 2-substituted furans and maleic anhydride or N-phenylmaleimide.\textsuperscript{147} Therefore, we have attempted to synthesize a variety of C\textsuperscript{1}-substituted oxanorbornenes by using literature reported methods.

2.5.1 **Background**

The [4+2] Diels-Alder cycloaddition reaction of 2-substituted furans with maleic anhydride and N-phenylmaleimide will allow us to form a variety of C\textsuperscript{1}-substituted norbornenes that is necessary for studying the regio- and stereo-selectivity of the 1,3-dipolar cycloadditions. However, the use of furan adducts presents a potential problem as they are considerably less stable and tend to undergo a retro-Diels-Alder (rDA) reaction. The barrier to the rDA reaction of furans DA adducts has been calculated to be ca. 37-40 kJ/mol lower than that for corresponding cyclopentadiene cycloadducts.\textsuperscript{148} This rate enhancement of rDA reaction of furan adducts is believed to reflect the restoration of
some aromatic character in the furan moiety at the transition state for the cycloreversion.\textsuperscript{148} The facile rDA reaction of the furan-maleic anhydride cycloadduct is experimentally demonstrated by the rapid isomerization of the initially formed \textit{endo} adduct to the more stable \textit{exo} adduct. Lee et al. reported that the rate of the rDA reaction of the \textit{endo} adduct is four orders of magnitude greater than that of the \textit{exo} adduct.\textsuperscript{149} There has not been a general consensus on the detailed mechanism of the DA reaction, whether the two new bonds are formed in two separate steps or in one concerted step with equal or unequal bond making. Several new approaches have been used to distinguish between these possibilities but disagreement still exists. The $\alpha$- and $\beta$-deuterium effects\textsuperscript{147g} in the rDA reaction of adduct derived from 2-methylfuran and maleic anhydride and kinetic experiments of the DA reaction of 2-methylfuran with maleic acid revealed that these cycloadditions proceed by a concerted process.\textsuperscript{147h} Furan cycloadducts are not only interesting due to their mechanistic studies, but they have shown their ability in biological activity such as inhibiting protein phosphatases 1 (PP1) and 2A (PP2A).\textsuperscript{147c}

We employed the Diels-Alder reaction using 2-substituted furans with maleic anhydride and N-phenylmaleimide for the preparation of C$^1$-substituted 7-oxanorbornenes.

\textbf{2.5.2 Results of Reactions Between 2-Substituted Furans with Maleic Anhydride}

We studied the Diels-Alder reactions of 2-substituted furans with maleic anhydride \textbf{2-39} and the results are shown in Table 2.6.
Table 2.6. DA reactions of 2-substituted furans with maleic anhydride.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Furan</th>
<th>Product</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-12ac</td>
<td>2-40a</td>
<td>2</td>
<td>35</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>2-12k</td>
<td>2-40b</td>
<td>2</td>
<td>35</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>2-12ad</td>
<td>2-40c</td>
<td>3</td>
<td>35</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>2-12ae</td>
<td>2-40d</td>
<td>2</td>
<td>35</td>
<td>45</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield after crystallization from ether.
We found that the Diels-Alder reactions of 2-substituted furans $2\text{-}12k, 2\text{-}12\text{ac-ae}$ gave moderate isolated yields after crystallization from ether. Some quantities of the products and starting materials (due to rDA) remained in the mother liquor. In all the reactions we observed exclusively the *exo* adduct by NMR. DA adduct $2\text{-}40a$ was unstable as it decomposed after a couple of months of storage at 5-10 °C. Adducts $2\text{-}40b$ and $2\text{-}40c$ were relatively stable compared to $2\text{-}40a$ but they also seemed to degrade upon storage for a couple of months. Adduct $2\text{-}40d$ was the least stable product as it began to decompose after only a couple of weeks.

### 2.5.3 Results of Reactions Between 2-Substituted Furans with N-Phenylmaleimide

Our next target was to investigate the Diels-Alder reaction between 2-substituted furans $2\text{-}12$ with N-phenylmaleimide $2\text{-}42$. We began the DA reaction of 2-substituted furans $2\text{-}12k, 2\text{-}12\text{ac-ag}$ with N-phenylmaleimide $2\text{-}42$ in diethyl ether (rt, reflux) but unfortunately no formation of the desired product was observed. The reason the reaction did not proceed may be due to the insolubility of N-phenylmaleimide in diethyl ether. In our next attempt we chose chloroform as the solvent to aid the solubility, and the reaction was stirred at room temperature. As there was no progress at room temperature after 6 hours, the temperature was increased to reflux. After refluxing for 24 to 72 h we obtained the products and the results are shown in Table 2.7.
Table 2.7. DA reactions of 2-substituted furans with N-phenylmaleimide.

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Furan</th>
<th>Product</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-12ac</td>
<td>2-43a</td>
<td>48</td>
<td>61</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>2-12k</td>
<td>2-43b</td>
<td>48</td>
<td>61</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>2-12ad</td>
<td>2-43c, 2-44c</td>
<td>24</td>
<td>61</td>
<td>63, 63:37</td>
</tr>
<tr>
<td>4</td>
<td>2-12ae</td>
<td>2-45</td>
<td>48</td>
<td>61</td>
<td>10</td>
</tr>
<tr>
<td>Entry</td>
<td>Furan</td>
<td>Product</td>
<td>Time (h)</td>
<td>Temp (°C)</td>
<td>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>-------</td>
<td>------------</td>
<td>--------------</td>
<td>----------</td>
<td>-----------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>5</td>
<td>2-12af</td>
<td><img src="image1.png" alt="Image" /></td>
<td>48</td>
<td>61</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2-43e</td>
<td><img src="image2.png" alt="Image" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2-12ag</td>
<td><img src="image3.png" alt="Image" /></td>
<td>72</td>
<td>61</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2-43f</td>
<td><img src="image4.png" alt="Image" /></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield after column chromatography.

2-Substituted furans with primary alkyl groups (2-12ac, 2-12k, R = Me and Et respectively) produced C<sup>1</sup>-substituted oxanorbornenes in very good yields (82 and 78%, Table 2.9, entries 1, 2 respectively). In both cases the product was confirmed as the exo adduct by NMR. The Diels-Alder reaction with furfuryl alcohol (2-12ad) gave a mixture of exo and endo adducts with a ratio of 63:37 (exo:endo) with 63% combined yield. The Diels-Alder product of 2-methoxy furan (2-12ae) with N-phenylmaleimide was not stable under the reaction conditions (chloroform reflux), so we were only able to isolate the aromatized product 2-45, which was confirmed by NMR and mass spectral analysis. Reaction involving the 2-substituted furans with electron withdrawing groups, 2-12af and 2-12ag gave extremely poor yields 2%, 3% respectively (Table 2.9, entries 5-6). The low yields are likely due to electron withdrawing groups making the diene electron poor.
In conclusion, we have successfully synthesized C\textsuperscript{1}-substituted 7-oxanorbornenes \textbf{2-40a} to \textbf{2-40d}, by the Diels-Alder reaction between 2-substituted furans and maleic anhydride in moderate yields. C\textsuperscript{1}-substituted 7-oxanorbornenes \textbf{2-43a} to \textbf{2-43c}, \textbf{2-44c} and \textbf{2-43e} to \textbf{2-43f} have also been synthesized by the Diels-Alder reaction between 2-substituted furans and N-phenylmaleimide with low to very good yields. These C\textsuperscript{1}-substituted 7-oxanorbornenes will be used in the mechanistic studies to examine the 1,3-DCA reaction, which will be discussed in Chapter 3.

\textbf{2.6 Synthesis of C\textsuperscript{1}-Substituted Oxabenzonorbornadienes}

\textbf{2.6.1 Background}

Oxabenzonorbornadienes are valuable intermediates because they can serve as a general template with which to create highly substituted ring systems\textsuperscript{11b, 11c}. To our surprise, a literature search has shown that very few unsymmetrical C\textsuperscript{1}-substituted oxabenzonorbornadienes (\textbf{2-49a-f}) have been synthesized to date (Figure 2.2),\textsuperscript{72, 150} and 1-trimethylsilyloxabenzonorbornadiene \textbf{2-49f} has been obtained only in very low yield.

![Figure 2.2. Known C\textsuperscript{1}-substituted oxabenzonorbornadienes.](image)

C\textsuperscript{1}-Substituted oxabenzonorbornadienes are synthesized by the Diels-Alder reaction between benzyne and 2-substituted furans. The benzyne is a highly reactive intermediate with a very short lifetime. Many different techniques for benzyne generation
are available, depending on the reaction conditions. It can be generated by one of several methods including thermal decomposition of o-diazonium benzoate, fluoride induced elimination of the aryl silyl triflates or lithium halide exchange of di-ortho halogenated aromatics followed by lithium-halide elimination.\textsuperscript{150d, 150e}

2.6.2 Results and Discussions

Taking the 2-substituted furans that were synthesized in Section 1.3 and 2.4, we began to study the Diels-Alder reactions of 2-substituted furans with benzyne 2-48 which was generated \textit{in situ} from anthranilic acid 2-46 and isoamyl nitrite 2-47 (Table 2.8). The results have been published in the literature.\textsuperscript{151}

The primary alkyl furans underwent cycloaddition in good to moderate yields. An increase in the length of the alkyl chain resulted in a decrease in yield of the cycloadduct. In the case of 2-ethylfuran 2-12k, the product was obtained in 80\% yield (Table 2.8, entry 1) whereas the longer alkyl chain 2-\textsuperscript{8}butylfuran 2-12p and 2-dodecylfuran 2-12v provided yields of 55 and 58\%, respectively (entries 2 and 3). When secondary linear alkyl groups were examined, the size of the substituent seemed to have a profound effect on the yield, as seen by comparing 2-isopropylfuran 2-12y (70\%) and 2-\textsuperscript{8}butylfuran 2-12q (29\%) (entries 4 and 5). 2-\textsuperscript{3}Butylfuran 2-12q has a bulkier substituent which resulted in a much lower yield of the C\textsuperscript{1}-benzooxanorbornadiene than when 2-isopropylfuran 2-12y was used in the cycloaddition. The tertiary alkyl group, 2-\textsuperscript{4}butylfuran 2-12z was also explored with the expectation that the yield of its cycloadduct would be lower than the less bulky systems. However, the bulkier 2-\textsuperscript{4}butylfuran 2-12z underwent cycloaddition in higher yield than 2-\textsuperscript{8}butylfuran 2-12q (66\%) (Table 2.8, entry 6). We expanded the range of suitable secondary alkyl groups to include cycloalkyl substituents, which produced the
desired products in low to moderate yields. 1-Ethylbenzonorbornadiene (80%) and 1-
butyloxabenzonorbornadiene (29%) remained the highest and lowest yielding C1-
secondary linear alkyl oxabenzonorbornadienes with all of the cycloalkyl substituent
yields falling between these two extremes. 2-Cyclobutylfuran 2-12r (entry 8) provided
the highest yield of all the cycloadducts with 62%. Low yields were observed for 2-
cyclopropylfuran 2-12o, 2-cyclopentylfuran, 2-12s, and 2-cycloheptylfuran 2-12u of 29,
33, and 32%, respectively (entries 7, 9 and 11). A slightly higher yield of 45% was
obtained for 2-cyclohexylfuran 2-12t (entry 10).

The cycloaddition of a variety of 2-arylfurans 2-12a-d and 2-12h-j provided the
corresponding 1-aryloxabenzonorbornadiene in moderate yields. The unsubstituted 2-
phenylfuran 2-12a underwent cycloaddition in 43% yield (entry 12). Introduction of the
substituent on the phenyl ring of the 2-phenylfuran resulted in either an increase or
decrease of yields depending on the substituent. For example, arylfurans containing an
extended \( \pi \)-system, 2-(1-naphthyl)furan 2-12n and 2-(4-biphenyl)furan 2-12m, both
provided much lower yields of 24 and 16%, respectively (entries 19 and 20), relative to a
simple phenyl ring. Examining the results of cycloaddition reactions with the ortho-,
meta-, and para- tolyl 2-12b-d (entries 13-15) and chloro 2-12h-j (entries 16-18) systems
showed that the presence of an electron donating or withdrawing group on the aryl ring
provided generally higher yields than the unsubstituted 2-phenylfuran. Of the tolyl
systems, a range in yields from 31% for the para- to 53% for the meta-substituted was
observed. This contrasts the chloro-substituted reactions where the para-system provided
the highest yield of the group with 63%. The yields were higher overall for the chloro-
substituted 1-aryloxabenzonorbornadienes 2-12h-j which ranged from 51-63%.
In further investigations, three other systems were explored resulting in a wide range of yields. 2-Trimethylsilylfuran 2-12aa formed the bicyclic alkene 2-12f in 75% yield (Table 2.8, entry 21) which was higher than the 66% yield from the comparable system of 2-‘butylfuran 2-12z. Due to the steric similarities of these two systems, the difference in yields may be due to the stronger electron donating effect of the silicon from the TMS group relative to the carbon of the ‘Bu substituent.

2-Bromofuran 2-2 provided the halogenated cycloadduct (2-12aa) in only 36% yield (entry 22). Sterically, we would expect the bromo substituent to result in a higher yield, therefore it is thought that the electronic effects of this substituent are responsible for the low yield observed. Slight decomposition was noted during the purification (column chromatography) of 2-12aa. The tertiary alcohol-containing furan 2-12ab underwent cycloaddition in 47% yield (entry 23) which is much lower than its tertiary alkyl counterpart 2-‘butylfuran. The cycloaddition of furan gave cycloadduct with 55% yield (entry 24).
Table 2.8. Synthesis of C₁-substituted oxabenzenorbornadienes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Furan</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-12k</td>
<td>4</td>
<td>55</td>
<td><img src="O" alt="2-49g" /></td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>2-12p</td>
<td>3</td>
<td>45</td>
<td><img src="nBu" alt="2-49h" /></td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>2-12v</td>
<td>3</td>
<td>45</td>
<td><img src="CH%E2%82%82%E2%82%81%E2%82%81CH%E2%82%83" alt="2-49i" /></td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>2-12y</td>
<td>3</td>
<td>45</td>
<td><img src="iPr" alt="2-49j" /></td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>2-12q</td>
<td>3</td>
<td>45</td>
<td><img src="sBu" alt="2-49k" /></td>
<td>29</td>
</tr>
</tbody>
</table>

*O₈R₂₁⁻¹₂a-d, h-k, m-v, y-ab, 2-2⁴⁵⁻⁵⁵°C*
<table>
<thead>
<tr>
<th>Entry</th>
<th>Furan</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>2-12z</td>
<td>3</td>
<td>45</td>
<td>2-49l</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>2-12o</td>
<td>3</td>
<td>50</td>
<td>2-49m</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>2-12r</td>
<td>3</td>
<td>50</td>
<td>2-49n</td>
<td>62</td>
</tr>
<tr>
<td>9</td>
<td>2-12s</td>
<td>3</td>
<td>45</td>
<td>2-49o</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>2-12t</td>
<td>3</td>
<td>45</td>
<td>2-49p</td>
<td>45</td>
</tr>
<tr>
<td>Entry</td>
<td>Furan</td>
<td>Time (h)</td>
<td>Temp (°C)</td>
<td>Product</td>
<td>Yield (%)^a</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>----------</td>
<td>-----------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="2-12u" /></td>
<td>4</td>
<td>50</td>
<td><img src="image" alt="2-49q" /></td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="2-12a" /></td>
<td>3</td>
<td>45</td>
<td><img src="image" alt="2-49r" /></td>
<td>43</td>
</tr>
<tr>
<td>13</td>
<td><img src="image" alt="2-12d" /></td>
<td>4</td>
<td>45</td>
<td><img src="image" alt="2-49s" /></td>
<td>47</td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="2-12c" /></td>
<td>3.5</td>
<td>45</td>
<td><img src="image" alt="2-56t" /></td>
<td>53</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="2-12b" /></td>
<td>3.5</td>
<td>45</td>
<td><img src="image" alt="2-49u" /></td>
<td>31</td>
</tr>
<tr>
<td>Entry</td>
<td>Furan</td>
<td>Time (h)</td>
<td>Temp (°C)</td>
<td>Product</td>
<td>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
<td>----------</td>
<td>-----------</td>
<td>---------</td>
<td>----------------------</td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Furan 2-12j" /></td>
<td>4</td>
<td>45</td>
<td><img src="image" alt="Product 2-49v" /></td>
<td>51</td>
</tr>
<tr>
<td>17</td>
<td><img src="image" alt="Furan 2-12i" /></td>
<td>4</td>
<td>45</td>
<td><img src="image" alt="Product 2-49w" /></td>
<td>52</td>
</tr>
<tr>
<td>18</td>
<td><img src="image" alt="Furan 2-12h" /></td>
<td>2.5</td>
<td>45</td>
<td><img src="image" alt="Product 2-49x" /></td>
<td>63</td>
</tr>
<tr>
<td>19</td>
<td><img src="image" alt="Furan 2-12n" /></td>
<td>3</td>
<td>45</td>
<td><img src="image" alt="Product 2-49y" /></td>
<td>24</td>
</tr>
<tr>
<td>20</td>
<td><img src="image" alt="Furan 2-12m" /></td>
<td>3</td>
<td>45</td>
<td><img src="image" alt="Product 2-49z" /></td>
<td>16</td>
</tr>
<tr>
<td>Entry</td>
<td>Furan</td>
<td>Time (h)</td>
<td>Temp (°C)</td>
<td>Product</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
<td>----------</td>
<td>-----------</td>
<td>------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>21</td>
<td>2-12aa</td>
<td>3</td>
<td>45</td>
<td>2-49f</td>
<td>75</td>
</tr>
<tr>
<td>22</td>
<td>2-2</td>
<td>3</td>
<td>55</td>
<td>2-49aa</td>
<td>36</td>
</tr>
<tr>
<td>23</td>
<td>2-12ab</td>
<td>3</td>
<td>45</td>
<td>2-49ab</td>
<td>47</td>
</tr>
<tr>
<td>24</td>
<td>2-12ac</td>
<td>3</td>
<td>45</td>
<td>2-49ac</td>
<td>55</td>
</tr>
</tbody>
</table>

* isolated yields after column chromatography.

In conclusion, we have successfully synthesized a wide range of novel C1-substituted oxabenzonorbornadienes with a variety of alkyl and aryl substituents. These compounds may prove useful for further studies into the scope and mechanism of reactions of oxabenzonorbornadienes.
Chapter 3

1,3-Dipolar Cycloadditions between Bicyclic Alkenes and Nitrile Oxides
3.1 Introduction

1,3-Dipolar cycloadditions offer convenient one-step synthetic routes for the construction of a variety of five-membered heterocycles.\textsuperscript{5a, 6e} The cycloaddition of nitrile oxides to olefins is of considerable interest as the resulting 2-isoxazolines are found in many compounds exhibiting biological activity,\textsuperscript{94-104} and are also key intermediates in the synthesis of a variety of natural products.\textsuperscript{6f, 152} Although carbobicyclic substrates have received much attention over the last few decades in studies of 1,3-DCA reactions, we noticed that there has been little precedent of heterobicyclic compounds partaking in 1,3-DCA reactions. Apart from the limited reports on the unsubstituted 7-oxabenzonorbornadiene 3-1 (X=\(Y=\text{H}\)) and 7-azabenzonorbornadienes 3-2, there were few examples of functionalized heterobicycles 3-1 or 3-2 contributing to these reactions.\textsuperscript{153} Due to the presence of a hetero atom (O or N) in their bridge, we anticipated different and possibly novel reactivities for these compounds from their carbobicyclic counterparts. This chapter studies the 1,3-dipolar cycloaddition reaction between nitrile oxides and a variety of symmetrical and unsymmetrical heterobicyclic alkene frameworks, while investigating the regio- and stereoselectivities. This research study could be used to create new routes towards 2-isoxazoline rings fused to bicyclic skeletons (Scheme 3.1).
Scheme 3.1. Possible cycloadducts from 1,3-dipolar cycloaddition of bicyclic alkenes with nitrile oxides.

Effective synthesis of 2-isoxazoline rings fused to bicyclic skeletons is advantageous as the reductive cleavage of the N-O bond leads to β-hydroxycarbonyl derivatives (3-13) and γ-aminoalcohols (3-14). Also, substituted cyclopentane rings (3-15), can also be achieved by a N-O bond cleavage and a retro-aldol reaction (Scheme 3.2). The Tam group has previously demonstrated the molybdenum mediated N-O bond cleavage of 2-isoxazolines fused to bicyclic frameworks to provide substituted cyclopentane rings with high degree of stereoselectivity. Therefore, having a stereo- and regioselective method for generating bicyclic 2-isoxazolines offers increased control over the stereochemistry of the N-O bond cleavage products that are formed.
Scheme 3.2. Cycloaddition-cleavage approach of bicyclic alkenes.

This chapter summarizes the results for 1,3-dipolar cycloaddition reactions of nitrile oxides (acetonitrile oxide and benzonitrile oxide) with various bicyclic alkenes that have been studied. Figure 3.1 shows the bicyclic alkenes that have been chosen to study the 1,3-dipolar cycloaddition reactions. The results of the acetonitrile oxide and benzonitrile oxide cycloadditions with bicyclic alkenes 3-1 to 3-6 are discussed in the following sections.

Figure 3.1. Bicyclic alkenes used for 1,3-dipolar cycloaddition reactions with nitrile oxides.
3.2 Proposed Methodology

In order to initiate a systematic investigation of the cycloadditions of nitrile oxides with bicyclic alkenes, a method for the generation of the nitrile oxide in situ first had to be rationalized. The most popular methods for in situ generation of nitrile oxide are dehydrohalogenation of hydroxamoyl chlorides with triethylamine or the dehydration of the corresponding nitroalkanes. Commonly used methods for dehydration of nitroalkanes are the Mukaiyama aromatic isocyanate method,\(^\text{34}\) the Shimizu ethyl chloroformate method,\(^\text{35}\) and Hassner’s (BOC)\(_2\)O/DMAP method.\(^\text{36}\) The preparation of hydroxamoyl chloride involves multiple synthetic steps (oxime formation and halogenation), while the Mukaiyama and Shimizu dehydration methods require high reaction temperatures. We chose to follow Hassner’s approach of nitroalkane dehydration, as the reaction can be conducted at room temperature, which reduces the possibility of nitrile oxide dimerization or polymerization, often resulting in better yields (Scheme 3.3).\(^\text{6h, 36}\)

![Scheme 3.3. Proposed methodology for 1,3-dipolar cycloaddition of bicyclic alkenes with nitrile oxides.](image-url)
As discussed in Chapter 2, various symmetrical and unsymmetrical bicyclic alkenes have been synthesized through numerous chemical transformations. Using the in situ generated nitrile oxides in combination with previously synthesized bicyclic alkenes a variety of 1,3-dipolar cycloaddition products can be generated. The newly generated cycloadducts have been investigated in order to determine all regiochemical and stereochemical aspects of the products. The information gathered during this process was then compiled into a general synthetic methodology that describes the limitations and advantages of the project.

3.3 Stereochemical Considerations

Two products, the exo and endo adducts, can be formed through any type of 1,3-dipolar cycloaddition involving bicyclic olefins. The study of the stereochemistry of the 1,3-dipolar cycloaddition has been a focus for many researchers, as this would allow us to predict with certainty the formation of only one product. Alder and Stein have established an “exo rule” for the 1,3-dipolar cycloaddition between bicyclo[2.2.1]heptane skeleton as a bicyclic olefin and phenyl azide as a dipole since the reactions solely forms the exo-adduct. However the cycloaddition of nitrile oxides and nitrones to norbornadiene tends to produce small amounts of endo as along with the exo adducts. Inagaki proposed that the π electron distribution of norbornene extends more to the exo face than the endo face due to the interactions between the π-orbital and methano bridge orbital. Similar interactions may be present in norbornadiene, which would help to explain the dominant exo adduct formation. In addition, homoconjugation is present on the endo face of norbornadiene. This homoconjugation may result in extending the π electron distribution toward the endo side. Consequently, the difference in π electron distribution
between the *exo* and *endo* face of norbornadiene is smaller than that in norbornene and therefore small amounts of the *endo* adduct is observed in 1,3-dipolar cycloadditions with norbornadiene (Scheme 3.4).

\[ \text{Scheme 3.4. Results of 1,3-dipolar cycloaddition of substituted norbornadienes with nitrile oxide.} \]

In this project, the 1,3-dipolar cycloaddition using symmetrical bicycloalkenes 3-1 to 3-3 could potentially generate the *exo* and/or *endo* adducts. Both of the possible cycloadducts are shown in Scheme 3.5.

\[ \text{Scheme 3.5. Possible cycloadducts from 1,3-dipolar cycloaddition of symmetrical bicyclic alkenes with nitrile oxides.} \]

In the case of unsymmetrical 7-oxabenzonebornadiene type bicycloalkenes 3-4 to 3-6, there is the possibility of forming four cycloadducts as a result of regio- and stereoisomers (Scheme 3.1, R≠H). The stereochemical isomers are formed by the possibility of the cycloadditions occurring from either the *exo* or *endo* face, which would generate two stereoisomers. For each face of the bicyclic alkene upon which
cycloaddition occurs, two regioisomers are possible. Therefore, if the cycloaddition did proceed on both the \textit{exo} and \textit{endo} face, a maximum of four cycloadducts could be generated. These regiochemical and stereochemical concerns must be addressed during the investigation of 1,3-dipolar cycloadditions nitrile oxides using various bicyclic alkenes.

3.4 Results and Discussion

The results of 1,3-DCA reactions between a variety of symmetrical and unsymmetrical bicyclic alkenes using acetonitrile oxide and benzonitrile oxide are outlined in the following sections.

3.4.1 Cycloadditions with Symmetrical Bicyclic Alkenes

We have studied 1,3-DCA reactions on symmetrical bicyclic alkenes (7-oxabenzonorbornadienes 3-1, 7-azabenzonorbornadienes 3-2, and 5,6-bis-methoxymethyl-7-oxa-bicyclo[2.2.1]hept-2-ene 3-3) using acetonitrile oxide and benzonitrile oxide as dipoles.

3.4.1.1 1,3-Dipolar Cycloadditions of Symmetrical 7-Oxabenzonorbornadienes

Bicyclic alkenes 3-1a to 3-1f were prepared using benzyne furan Diels-Alder reaction according to literature procedures,\(^ {155}\) as described in Chapter 2. Since compounds 3-1a-f are symmetrical bicyclic systems, regioselectivity is not a factor in the 1,3-DCA reactions. The nitrile oxide could approach either from the \textit{exo} or from \textit{endo} face thereby generating the respective \textit{exo} or \textit{endo} cycloadducts. Acetonitrile oxide and benzonitrile oxides were prepared from nitroethane and phenyl nitromethane respectively using (BOC)\(_2\)O/DMAP in the presence of bicyclic alkenes 3-1a to 3-1f and the 1,3-DCA
reactions were studied for their reactivity and stereoselectivity (Table 3.1). The results have been published in the literature.  

Table 3.1. 1,3-Dipolar cycloaddition with symmetrical 7-oxabenzonorbornadienes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bicycloalkene</th>
<th>Nitrile oxide</th>
<th>Product</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-1a</td>
<td>Acetonitrile oxide</td>
<td>3-20aa</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>3-1a</td>
<td>Benzonitrile oxide</td>
<td>3-20ab</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>3-1b</td>
<td>Acetonitrile oxide</td>
<td>3-20ba</td>
<td>68</td>
</tr>
</tbody>
</table>

R = a: Me, b: Ph

X = H, OMe, Me, F
Y = H, OMe, Br, F

59-98%  

exo
<table>
<thead>
<tr>
<th>Entry</th>
<th>Bicycloalkene</th>
<th>Nitrile oxide</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image1" alt="Bicycloalkene" /></td>
<td>Benzonitrile oxide</td>
<td><img src="image2" alt="Product" /></td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td><img src="image3" alt="Bicycloalkene" /></td>
<td>Acetonitrile oxide</td>
<td><img src="image4" alt="Product" /></td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td><img src="image5" alt="Bicycloalkene" /></td>
<td>Benzonitrile oxide</td>
<td><img src="image6" alt="Product" /></td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Bicycloalkene" /></td>
<td>Acetonitrile oxide</td>
<td><img src="image8" alt="Product" /></td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td><img src="image9" alt="Bicycloalkene" /></td>
<td>Benzonitrile oxide</td>
<td><img src="image10" alt="Product" /></td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td><img src="image11" alt="Bicycloalkene" /></td>
<td>Acetonitrile oxide</td>
<td><img src="image12" alt="Product" /></td>
<td>68</td>
</tr>
<tr>
<td>Entry</td>
<td>Bicycloalkene</td>
<td>Nitrile oxide</td>
<td>Product</td>
<td>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="3-1e" /></td>
<td>Benzonitrile oxide</td>
<td><img src="image" alt="3-20eb" /></td>
<td>59</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="3-1f" /></td>
<td>Acetonitrile oxide</td>
<td><img src="image" alt="3-20fa" /></td>
<td>60</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="3-1f" /></td>
<td>Benzonitrile oxide</td>
<td><img src="image" alt="3-20fb" /></td>
<td>60</td>
</tr>
</tbody>
</table>

<sup>a</sup> isolated yields after column chromatography.

The 1,3-DCA reactions with oxabicycles 3-1a to 3-1f revealed that these bicyclic ring systems are good reaction partners for generating the cycloaddition products effectively, with moderate to excellent yields (59-98%). Interestingly, these cycloadditions were found to be completely stereoselective and produced exclusively the *exo* stereoisomers. Furthermore, it was noted that the electronics of the arene substituents influence the product yields. For the reactions involving acetonitrile oxide (3-8a) (R=Me), cycloaddition with unsubstituted parent compound 3-1a (X = H, Y = H) gave cycloadduct 3-20aa in 90% (Table 3.1, entry 1). Conducting the cycloaddition with dimethoxy functionalized substrates, we found that the arene 6,7-disubstituted compound 3-1c (entry 3) showed slightly improved conversion over its 5,8-disubstituted compound.
3-1b (entry 5). Furthermore, the dimethyl functionalized substrate 3-1d gave the highest yield of 98% for 3-20da (entry 7), while reactions suffered when halogens were present on the aromatic ring: the ortho-dibromo derivative 3-1e gave a modest 68% yield (entry 9) and the tetrafluoro derivative 3-1f gave an even lower yield of 60% (entry 11).

Similar results were observed for cycloadditions involving benzonitrile oxide 3-8b (R=Ph) with oxabicycles 3-1a to 3-1f: the parent compound 3-1a gave an appreciable 93% yield of cycloadduct 3-20ab (Table 3.1, entry 2), while the arene 6,7-dimethoxy substrate 3-1c again provided better reactivity than its 5,8-dimethoxy counterpart 3-1b (entries 6, 4 respectively). The dimethyl substituted 3-1d showed moderate conversion (entry 8), and halogen substituents once more diminished the yields of cycloadducts to ≤60% (entries 10, 12). Overall, highest yields were seen for no substitution, arene 6,7-dimethoxy, or 5,8-dimethyl substitution. The difference in the yields between bicyclic alkenes 3-1b and 3-1c could be a result of net electronic (resonance and inductive) effect of methoxy groups on the reactivity of bicyclic alkene towards cycloaddition. The lower yields of reactions with electron poor bicyclic alkenes (3-1e, 3-1f) could be due to a lower reactivity of the oxabicycle due to a lack of electron density on the olefin.

![Figure 3.2. Assignment of stereochemistry of cycloadducts 3-20aa-3-20fb.](image)

As mentioned, all of the cycloadducts 3-20aa to 3-20fb were formed as exo products. The stereochemistry of these cycloadducts were determined by inspection of their coupling pattern of H\textsuperscript{a} to H\textsuperscript{b}, as well as H\textsuperscript{c} to H\textsuperscript{d} in each \textsuperscript{1}H NMR spectrum of the
adducts. This assignment was based on prior knowledge of similar 2-isoxazoline geometries reported by the Tam group for similar 2-isoxazoline compounds (Figure 3.2). Since the dihedral angle \( \theta \) between \( H^a \) and \( H^b \) or \( H^c \) and \( H^d \) in the \( \text{exo} \) cycloadduct are near 90\(^{\circ} \), their coupling constant is expected to be very small (\( J = 0-2 \text{ Hz} \)). The corresponding \( \text{endo} \) cycloadduct on the other hand, has its protons held in a rigid \( \sim 42^{\circ} \) angle. This should give a coupling constant of \( J \sim 5 \text{Hz} \), which was not observed in cycloadducts 3-20aa-3-20fb. All cycloadducts showed both \( H^a \) and \( H^c \) as doublets, while \( H^b \) and \( H^d \) were singlets, therefore these cycloadducts must possess \( \text{exo} \) stereochemistry.

### 3.4.1.2 1,3-Dipolar Cycloadditions of Symmetrical 7-Azabenzonorbornadienes

Encouraged by the results of the oxabicyclic cycloadditions, we then proceeded to cycloadditions of azabicyclic derivatives. We chose pivaloyl, tosyl, Boc protected azabicycloalkenes 3-2a to 3-2c for cycloaddition. The reactions were performed by \textit{in situ} generation of the nitrile oxides from the corresponding nitroalkanes using \((\text{BOC})_2\text{O}/\text{DMAP}\) in the presence of bicyclic alkenes. The 1,3-dipolar cycloaddition reactions of bicyclic alkenes 3-2a to 3-2c with nitrile oxides 3-8a-b proceeded smoothly to give the desired cycloadducts in good to excellent yields of 52-99\% and complete \( \text{exo} \) stereoselectivity (Table 3.2).

Reaction of acetonitrile oxide 3-8a with Piv-protected azabicycle 3-2a proceeded with a satisfactory 88\% yield (Table 3.2, entry 1). When extending this to Ts-protected 3-2b, a precipitous drop in yield to 52\% was observed (entry 3). However, to our delight, the Boc-protected amine 3-2c gave the highest yields obtained thus far at 99\% (entry 5). Upon repeating the reactions with benzonitrile oxide 3-8b, it became apparent that substituent-dependent trends observed for the oxabicycloalkene arene substitution were
not as easily discernable with amine substitution (entries 2, 4, 6). Surprisingly, the azabicyclic substrate 3-2b which gave a 52% yield when treated with acetonitrile oxide, provided a much higher 95% yield upon treatment with benzonitrile oxide (entries 3 and 4), while the Boc-protected amine 3-2c gave near quantitative conversion of 99% and 97% yield under both acetonitrile oxide and benzonitrile oxide treatment, respectively (entries 5 and 6).

Table 3.2. 1,3-Dipolar cycloadditions of symmetrical 7-azabenzonorbornadienes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bicycloalkene</th>
<th>Nitrile oxide</th>
<th>Product</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-2a</td>
<td>Acetonitrile oxide</td>
<td>3-21aa</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>3-2a</td>
<td>Benzonitrile oxide</td>
<td>3-21ab</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>3-2b</td>
<td>Acetonitrile oxide</td>
<td>3-21ba</td>
<td>52</td>
</tr>
<tr>
<td>Entry</td>
<td>Bicycloalkene</td>
<td>Nitrile oxide</td>
<td>Product</td>
<td>Yield (%)(^a)</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>------------------</td>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>4</td>
<td><img src="bicycloalkene.png" alt="" /> Ts</td>
<td>Benzonitrile oxide</td>
<td><img src="product.png" alt="" /> 3-21bb</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td><img src="bicycloalkene.png" alt="" /> Boc</td>
<td>Acetonitrile oxide</td>
<td><img src="product.png" alt="" /> 3-21ca</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td><img src="bicycloalkene.png" alt="" /> Boc</td>
<td>Benzonitrile oxide</td>
<td><img src="product.png" alt="" /> 3-21cb</td>
<td>97</td>
</tr>
</tbody>
</table>

\(^a\) isolated yields after column chromatography.

![Figure 3.3](image)

**Figure 3.3. Assignment of stereochemistry of cycloadducts 9aa-9cb.**

The stereochemistry of cycloadduct 3-21aa-3-21cb was assigned by the coupling pattern of H\(^a\) to H\(^b\), as well as H\(^c\) to H\(^d\) in each \(^1\)H NMR spectrum of the adducts similar to cycloadducts 3-20aa-3-20fb (Figure 3.3). All cycloadducts showed both H\(^a\) and H\(^c\) as doublets, while H\(^b\) and H\(^d\) were singlets. Therefore, these cycloadducts must possess \textit{exo} stereochemistry.
3.4.1.3 1,3-Dipolar Cycloaddition of 5,6-Bis-methoxymethyl-7-oxa-bicyclo[2.2.1]hept-2-ene

To verify the versatility and compatibility of the 1,3-dipolar cycloaddition with other symmetrical heterobicycloalkenes, we also subjected 5,6-bis-methoxymethyl-7-oxa-bicyclo[2.2.1]hept-2-ene 3-3 to nitrile oxide cycloaddition with nitrile oxides 3-8a-b (Scheme 3.6).

![Scheme 3.6. 1,3-Dipolar cycloaddition of bicyclic alkene 3-3.](image)

The cycloadditions proceeded well, producing high yields of the desired cycloadducts. A yield of 79% was obtained with acetonitrile oxide and 96% with the benzonitrile oxide. In both of the cases the exo product was exclusively formed. The stereochemistry of cycloadduct 3-22a, and 3-22b was assigned by the coupling pattern of H\(^a\), H\(^b\), H\(^c\) and H\(^d\) in the \(^1\)H NMR spectra showed a coupling pattern similar to cycloadducts 3-20aa-3-20fb.

In conclusion, we have studied the 1,3-dipolar cycloaddition between nitrile oxides and variety of symmetrical bicyclic alkene systems, which is comprised of 7-oxabenzonorbornadienes 3-1, 7-azabenzonorbornadienes 3-2, and 5,6-bis-methoxymethyl-7-oxa-bicyclo[2.2.1]hept-2-ene 3-3. For each of these cycloadditions, the nitrile oxide dipole could in theory approach from either the exo face or the endo face of the bicyclic substrates. As a result, two stereoisomeric outcomes for the cycloadducts.
could be envisioned. In practice, however, only the \textit{exo} stereoisomers were obtained in all cases. It is evident that the nitrile oxide dipole shows a strong preference for approach to the bicyclic framework from the \textit{exo} face. Furthermore, with oxabenzonorbornadienes 3-1, the arene substitution pattern appeared to influence the yields, while the effects of modifying azabicycloalkene amine substitution was not as pronounced. Upon completing the study of symmetrical bicyclic alkenes, our focus shifted to unsymmetrical bicyclic alkenes to see if the similar reactivities were observed and to investigate the regioselectivities.

\subsection*{3.4.2 Cycloadditions with Unsymmetrical Bicyclic Alkenes}

Previously, the Tam group has addressed the issue of regioselectivity using unsymmetrical norbornenes.\textsuperscript{71b} In order to extend the substrate scope of reactive substrates for 1,3-DCA reactions of bicyclic alkenes, we chose to study the 1,3-DCA reaction between of unsymmetrical heterobicyclic alkenes and nitrile oxides. This study focuses on C\textsubscript{1}-substituted 7-oxabenzonorbornadienes 3-4, C\textsubscript{1}-substituted-7-azanorbornenes 3-5, and N-acyl-2-oxa-3-azanorborn-5-enes 3-6 and investigates the effects on regio- and stereoselectivity with varying substitutions.

\subsubsection*{3.4.2.1 1,3-Dipolar Cycloaddition of C\textsubscript{1}-Substituted-7-oxabenzonorbornadienes}

C\textsubscript{1}-Substituted-7-oxabenzonorbornadienes 3-4a to 3-4g were synthesized using the process of benzyne-furan cycloaddition as discussed in Chapter 2. Arene substituents (5,8-dimethoxy groups) were incorporated following methods described by Lautens and Fagnou.\textsuperscript{154e} The nitrile oxides were generated \textit{in situ} from nitroethane and phenyl nitromethane using the (BOC)\textsubscript{2}O and DMAP. The results of the 1,3-DCA reactions on C\textsubscript{1}-substituted-7-oxabenzonorbornadienes (3-4a to 3-4g) using acetonitrile oxide and
benzonitrile oxide as dipoles are summarized in Table 3.3. The results have been published in the literature.\textsuperscript{157}

Table 3.3. 1,3-Dipolar cycloaddition with C\textsuperscript{1}-substituted 7-oxabenzonorbornadienes.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bicycloalkene</th>
<th>Nitrile oxide</th>
<th>Product (ratio)</th>
<th>Yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-4a</td>
<td>Acetonitrile oxide</td>
<td>3-23aa to 3-23gb</td>
<td>(85:15) 96</td>
</tr>
<tr>
<td></td>
<td>3-4b</td>
<td>Acetonitrile oxide</td>
<td>3-23ba to 3-23gb</td>
<td>(92:8) 92</td>
</tr>
<tr>
<td></td>
<td>3-4c</td>
<td>Acetonitrile oxide</td>
<td>3-23ca to 3-23gb</td>
<td>(90:10) 53</td>
</tr>
<tr>
<td></td>
<td>3-4a</td>
<td>Benzonitrile oxide</td>
<td>3-24aa to 3-24gb</td>
<td>(85:15) 86</td>
</tr>
<tr>
<td></td>
<td>3-4b</td>
<td>Benzonitrile oxide</td>
<td>3-24ba to 3-24gb</td>
<td>(92:8) 86</td>
</tr>
<tr>
<td></td>
<td>3-4c</td>
<td>Benzonitrile oxide</td>
<td>3-24ca to 3-24gb</td>
<td>(90:10) 53</td>
</tr>
<tr>
<td>Entry</td>
<td>Bicycloalkene</td>
<td>Nitrile oxide</td>
<td>Product (ratio)</td>
<td>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>---------------</td>
<td>-----------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Acetonitrile</td>
<td>3-23da (75:25)</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>3-4d</td>
<td>oxide</td>
<td>3-24da</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Acetonitrile</td>
<td>3-23ea (64:36)</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>3-4e</td>
<td>oxide</td>
<td>3-24ea</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Benzonitrile</td>
<td>3-23eb (48:52)</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>3-4e</td>
<td>oxide</td>
<td>3-24eb</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>Acetonitrile</td>
<td>3-23fa</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>3-4f</td>
<td>oxide</td>
<td>3-23fa</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>Acetonitrile</td>
<td>3-23ga (89:11)</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>3-4g</td>
<td>oxide</td>
<td>3-24ga</td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>Bicycloalkene</td>
<td>Nitrile oxide</td>
<td>Product (ratio)</td>
<td>Yield (%)(^a)</td>
</tr>
<tr>
<td>-------</td>
<td>---------------</td>
<td>---------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="3-4g" /></td>
<td>Benzonitrile oxide</td>
<td><img src="image" alt="3-23gb" /> <img src="image" alt="3-24gb" /> (90:10)</td>
<td>91</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yields after chromatography.

All the cycloaddition reactions with C\(^1\)-substituted-7-oxabenzonorbornadienes and the corresponding nitrile oxides were found to be completely stereoselective producing only the \textit{exo} adduct. In terms of regioselectivity, both possible regioisomers were obtained with varying ratios depending on the physical demand of the C\(^1\)-substituent. In most cases, the major isomer was found to be in the form of 3-23, with the nitrile oxide R’ group (R’ = Me, Ph) positioned \textit{anti} to the C\(^1\)-substituent, whereas the minor isomer 3-24 had the nitrile oxide R’ group \textit{syn} to the C\(^1\)-bridgehead position. Cycloaddition of alkene 3-4a bearing a C\(^1\)-methyl group with acetonitrile oxide was high yielding at 96 %, and resulted in an 85:15 regioisomeric mixture of products 3-23a to 3-24a (Table 3.3, entry1). Reacting the same substrate with benzonitrile oxide gave a slightly lower yield of 86 % but considerably higher regioselectivity (entry 2), which was also noted for the reaction of C\(^1\)-ethyl substituted alkene 3-4b with acetonitrile oxide (entry 3). When a primary alcohol was introduced at the C\(^1\)-position the yields were diminished to 53 % but good \textit{anti-syn} regioselectivity of 90:10 was still noted (entry 4). The use of more strongly electron-withdrawing carbonyl substituents at the C\(^1\)-position overall showed improved yields (up to 98 %), though this again was accompanied with the loss of regioselectivity (entries 5-7). The presence of a trimethylsilyl group
demonstrated an extreme example of exclusive 100:0 regiochemical preference, albeit at the cost of reduced yields once again (entry 8). Finally, when 5,8-dimethoxy substituents were present on the arene in addition to C1-methyl substitution, both regioselectivity (90:10) and yields (> 90 %) showed satisfactory results (entries 9 and 10).

From these observations, it appears that both steric and electronic factors are influencing the outcome of the cycloaddition reactions. Comparison of steric bulk of C1-substituents Me, Et, and TMS, for instance, shows selectivity for regioisomer 3-23 increasing with substituent size (Me<Et<TMS, Table 3.3, entries 1, 3 and 8). The cycloaddition results also indicate that the electronic factors of the C1 substituent has significant effect on the regioselectivity. An increase in the electron withdrawing nature of the C1 substituent results in an increase of the formation of the regioisomer 3-24, SiMe3<Et<Me<C(O)Me<CO2Me (entries 8, 2, 1, 5 and 6). A theoretical calculation of atomic charge densities for compounds 3-4a (R1 = Me) and 3-4d (R1 = C(O)Me) showed that for both +I and –I substituents, a higher relative charge resides on C3 atom of the alkene than on C2 (Scheme 3.7). This explains the overall preference of the nitrile oxide dipole to orient itself such that the oxygen is adjacent to C2, giving rise to major isomer 3-23.

![Scheme 3.7](image)

Scheme 3.7. Relative charge densities on C2 and C3 of oxabenzonorbornadiene 3-4 and the preferred approach of nitrile oxide to afford major regioisomer 3-23.
However, the relative increase in proportion of 3-24 with increased electron-withdrawing strength must arise from combined effects of sterics and electronics that could involve more complex orbital interactions akin to those that Tam group has addressed in previous computational work of C^2- and C^7-substituted bicycloalkenes.\textsuperscript{67b,158}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3_4.png}
\caption{Assignment of regiochemistry of cycloadducts 3-23aa to 3-24gb.}
\end{figure}

The stereochemistry of cycloadducts 3-23aa to 3-24gb (Figure 3.4) was assigned using the coupling pattern of H^a, H^b and H^c in the \textsuperscript{1}H NMR spectra as previously mentioned for cycloadducts 3-20aa-3-20fb (Figure 3.2). In major cycloadduct 3-23, both H^a and H^b are doublets (coupled only to each other but H^b not coupled to H^c) and H^c is a singlet (not coupled to H^b), therefore this cycloadduct must possess \textit{exo} stereochemistry. In the minor cycloadduct 3-24, both H^a and H^b are doublets (coupled only to each other but H^a not coupled to H^c) and H^c is a singlet (not coupled to H^a), so therefore this cycloadduct must also possess \textit{exo} stereochemistry.

The regiochemistry of the major cycloadduct 3-23 was determined by NOESY experiments (nOe experiments).\textsuperscript{159} By NMR, irradiation of H^b on the cycloadduct 3-23 showed a positive nuclear Overhauser enhancement of H^a, H^c, and, more importantly the methyl group protons of the 2-isoxazoline ring (where R = Me). For the cycloadducts bearing a C^1-methyl group (R^1 = Me), irradiation of H^a displayed positive enhancement of the C^1-methyl protons peaks. These nOe correlations distinctly reveal that the R
substituent of isoxazoline ring is situated anti to the C¹-substituent indicating regioisomer 3-23. Similarly, the regiochemical assessment of minor adduct 3-24 followed in such a way that irradiation of H⁹ resulted in enhancement Hᵇ and Hᶜ (but no methyl protons). While irradiation of Hᵇ resulted in enhancement of H⁹ and the methyl protons of the isoxazoline ring (R = Me) as well as C¹-methyl protons for those adducts bearing C¹-methyl groups (Rˡ = Me). Therefore, these nOe correlations confirm the R substituent of isoxazoline ring is syn to the C¹-substituent which confirms the structure of 3-24.

An X-ray crystal structure of adduct 3-23gb (X = OMe, R = R’ = Me) unambiguously confirmed the isoxazoline methyl group situated across the framework from the C¹-methyl group, pointing away in the opposite direction.¹⁶⁰ A two-bond separation between the isoxazoline oxygen and the C¹-carbon (to which the methyl group is attached) was also apparent.

In conclusion, we have investigated the stereochemical and regiochemical outcomes of 1,3-dipolar cycloaddition reactions on various unsymmetrical C¹-substituted oxabenzonorbornadienes 3-4 with acetonitrile and benzonitrile oxides. The resulting isoxazolines showed complete exo-stereoselectivity and major preference for positioning of nitrile oxide R moiety anti to the C¹-substituent as confirmed by NMR and X-ray analysis. The relative distributions of the regiochemical 2-isoxazolines suggested some steric and electronic contributions of the C¹-substituent toward these reactions. The moderate to excellent yields (53%-98%), good regioselectivity, and steadfast stereoselectivity observed in these reactions make this method a convenient approach to the synthesis of oxabicycle-fused 2-isoxazolines.
3.4.2.2 1,3-Dipolar Cycloadditions of C1-substituted N-Phenylmaleimide Fused Oxanorbornenes

To continue the study of 1,3-DCA reactions with unsymmetrical bicyclic alkenes, we wanted to demonstrate the versatility of this transformation with more unsymmetrical oxabicyclic systems. We therefore subjected N-phenylmaleimide-fused versions of C1-substituted oxabicycloalkenes 3-5 to 1,3-dipolar cycloaddition with acetonitrile oxide (Table 3.4). These bicyclic alkenes are prepared by a Diels-Alder reaction between N-phenylmaleimide and substituted furans as outlined in Chapter 2. Acetonitrile oxide was prepared in situ from nitroethane using the (BOC)2O and DMAP. The cycloaddition reactions were performed at 60 °C as initial cycloaddition reactions did not proceed at room temperature. The results are outlined in Table 3.4.

Table 3.4. 1,3-Dipolar cycloadditions of C1-substituted N-phenylmaleimide fused oxanorbornenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bicycloalkene</th>
<th>Nitrile oxide</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-5a</td>
<td>Acetonitrile oxide</td>
<td>3-25a</td>
<td>52</td>
</tr>
</tbody>
</table>

![Diagram of the reaction](image-url)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Bicycloalkene</th>
<th>Nitrile oxide</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image" alt="3-5b" /></td>
<td>Acetonitrile oxide</td>
<td><img src="image" alt="3-25b" /></td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="3-5c" /></td>
<td>Acetonitrile oxide</td>
<td><img src="image" alt="3-26" /></td>
<td>41&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="3-5d" /></td>
<td>Acetonitrile oxide</td>
<td><img src="image" alt="3-25e" /></td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="3-5e" /></td>
<td>Acetonitrile oxide</td>
<td>No reaction</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields.<br> <sup>b</sup>By-product yield.

All the cycloaddition reactions that worked were found to be completely stereoselective producing the *exo* adducts. Interestingly, in all cases a single regioisomer was formed, which was determined to be the regioisomer 3-25 where the methyl group of acetonitrile oxide is *anti* to the C<sup>1</sup>-substituent. Both C<sup>1</sup>-methyl (3-5a) and C<sup>1</sup>-ethyl (3-5b) derivatives showed good conversions of 52 % and 63 %, respectively (Table 3.4, entries 1,2). The cycloaddition reaction with bicyclic alkene 3-5c did not proceed to give any
cycloadduct (entry 3). Surprisingly, a by-product from the reaction with 3-5c was isolated which was found to be the bicyclic alkene with a BOC protecting group on the hydroxyl methyl, 3-26 (Figure 3.5). While the adduct 3-5e containing an electron-withdrawing C^1-ester substituent was reluctant to react (entry 5), the bicyclic alkene 3-5e with C^1-acetyl substituent managed to give product with 14% yield (entry 4). Therefore, three of the five reactions proceeded to give the desired product with high stereo- and regioselectivity in modest yields.

![Figure 3.5. By-product from 1,3-dipolar cycloaddition of 3-5c.](image)

Figure 3.5. By-product from 1,3-dipolar cycloaddition of 3-5c.

![Figure 3.6. Assignment of stereo and regiochemistry of cycloadducts 3-25a, 3-25b and 3-25e.](image)

Figure 3.6. Assignment of stereo and regiochemistry of cycloadducts 3-25a, 3-25-b and 3-25e.

The stereochemistry of *exo* cycloadducts 3-25a, 3-25-b and 3-25e was assigned by the coupling pattern of H^a, H^b and H^c in the ^1^H NMR spectra (Figure 3.6) similar to cycloadducts 3-20aa to 3-20gb. The regiochemistry of the cycloadduct 3-25 was determined by NOESY experiments (nOe experiments). In the cycloadduct 3-25, H^b showed a positive nOe effect with H^a, H^c and methyl group on 2-isoxazoline ring. H^a showed positive nOe effect with H^b and with methyl group attached to C^1^-carbon (R^1 = Me). Therefore, this confirmed structure of the regioisomer as illustrated in Figure 3.6.
In summary, we have investigated the 1,3-DCA reactions on C^1-substituted N-phenylmaleimide fused oxanorbornene compounds 3-5 using acetonitrile oxide. We were able to achieve the cycloaddition products for substrates 5a, 5b and 5e. We have learned that the cycloaddition is forms exclusively exo-cycloadducts and regioisomer 3-25. These N-phenylmaleimide fused bicyclic alkene compounds are less reactive toward cycloaddition with acetonitrile oxide, therefore generally low yields were observed. By introducing the electron withdrawing group at the C^1 position, the reactivity is further reduced and the yields suffered. With an acetyl group at the C^1 position 3-25e we obtained very low yield and with an ester group 3-5f we did not get the cycloaddition product. In all the successful examples, regioisomer 3-25 was formed exclusively.

3.4.2.3 1,3-Dipolar Cycloaddition of N-Acyl-2-oxa-3-azanorborn-5-enes

N-Acyl-2-oxa-3-azanorborn-5-enes systems 3-6 are another variety of unsymmetrical bicyclic alkenes that we examined for their stereo- and regioselectivities in 1,3-DCA reactions. Nitrile oxides were again generated in situ from nitroethane and phenyl nitromethane using the (BOC)_2O and DMAP in the presence of bicyclic alkenes 3-6 at room temperature. The results are summarized in Table 3.5.
Table 3.5. Results of 1,3-dipolar cycloaddition with N-Acyl-2-oxa-3-azanorborn-5-enes.

\[
\begin{align*}
 R \text{NO}_2 \quad \text{(Boc)}_2\text{O} \quad \text{DMAP} \quad \text{Toluene} \quad \text{rt} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bicycloalkene</th>
<th>Nitrile oxide</th>
<th>Product (ratio)</th>
<th>Yield (%) (^{a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-7a, 3-7b</td>
<td>Acetonitrile oxide</td>
<td>3-27aa to 3-27bb</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>3-6a</td>
<td>Acetonitrile  oxide</td>
<td>3-27ba to 3-27bb</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-6b</td>
<td>3-28aa to 3-28bb</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Me</td>
<td>3-28ba</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3-6a</td>
<td>Benzonitrile  oxide</td>
<td>3-27ab to 3-27bb</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph</td>
<td>3-28ab</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3-6b</td>
<td>Acetonitrile  oxide</td>
<td>3-27ba to 3-27bb</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Me</td>
<td>3-28ba</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3-6b</td>
<td>Benzonitrile  oxide</td>
<td>3-27bb to 3-27bb</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph</td>
<td>3-28bb</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Isolated yields after chromatography.
The cycloadditions of bicyclic alkenes (3-6a, 3-6b) with acetonitrile oxide and benzonitrile oxide were found to be completely stereoselective producing only the \( \text{exo} \) adducts. In all cases the cycloaddition reactions produced a mixture of both regioisomers, which are referred to as \( \text{syn} \) (two oxygens on the same side of the molecule) and \( \text{anti} \) (two oxygens on the opposite sides of the molecule) isomers relative to the positions of the two oxygens in the cycloadducts. The 1,3-dipolar cycloaddition of N-Boc-2,3-oxazanorborn-5-ene (3-6a) with acetonitrile oxide gave two regioisomeric \( \text{exo} \) cycloadducts in the ratio of 25:75 with a combined yield of 52%. The major product was found to be the \( \text{syn} \) regioisomer 3-28aa, and the minor product was the \( \text{anti} \) isomer (entry 1). In the cycloaddition of 3-6a with benzonitrile oxide the amount of the \( \text{anti} \) isomer increased, resulting in a 1:1 of \( \text{syn/anti} \) isomers with a combined yield of 79% (entry 2).

Similarly, the cycloaddition of N-benzoyl-2,3-oxazanorborn-5-ene (3-6b) with acetonitrile oxide produced a mixture of regioisomers in a 30:70 ratio, \( \text{anti/syn} \), with a combined yield of 87% (entry 3). The cycloaddition with 3-6b and benzonitrile also resulted in an increase in the formation of the \( \text{anti} \) isomer, with an observed product ratio of 60:40 favouring the \( \text{anti} \) isomer. In these four examples exclusive formation of the \( \text{exo} \) cycloadducts was observed, as well as general increase in the production of the \( \text{anti} \) isomer when benzonitrile oxide is used.

![Figure 3.7. Assignment of stereo and regiochemistry of cycloadducts 3-27aa to 3-21bb.](image)

122
The *exo* stereochemistry of cycloadducts 20aa-21bb was assigned by the coupling pattern of H\textsuperscript{a}, H\textsuperscript{b}, H\textsuperscript{c} and H\textsuperscript{d} in the \textsuperscript{1}H NMR spectra (Figure 3.7). The cycloadducts 3-27aa-3-27bb, and 3-28aa to 3-28bb, follow the standard \textsuperscript{1}H NMR coupling pattern for *exo* stereoisomers where H\textsuperscript{a} and H\textsuperscript{b} are doublets, and H\textsuperscript{c} and H\textsuperscript{d} are singlets.

The regiochemistry of the cycloadducts 3-27aa to 3-28bb was determined by NOESY experiments (nOe experiments). In the cycloadduct 3-27, H\textsuperscript{b} showed positive nOe effect with H\textsuperscript{a} and H\textsuperscript{c}. H\textsuperscript{c} showed positive nOe with H\textsuperscript{b}. These correlations indicate an *anti* configuration relative to the cycloadduct oxygens.

In the *syn* cycloadduct 3-28, H\textsuperscript{a} showed a positive nOe effect with H\textsuperscript{b}. H\textsuperscript{b} showed positive nOe with H\textsuperscript{a}, and H\textsuperscript{d}. The nOe correlations confirms the assignment as a *syn* regioisomer.

The regiochemistry of the cycloadducts 3-27bb and 3-28bb was confirmed by comparing the recorded \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra with previously reported data.\textsuperscript{59} Regiochemistry of cycloadducts 3-27aa to 3-28ba were assigned based on the \textsuperscript{1}H NMR and \textsuperscript{13}C NMR confirmed data of cycloadducts 3-27bb and 3-28bb. Tables 3.6 and Table 3.7 summarize the data comparison of cycloadducts 3-27bb and 3-28bb with literature reported \textsuperscript{1}H and \textsuperscript{13}C data respectively. Tables 3.8 and Table 3.9 describe the assignment of regioisomers based on the data comparison of cycloadducts 3-27aa-3-28ba with \textsuperscript{1}H and \textsuperscript{13}C data of the confirmed regioisomers 3-27bb and 3-28bb respectively.

An X-ray crystal structure of adduct 3-28ba unambiguously confirmed that it is the *exo* isomer with a *syn* arrangement of two “O” atoms in the isoxazole and oxazine rings.\textsuperscript{161}
Table 3.6. Confirmation of regiochemistry of cycloadducts 27bb and 28bb by comparing $^1$H NMRs to previously reported data.

<table>
<thead>
<tr>
<th>Cycloadduct</th>
<th>H$^a$, (d)</th>
<th>H$^b$, (d)</th>
<th>H$^c$, (s)</th>
<th>H$_d$, (s)</th>
<th>CH$_2$, (m)</th>
<th>J$_{a,b}$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="3-27bb" /></td>
<td>5.19</td>
<td>4.24</td>
<td>5.02</td>
<td>5.12</td>
<td>2.08(s)</td>
<td>8.2</td>
</tr>
<tr>
<td>Reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="3-28bb" /></td>
<td>5.19</td>
<td>4.24</td>
<td>5.02</td>
<td>5.12</td>
<td>2.07(s)</td>
<td>8.2</td>
</tr>
<tr>
<td>Obtained (3-27bb)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Reported" /></td>
<td>5.02</td>
<td>4.34</td>
<td>4.94</td>
<td>5.13</td>
<td>2.02-2.14</td>
<td>8.4</td>
</tr>
<tr>
<td><img src="image" alt="Obtained (3-28bb)" /></td>
<td>5.02</td>
<td>4.33</td>
<td>4.93</td>
<td>5.12</td>
<td>2.02-2.13</td>
<td>8.3</td>
</tr>
</tbody>
</table>

59
Table 3.7. Confirmation of regiochemistry of cycloadducts 27bb and 28bb by comparing $^{13}$C NMRs to previously reported data.\textsuperscript{59}

![Cycloadducts 27bb and 28bb](image)

<table>
<thead>
<tr>
<th>Cycloadduct</th>
<th>$C^1$</th>
<th>$C^4$</th>
<th>$C^5$</th>
<th>$C^6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-27bb</td>
<td>80.0</td>
<td>61.9</td>
<td>82.7</td>
<td>57.3</td>
</tr>
<tr>
<td>3-28bb</td>
<td>80.0</td>
<td>61.9</td>
<td>82.7</td>
<td>57.4</td>
</tr>
</tbody>
</table>

The chemical shifts from $^1$H NMR of known regioisomers from the literature reveal that the chemical shift of $H^a$ for regioisomer 3-27bb ($\delta$ 5.19) is higher than the chemical shift of $H^a$ ($\delta$ 5.02) for regioisomer 3-28bb. Chemical shift of $H^b$ ($\delta$ 4.24) for 3-27bb is lower than $H^b$ ($\delta$ 4.34) for 3-28bb. A similar ordering of the chemical shifts was observed in other regioisomeric pairs (3-27ba/3-28ba and 3-27aa/3-28aa) as summarized in Table 3.8.
Table 3.8. Assignment of regiochemistry of cycloadducts 3-27aa to 3-28ba based on confirmed $^1$H data of regioisomers 3-27bb and 3-28bb.

<table>
<thead>
<tr>
<th>Cycloadduct</th>
<th>H$^a$, (d)</th>
<th>H$^b$, (d)</th>
<th>H$^c$, (s)</th>
<th>H$^d$, (s)</th>
<th>CH$_2$, (m)</th>
<th>$J_{a,b}$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-27aa to 3-27bb</td>
<td>5.19</td>
<td>4.24</td>
<td>5.02</td>
<td>5.12</td>
<td>2.07 (s)</td>
<td>8.2</td>
</tr>
<tr>
<td>3-28aa to 3-28bb</td>
<td>5.02</td>
<td>4.33</td>
<td>4.93</td>
<td>5.12</td>
<td>2.02-2.13</td>
<td>8.3</td>
</tr>
<tr>
<td>Conformed with literature data (3-27bb)</td>
<td>4.96</td>
<td>3.67</td>
<td>4.84</td>
<td>4.97</td>
<td>2.93-2.02</td>
<td>8.0</td>
</tr>
<tr>
<td>Conformed with literature data (3-28bb)</td>
<td>4.82</td>
<td>3.76</td>
<td>4.81</td>
<td>5.06</td>
<td>1.9-1.96</td>
<td>8.1</td>
</tr>
<tr>
<td>(3-27ba)</td>
<td>4.81</td>
<td>3.55</td>
<td>4.73</td>
<td>4.70</td>
<td>1.83-1.9</td>
<td>8.2</td>
</tr>
<tr>
<td>(3-28ba)</td>
<td>4.76</td>
<td>3.57</td>
<td>4.75</td>
<td>4.62</td>
<td>1.77-1.85</td>
<td>8.4</td>
</tr>
<tr>
<td>(3-27aa)</td>
<td>4.76</td>
<td>3.57</td>
<td>4.75</td>
<td>4.62</td>
<td>1.77-1.85</td>
<td>8.4</td>
</tr>
<tr>
<td>(3-28aa)</td>
<td>4.76</td>
<td>3.57</td>
<td>4.75</td>
<td>4.62</td>
<td>1.77-1.85</td>
<td>8.4</td>
</tr>
</tbody>
</table>
The chemical shifts from $^{13}$C NMR of known regioisomers similarly reveal that the chemical shift of C$^1$ carbon for regioisomer 3-27bb ($\delta$ 80.0) is lower than the chemical shift of C$^1$ carbon ($\delta$ 81.1) for regioisomer 3-28bb. Chemical shift of C$^4$ carbon ($\delta$ 61.9) for 3-27bb is higher than C$^4$ carbon ($\delta$ 58.9) for 3-28bb. Once again, a similar ordering of the chemical shifts was observed in the other regioisomeric pairs (3-27ba/3-28ba and 3-27aa/3-28aa), and the chemical shift for C$^6$ carbon ($\delta$ 57.3) of 3-27bb (carbon adjacent to the C=N in the 2-isoxazoline ring) is also higher than the chemical shift of C$^5$ carbon ($\delta$55.4) of 3-28bb (carbon adjacent to the C=N in the 2-isoxazoline ring). Again a similar ordering of the chemical shifts was observed in other regioisomeric pairs (3-27ba/3-28ba and 3-27aa/3-28aa) as summarized in Table 3.9.

Table 3.9. Assignment of regiochemistry of cycloadducts 3-27aa to 3-28ba based on confirmed $^{13}$C data of regioisomers 3-27bb and 3-28bb.

<table>
<thead>
<tr>
<th>Cycloadduct</th>
<th>C$^1$</th>
<th>C$^4$</th>
<th>C$^5$</th>
<th>C$^6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-27bb</td>
<td>80.0</td>
<td>61.9</td>
<td>82.7</td>
<td>57.4</td>
</tr>
<tr>
<td>Confirmed with literature data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-28bb</td>
<td>81.1</td>
<td>58.9</td>
<td>55.4</td>
<td>82.7</td>
</tr>
<tr>
<td>Confirmed with literature data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In summary, we have found that the 1,3-DCA reactions between N-acyl-2-oxa-3-azanorborn-5-enes (3-6a, 3-6b) and acetonitrile oxide or benzonitrile oxide form exclusively the exo cycloadducts. The ratio of regioisomers for each reaction varies with steric and electronic effects of the nitrile oxides as well as the protecting group on the nitrogen of the bicyclic alkene.

3.5 Conclusions

We have demonstrated the 1,3-dipolar cycloaddition reactions involving variously substituted 7-aza-and 7-oxabenzonorbornadienes (3-1, 3-2 and 3-4) with nitrile oxides. The reaction also proceeded well with 7-oxanorbornenes (3-3 and 3-5) and 2-oxa-3-azanorbornene (3-6) frameworks. With the oxabenzonorbornadienes, arene substitution patterns appeared to have an appreciable effect on yields, while the effects of modifying azabicycloalkene amine substituents was not as pronounced. Also we have investigated
the stereochemical and regiochemical outcomes of 1,3-dipolar cycloaddition reactions on various unsymmetrical C^1-substituted oxabenzonorbornadienes (3-4) with acetonitrile and benzonitrile oxides. The resulting isoxazolines showed complete exo-stereoselectivity and major preference for anti positioning of the nitrile oxide R’ moiety from the C^1-substituent, which was confirmed by NMR and X-ray structures. The relative distributions of the regiochemical 2-isoxazolines suggested some steric and electronic contributions of the C^1-substituent toward these reactions. Interestingly, the cycloadditions involving C^1-substituted oxabenzonorbornadienes (3-5) showed complete exo-stereoselectivity and regioselectivity for anti positioning of the nitrile oxide R’ moiety from the C^1-substituent. Also investigation of 1,3-DCA reactions of 2-oxa-3-azanorbornene systems (3-6) with nitrile oxides revealed that cycloadditions are completely exo-selective and regioisomeric ratio was effected by the nature of the nitrile oxide used. The moderate to excellent yields (up to 99%), good regioselectivity and steadfast stereoselectivity observed in these reactions make this method a convenient approach to the synthesis of oxabicycle-fused isoxazolines. In the following chapter, we wish to discuss the cleavage of these isoxazoline ring systems to arrive at various useful structural frameworks.
Chapter 4

Cleavage of Bicyclic Alkene-fused 2-Isoxazolines
4.1 Introduction

2-Isoxazolines are practical precursors to countless structural motifs found in nature. For instance, structures including various carbonyl compounds, β-hydroxyimines, β-hydroxynitriles, β-aminoketones, γ-aminoalcohols and oximes can all be readily attained through ring-cleavage of 2-isoxazolines using suitable reagents for each transformation. In recent years, there has been a huge push to apply this isoxazoline-cleavage methodology to the preparation of biologically active natural products including novel antibacterial, antifungal and anticancer treatments. Some common methods of reductive N-O bond cleavage in isoxazolines include hydrogenolysis using Raney-nickel, reduction by LiAlH₄, TiCl₃, SmI₂, or by treatment with Mo(CO)₆. The Tam group has pioneered Mo(CO)₆-mediated cleavage studies of the N-O bond in carbobicycle-fused 2-isoxazolines as a method to generate substituted cyclopentene, cyclopentane and attached-ring systems in a highly stereoselective manner. As discussed in Chapter 3, we have developed highly regio- and stereoselective preparations of heterobicycle-fused 2-isoxazolines. Our next logical step, then, was to explore various means of cleavage reactions on these heterobicycle-fused 2-isoxazolines. Selective cleavage of the N-O bond or simultaneous cleavage of both N-O and bridge C-C bonds of the isoxazoline could provide novel routes to the aforementioned functionalities attached to heterobicyclic ring systems such as β-hydroxycarbonyl derivatives, γ-aminoalcohols, as well as carbonyl compounds including phthalan and isoindoline derivatives (Scheme 4.1). The selective cleavage of N-O bond (a) would lead to the formation of β-hydroxycarbonyl ring systems and γ-aminoalcohols, while the simultaneous
cleavage of the N-O bond (a) and the C-C bond (b) would lead to the formation of substituted ring systems 4-4.

Scheme 4.1. Cycloaddition-cleavage approach of bicyclic alkenes.

This chapter outlines the research done to develop a method for reductive cleavage of the N-O bond on bicycloalkene substituted 2-isoxazolines to form β-hydroxycarbonyls.

4.2 Development of Cleavage Methodology for 2-Isoxazolines

Several methods for the cleavage of 2-isoxazolines are known in the literature.¹⁶¹ These literature methods involve reductive cleavage, oxidative cleavage, transition metal carbonyl promoted cleavage, photochemical cleavage, thermolytic cleavage, flash vacuum thermolysis (FVT), base promoted cleavage and mineral acid promoted cleavage. We originally planned to attempt the cleavage of the 2-isoxazoline ring systems synthesized in Chapter 3 by transition metal carbonyl promoted cleavage with Mo(CO)₆ as a catalyst. Mo(CO)₆ catalyzed cleavage of carbobicyclic isoxazolines had been previously demonstrated by the Tam group.⁶² The transformation was believed to
proceed by a two-step process: cleavage of bond (a) followed by a retro-Aldol reaction that would lead to the formation of substituted ring systems 4-4. The other possibility was an N-O bond cleavage followed by hydrolysis of an imine to generate the β-hydroxyketone 4-2 (Scheme 4.2). Therefore, before beginning cleavage studies on 2-isoxazoline derivatives synthesized in Chapter 3, a systematic study examining the process of Mo(CO)$_6$ catalyzed cleavage was performed.

Scheme 4.2. Expected Mo(CO)$_6$ mediated cleavage pathways for 2-isoxazoline 4-1 based on previously reported results from Tam group.

In order to establish the cleavage conditions, we selected two model compounds; 4-9aa from 3-methyl-2-isoxazoline series and 4-9ab from 3-phenyl-2-isoxazoline series.

Figure 4.1. Representative 2-isoxazolines for cleavage reactions.
4.3 Molybdenum-Mediated Cleavage of 2-Isoxazolines

Molybdenum carbonyl promoted N-O bond cleavage of 2-isoxazolines was first reported by Nitta group.\textsuperscript{87a} Since then, there has been much attention to utilize this methodology in deriving biologically active natural products.\textsuperscript{106, 165} This section details the development and challenges of a molybdenum-mediated cleavage of 2-isoxazoline rings fused to heterobicyclic frameworks.

4.3.1 Tam Group Research on Molybdenum-Mediated Cleavage Reactions of 2-Isoxazolines

The Tam research group has demonstrated the first examples of the molybdenum-mediated cleavage reactions of 2-isoxazoline rings fused to bicyclic frameworks. The procedure involved a tandem N-O bond cleavage followed by retro-aldol reaction that led to a novel stereoselective synthesis of substituted cyclopentene and cyclopentane rings.\textsuperscript{62c} For the simpler system, this protocol afforded 1,3-disubstituted cyclopentenes and cyclopentanes in good to moderate yields (Scheme 4.3).
Scheme 4.3. Mo(CO)$_6$ mediated cleavage of 2-isoxazoline fused in bicyclic rings.

The molybdenum mediated cleavage reactions of 2-isoxazolines generated by an intramolecular nitrile oxide cycloaddition were found to produce attached cyclopentene-cyclopentane rings in good to moderate yields and represent an efficient assembly of complex attached-ring structures (Scheme 4.4).
A possible mechanism proposed by the Tam group for the tandem reductive N-O bond cleavage retro-aldol reaction to produce the cyclopentane ring systems is depicted in Scheme 4.5.

Scheme 4.5. Mo(CO)$_6$ mediated cleavage mechanism proposed by Tam group.
The nitrogen in the 2-isoxazoline ring 4-20 coordinates to Mo(CO)_6 to give complex 4-21 and facilitate the N-O bond cleavage. Cleavage of the N-O bond leads to the formation of the nitrene complex 4-22. This nitrene complex undergoes retro-aldol cleavage to give intermediate 4-23. Protonation of 4-23 would give 4-25 via the imine intermediate 4-24. The double bond in 4-25 isomerizes to give conjugated enal 4-26.

### 4.3.2 Results and Discussion on Molybdenum-Mediated Cleavage

With the 2-isoxazolines 4-9aa and 4-9ab in hand, we began the study of N-O bond cleavage reactions with Mo(CO)_6 mediated reaction conditions. Initially, the Mo(CO)_6 mediated cleavage was repeated according to previous conditions on substrate 4-20b to ensure that similar results were observed. The reaction conditions (Mo(CO)_6, acetonitrile-water at 80 °C) are capable of inducing an N-O bond cleavage (a) and a retro-aldol reaction (b) producing a disubstituted cyclopentene 4-26b (Scheme 4.6).

Scheme 4.6. Mo(CO)_6 mediated cleavage of 2-isoxazolines 4-20a.

After successfully reproducing compound 4-26b in moderate yield, we began our investigation on cleavage of 2-isoxazolines with test substrates, 4-9aa and 4-9ab, using standard Mo(CO)_6 mediated conditions (Mo(CO)_6/ACN-water, 80 °C). Scheme 4.7.

Scheme 4.7. Mo mediated cleavage of 2-isoxazolines 4-9aa, 4-9ab.
Mo mediated reaction conditions with 4-9aa at 80 °C generated multiple products that were observed by TLC, resulting in an inseparable reaction mixture. Our next attempt was to repeat the reaction at lower temperature to reduce the number of products being generated. Unfortunately, only starting material was observed on TLC indicating that there was no progress in the reaction at room temperature. The reaction was repeated again at 45-60 °C for 16-24 hours, which resulted in a series of spots observed on TLC of an inseparable mixture. When the solvent was changed from ACN to THF although the starting material was consumed, an inseparable mixture of products was again generated.

After unsuccessful attempts with Mo(CO)$_6$ mediated reactions, a solution of Mo(CO)$_3$(MeCN)$_3$ was prepared in situ by heating Mo(CO)$_6$ in refluxing anhydrous acetonitrile for 4 h. The resulting solution was used immediately for cleavage reactions. It is reported in literature that Mo(CO)$_3$(MeCN)$_3$ mediated reaction gave high yields for cleavage of 2-isoxazolines$^{88, 166}$ although in our case, reactions with Mo(CO)$_3$(MeCN)$_3$ at room temperature did not proceed and at 45-60 °C we obtained an inseparable reaction mixture similar to the Mo(CO)$_6$ trials. Although each of these reactions was carried out for a number of times, no product was isolated from the reactions. In the majority of the cases, it was observed by TLC that all the starting material had been consumed, producing a series of products, yet none of these UV active spots on TLC could be identified as a characterizable product.

Similar results were obtained in the cleavage of 4-9ab using Mo(CO)$_6$ in ACN-water reaction medium. The reaction did not proceed at room temperature, and when the reaction was performed at 80 °C a series of spots were observed on TLC, which were
inseparable by column chromatography. Due to unsuccessful results, we decided to pursue cleavage reactions mediated by other transition-metal catalysts.

4.4 Palladium-Mediated Cleavage of 2-Isoxazolines

Cleavage of the N-O bond of 2-isoxazolines in the presence of Pd/C is known to lead to the formation of β-hydroxyketones\(^76\) or γ-aminoalcohols\(^77\). Due to the unsuccessful attempts in generating β-hydroxyketones (4-27) or 4-28 using a Mo catalyst, the reaction conditions were changed to utilize Pd/C as the catalyst. Hydrogenation of 4-9aa using palladium on activated carbon resulted in only unreacted starting material and a streak of decomposed product as observed by TLC (Scheme 4.8). Various solvent systems (MeOH, MeOH-AcOH, AcOH-water) and hydrogen sources (H\(_2\), ammonium formate) were tested for the Pd-C mediated transformations but none of them resulted in a clean transformation to give a separable cleavage product. The reaction in presence of catalytic Pd(OH)\(_2\) in the presence of H\(_2\) also produced an inseparable mixture of spots which are observable by TLC.

![Scheme 4.8: Pd-C mediated cleavage of 2-isoxazolines 4-9aa, 4-9ab.](image)

2-Isoxazoline 4-9ab was subjected to various palladium catalyzed cleavage conditions (Pd/C and H\(_2\)), similar to those mentioned for 4-9aa. These reactions all generated multiple spots as observed by TLC, and when purification by column chromatography was attempted the products decomposed on the column. Reaction
conditions involving Pd(OH)$_2$ in the presence of H$_2$ with 4-9ab was also attempted, unfortunately producing an inseparable mixture.

All of the Pd mediated reactions for 4-9aa and 4-9ab were unsuccessful due to the formation of multiple products. In the majority of cases, using TLC, it was observed that all of the starting material had been consumed over a longer period of time, producing many spots although none of these spots could be identified as a characterizable product.

4.5 **Zinc-Mediated Cleavage Reactions of 2-isoxazolines**

Our next attempt utilized zinc dust in glacial acetic acid for the cleavage of the 2-isoxazolines (Scheme 4.9). Reactions with 4-9aa using Zn dust in AcOH-water medium were performed at room temperature and 80 °C. In both cases only unreacted starting material was observed on TLC, so our zinc-mediated cleavage attempts were abandoned.

![Scheme 4.9. Zn mediated cleavage of 2-isoxazoline 4-9aa.](image)

4.6 **Fe-NH$_4$Cl Mediated Cleavage of 2-isoxazolines**

We next turned to Fe-mediated reactions. Our plan was to adopt the optimized conditions developed by the Chen group$^{84}$ using iron and ammonium chloride in aqueous ethanol at reflux temperature (Scheme 4.10).

![Scheme 4.10. Fe-NH$_4$Cl mediated cleavage of 2-isoxazoline 4-9aa.](image)
Unfortunately, in the cleavage of 4-9aa many spots were observed by TLC and we were unable to isolate any product from the reaction mixture. We then repeated the reaction at room temperature, which resulted in fewer spots being generated as observed by TLC. All of the starting 2-isoxazoline (4-9aa) was consumed, producing a major cleavage product along with multiple impurities. Purification by column chromatography on silica was attempted; however the product did not elute from the column even with a polar solvent system such as 10% MeOH in DCM. The product from the cleavage of 4-9aa must be unstable on a silica column, and in the next attempt purification was attempted with neutral alumina column but unfortunately none of the products eluted from the column. Since the cleavage reactions involving Fe-NH₄Cl still did not produce one product, this method was not suitable for the cleavage of our 2-isoxazolines fused to oxabicyclic framework. Development of a cleavage method that gives a clean transformation to produce pure products without column purification is necessary.

4.7 Nickel-Mediated Cleavage of 2-isoxazolines

Nickel mediated cleavage of 2-isoxazolines is well documented in the literature.¹⁵⁵ Nickel salts such as NiCl₂ and NiSO₄ combined with borohydrides improve the efficiency of the reaction. Kozikowski’s group found that hydrogenation of 2-isoxazolines with W-2 Raney-nickel in the presence of 4 eq. of HCl in 5:1 methanol:water gives β-hydroxyketone with complete stereospecificity. By replacing HCl with AlCl₃ in the reaction conditions allowed for clean transformation with high yields on a variety of substituted 2-isoxazolines.⁷⁴ Later Litvinovskaya demonstrated that Raney-nickel/AlCl₃ conditions without hydrogen can lead to β-hydroxyketone formation.⁸₇ Nickel salts such as NiCl₂ and NiSO₄ combined with borohydrides
(sodium borohydride and zinc borohydride) have been used in successful conversion of 2-isoxazolines to γ-amino alcohols. The following section details the developments and challenges involved in nickel-mediated cleavage of 2-isoxazoline rings fused to bicyclic frameworks.

### 4.7.1 Results and Discussion on Nickel-Mediated Cleavage

The cleavage of 4-9aa was first attempted with Raney-nickel/H₂ in methanol, which generated multiple spots on TLC resulting in an inseparable mixture. The reaction was repeated for 4-9aa using Raney-nickel in acetic acid. Monitoring by TLC, a new spot was generated after few minutes, yet unfortunately it decomposed to generate a base line impurity over longer reaction times. As our target was to find cleavage conditions that produce a clean product without the need for column purification and further exploration into Ni-mediated cleavage conditions was required.

As Ni-mediated reactions have been reported to produce high yielding cleavage reactions for 2-isoxazolines in the presence of AlCl₃, these reaction conditions were the next choice to forming the desired cleavage products. We observed that the cleavage of 2-isoxazoline 4-9aa with Raney Ni/AlCl₃ in methanol-water gave a clean transformation and we were able to isolate the pure product without column purification as the product precipitated out as crystalline solid from hexanes after work-up. The crystalline solid was identified as β-hydroxyketone 4-27aa by NMR and mass spectra characterization (Scheme 4.11).

![Scheme 4.11. Raney Ni/AlCl₃ mediated cleavage of 3-methyl-2-isoxazoline 4-27aa.](image-url)
The cleavage reaction of 2-isoxazoline 4-9aa using Raney-nickel/AlCl₃ was optimized by repeating the reaction under different conditions to find the optimal amounts of AlCl₃, Raney-Ni as well as the optimal reaction temperature. The optimal cleavage conditions for 4-9aa involves 2.4g of Raney-nickel/mmol, 3 eq. of AlCl₃, and MeOH-water solvent system at temperature 0-5 °C. These reaction conditions were used in the cleavage of unsymmetrical and symmetrical 3-methyl-2-isoxazolines as will be described in sections 4.7.2 to 4.7.5.

Unfortunately, the cleavage of 4-9ab using aforementioned optimized (Raney-nickel/AlCl₃ in methanol-water at 0-5 °C) (Scheme 4.12) was unsuccessful. Although the starting material was consumed and a new spot was generated according to TLC, and during the work-up the new spot decomposed to give a baseline impurity. The remainder of this chapter examines the cleavage of substituted 3-methyl-2-isoxazolines.

**Scheme 4.12. Raney Ni/AlCl₃ mediated cleavage of 3-phenyl-2-isoxazoline 4-9ab.**

4.7.2 Cleavage of 2-isoxazolines Derived from Symmetrical 7-Oxabenzonorbornadienes

The optimal cleavage conditions for 3-methyl-2-isoxazolines was used to cleave the substituted 2-isoxazolines (4-9aa-4-9fa) that were obtained from 1,3-dipolar cycloadditions in Chapter 3. THF was added as co-solvent wherever the 2-isoxazoline starting material was not soluble in MeOH. **Table 4.1** summarizes the results of the Raney-nickel/AlCl₃ cleavage of symmetrical 2-isoxazolines.¹⁶⁹
Table 4.1: Cleavage of the 3-Methyl-2-isoxazolines derived from cycloaddition between acetonitrile oxide and 7-oxabenzonorbornadienes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Isoxazoline</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-9aa</td>
<td>4-27aa</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>4-9ba</td>
<td>4-27ba</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>4-9ca</td>
<td>4-27ca</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>4-9da</td>
<td>4-27da</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>4-9ea</td>
<td>4-27ea</td>
<td>71</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields after hexane trituration. Crude products were triturated in hexane, filtered and dried at room temperature under high vacuum.
As shown in Table 4.1 all of the cleavage reactions involving 3-methyl-2-isoxazolines successfully generated β-hydroxyketone products in good yields. The formation of a β-hydroxyketone indicates that two processes were taking place in one pot; the tandem reductive N-O cleavage followed by an imine hydrolysis. Compared to the parent compound 4-9aa which gave an appreciable 93% of corresponding β-hydroxyketone (entry 1), replacement of two of the arene hydrogens for bromine atoms in 4-9ea resulted in a lower tendency toward N-O bond cleavage (entry 5). In addition, while both 5,8- and 6,7-dimethoxy substituted compounds 4-9ba and 4-9ca gave excellent yields of 94% and 87%, respectively (entries 2, 3), the 5,8-dimethyl derivative 4-9da was slightly lower yielding, providing 76% isolated product (entry 4). All the products were purified by triturating the crude compounds with hexanes at room temperature and dried under high vacuum.

The 2-isoxazoline 4-30 that was prepared from the 1,3-dipolar cycloaddition of acetonitrile oxide with 5,6-disubstituted-7-oxanorbornene was subjected to cleavage conditions using Raney-nickel/AlCl₃ (Scheme 4.13). The reaction worked smoothly to give β-hydroxyketone product 4-31 with 82% yield.

**Scheme 4.13.** Raney Ni/AlCl₃ mediated cleavage of 2-isoxazoline 4-30.

Overall, 2-isoxazolines 4-9aa-ca and 4-30 all showed good conversion to their β-hydroxyketones. We then proceeded to expand the reaction scope to include unsymmetrical substrates, namely those with bridgehead (C¹) substituents.
4.7.3 Cleavage of 3-Methyl-2-isoxazolines Derived from C\textsuperscript{1} Substituted 7-Oxabenzonorbornadienes

The results of isoxazoline cleavage of unsymmetrical 2-isoxazolines are summarized in Table 4.2. Due to decreased solubility in aqueous methanol, the C\textsuperscript{1}-substituted compounds (4-32a-4-32g) were reacted in a 5:5:2 THF:MeOH:H\textsubscript{2}O solvent system.\textsuperscript{169} As the products are unstable on silica or neutral alumina columns all of products were purified by crystallization in hexanes to obtain the pure product as a solid.

Table 4.2: Cleavage of the 3-methyl-2-isoxazolines derived from cycloaddition between acetonitrile oxide and C\textsuperscript{1} substituted 7-oxabenzonorbornadienes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Isoxazoline</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-32a</td>
<td>4-33a</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>4-32b</td>
<td>4-33b</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>4-32c</td>
<td>4-33c</td>
<td>b</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Determined by NMR and mass spectrometry.
<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Isoxazoline</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image" alt="4-32d" /></td>
<td><img src="image" alt="4-33c" /></td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="4-32e" /></td>
<td><img src="image" alt="4-33e" /></td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="4-32f" /></td>
<td><img src="image" alt="4-33f" /></td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="4-32g" /></td>
<td><img src="image" alt="4-33g" /></td>
<td>86</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yields after hexane trituration. Crude products were triturated in hexane, filtered and dried at room temperature under high vacuum.

<sup>b</sup> Product decomposed during work-up.

The formation of the corresponding β-hydroxyketones was observed in all cases as a result of N-O bond cleavage followed by imine hydrolysis. Relative to the unsubstituted parent compound 4-9aa (Table 4.1, entry 1), reactions of 2-isoxazolines 4-32a and 4-32b bearing alkyl substituents in the C<sub>1</sub>-position were still reasonably good (Table 4.2, entries 1 and 2), and even with electron-withdrawing C<sub>1</sub>-substituents in...
compounds \(4-32d-f\), the yields did not suffer to any extreme (entries 5-6). The cleavage of compound with a TMS substituent in the \(C^1\)-position \(4-32c\) was observed to proceed to completion by TLC, however due to extensive decomposition during work-up no product was obtained (entry 3). In addition, the transformation to \(\beta\)-hydroxyketone succeeded with compound \(4-32g\) bearing both arene and \(C^1\)-substituents (entry 7) with 86% yield.

An X-ray crystal structure of adduct \(4-33g\) (\(X=\text{OME}, Y=\text{H}, R^1=\text{Me}\)) unambiguously confirmed the two-bond separation between the hydroxyl group and the \(C^1\)-carbon (to which the methyl group is attached).\(^{170}\)

### 4.7.4 Cleavage of 3-Methyl-2-isoxazolines Derived from \(C^1\) Substituted 7-Oxanorbornenes

The cleavage of unsymmetrical 3-methyl-2-isoxazolines \(4-34a\) and \(4-34b\) that we prepared from 1,3-DCA of acetonitrile oxide with 7-oxabenzonorbornenes was also performed (Table 4.3).\(^{169}\) The solvent system was modified to 15:5:2 THF:MeOH:H\(_2\)O to address the lower solubility of \(4-34a-b\) in aqueous MeOH. The cleavage of both \(4-34a\) and \(4-34b\) proceeded smoothly and gave the desired product with 80% and 70% yield, respectively.
Table 4.3: Cleavage of 2-isoxazolines derived from cycloaddition between acetonitrile oxide and 7-oxanorbornenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Isoxazoline</th>
<th>Product</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="4-34a" /></td>
<td><img src="image" alt="4-35a" /></td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="4-34b" /></td>
<td><img src="image" alt="4-35b" /></td>
<td>70</td>
</tr>
</tbody>
</table>

^a Isolated yields after hexane trituration. Crude products were triturated in hexane, filtered and dried at room temperature under high vacuum.

4.7.5 Cleavage of 3-Methyl-2-isoxazolines Derived from Symmetrical 7-Azabenzenonorbornadienes

The cleavage of 3-methyl-2-isoxazolines 4-36a to 4-36c that were prepared by 1,3-DCA between acetonitrile oxide and 7-azabenzenonorbornadienes was attempted using the optimal conditions (Table 4.4).^169 The cleavage reaction of 4-36a proceeded smoothly and gave the desired product in 66% yield. The cleavage of reaction of 4-36c also proceeded to give a new spot according to TLC, yet the product decomposed during the work-up. Unfortunately, the reaction with 4-36b did not proceed even after 24 hours, only unreacted starting material was recovered.
Table 4.4: Cleavage of 2-isoxazolines derived from cycloaddition between acetonitrile oxide and 7-azabenzonorbornadienes.

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-Isoxazoline</th>
<th>Product</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-36a</td>
<td>4-37a</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>4-36b</td>
<td>4-37b</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>4-36c</td>
<td>4-37c</td>
<td>b</td>
</tr>
</tbody>
</table>

^a Isolated yields after hexane pulp.
^b Product decomposed during work-up.

4.8 Conclusions

We have successfully developed a method for N-O bond cleavage of both symmetrical and unsymmetrical 3-methyl-2-isoxazolines fused to oxabicyclic and azabicyclic frameworks, which generates the corresponding β-hydroxyketone product in moderate to excellent yields. The transformation involves N-O bond cleavage of the 2-isoxazoline followed by imine hydrolysis, leading to a β-hydroxyketone. The results in
this thesis are the first examples of Raney-nickel/AlCl₃ cleavage reactions of 2-isoxazoline rings fused to oxabicyclic and azabicyclic frameworks. We have systematically investigated the efficacy of various cleavage conditions and found that although none of Mo(CO)₆, Zn/AcOH, Fe/NH₄Cl, Pd-C/H₂, Pd(OH)₂/H₂ or Raney-nickel/AcOH/H₂ is suitable for cleavage of 2-isoxazolines fused to heterobicyclic frameworks, the combination of Raney-nickel/AlCl₃ is an suitable mediator for N-O bond cleavage in a variety of heterobicycloalkene-fused isoxazoline systems. The versatility of this reaction with various derivatives of heterobicycloalkene-fused isoxazolines shows promise in future applications such as natural product synthesis.
Chapter 5

Epilogue
5.1 Synopsis

The primary focus of this thesis was to study the 1,3-dipolar cycloaddition reactions of symmetrical and unsymmetrical bicyclic alkenes with nitrile oxides and to develop the ring opening methodology of 2-isoxazolines that are fused to a bicyclic framework. In order to make this study possible, the synthesis of a large number of unsymmetrical bicyclic alkenes was required. As discussed in Chapter 2, the most direct synthetic route to access the C1-substituted bicyclic alkenes involved a Diels-Alder reaction between 2-substituted furans and an appropriate dienophile (N-phenylmaleimide, maleic anhydride and in situ generated 1,2-benzyne). Although N-phenylmaleimide and maleic anhydride are commercially available, benzyne can be prepared in situ preparation from anthranilic acid. Many of the required substituted furans were not commercially available and thus they had to be synthesized. We planned to synthesize the 2-substituted furans via metal catalyzed cross-coupling reactions between 2-bromofuran and arylboronic acids/alkylmagnesium halides. In contrast to the poor yields and lengthy reaction procedures in the literature to form 2-bromofuran, we developed a simple and scalable procedure using a cheap and non-hazardous brominating reagent. This newly developed procedure would allow us to access a large-scale preparation of 2-bromofuran from which various desired 2-substituted furans could be prepared.

While generating our required substituted furans, the palladium catalyzed Suzuki-Miyaura cross-coupling reactions between 2-bromofuran and a wide range of aryl boronic acids were optimized to produce good to excellent yields. Unfortunately, the palladium catalyzed reactions using alkyl boronic acids were unsuccessful, so an iron
catalyzed cross-coupling method was developed between 2-bromofuran and alkylmagnesium halides to successfully generate the 2-alkylfurans in moderate yields.

\[
\begin{align*}
\text{O\Br} + \text{Z} & \xrightarrow{\text{Pd catalysts}} \text{Z} \\
\text{K}_2\text{CO}_3 & \text{DMF-Water} \\
75-85 \degree \text{C} & \text{yield} \\
\text{56-85\%} & \text{14 examples}
\end{align*}
\]

\[
\begin{align*}
\text{O\Br} + \text{RMgX} & \xrightarrow{\text{Fe(acac)}_3} \text{R} \\
\text{DMPU, -25 \degree \text{C}} & \text{yield} \\
\text{15-56\%} & \text{9 examples}
\end{align*}
\]

**Scheme 5.1. Preparation of 2-arylfurans by Suzuki cross-coupling protocol (top) and 2-alkylfurans by iron cross-coupling protocol (bottom)**

With the 2-substituted furans in hand, we set out to synthesize C1-substituted oxabicyclic alkenes with which the 1,3-DCA reactions would be carried out. The easiest way to access the C1-substituted oxabicyclic alkenes was through Diels-Alder cycloaddition of 2-substituted furans with corresponding dienophile. A series of C1-substituted oxabicyclic alkenes were prepared with 2-substituted furans using maleic anhydride, N-phenylmaleimide and *in situ* generated benzyne as dienophiles.
Scheme 5.2. Preparation of C$^1$-substituted oxabicyclic alkenes

$\text{R} = \text{Me, Et, CH}_2\text{OH, OMe}$

$45-61\% \text{ yield}$

$4 \text{ examples}$

$\text{R} = \text{Me, Et, CH}_2\text{OH, OMe, COMe, CO}_2\text{Me}$

$2-82\% \text{ yield}$

$6 \text{ examples}$

$\text{R} = \text{alkyl, cycloalkyl, aryl, TMS, etc.}$

$16-80\% \text{ yield}$

$23 \text{ examples}$
Scheme 5.3. 1,3-DCA reactions of nitrile oxides with symmetrical bicyclic alkenes.

The 1,3-DCA reactions with symmetrical and unsymmetrical bicycloalkenes were found to be completely stereoselective, with exclusive formation of the exo cycloadduct. For cycloadditions of C\textsuperscript{1}-substituted-7-oxabenzonorbornadienes the regioselectivity was varied based on the steric and electronic effects of the substitution at C\textsuperscript{1} carbon of bicyclic alkene. In all cases, the major isomer was found to be the product with the oxygen of the nitrile oxide connected to C\textsuperscript{2} of the bicyclic alkene. The 1,3-DCA reactions with N-phenylmaleimide fused oxabicyclic alkene produced a single regioisomer, which was found to be the regioisomer where the oxygen of the nitrile oxide attached to the C\textsuperscript{2} of the bicyclic alkene. The 1,3-DCA reactions of N-acyl-2-oxa-3-azanorborn-5-ene
systems with nitrile oxides revealed that formation of the anti isomer is increased when coupling with benzonitrile oxide relative to acetonitrile oxide.

\[
\begin{align*}
\text{Scheme 5.4. 1,3-DCA reactions of nitrile oxides with unsymmetrical bicyclic alkenes.}
\end{align*}
\]

To generate the desired cleavage products, the suitability of various cleavage conditions of 2-isoxazolines was investigated. Unfortunately, it was found during this investigation that conditions involving Mo(CO)$_6$, Mo(CO)$_3$(MeCN)$_3$, Zn/AcOH, Fe/NH$_4$Cl, Pd-C/H$_2$, Pd(OH)$_2$/H$_2$, and Raney-nickel/AcOH/H$_2$ were unsuitable for generating the desired cleavage products.
Scheme 5.5. Investigation for the cleavage of 2-isoxazoline ring fused to bicyclic framework.

Fortunately, a procedure with Raney-Ni was developed with successful cleavage of the N-O bond in 3-methyl-2-isoxazolines fused to oxabicyclic and azabicyclic frameworks. The Raney-Ni was found to catalyze an N-O bond cleavage followed by an imine hydrolysis, which led to multiple β-hydroxyketone products with moderate to excellent yields.
Scheme 5.6. Cleavage of 2-isoxazolines with Raney-Ni/AlCl₃.

5.2 Future Perspective

The 2-isoxazolines are known for their use in medicinal applications, such as Acivicin and VGX-1027 as discussed in Section 1.6. The 2-isoxazolines fused to a bicyclic framework have not yet been screened for any medicinal applications. Therefore, the screening of these 2-isoxazoline structures for medicinal applications such as anti-inflammatory or anti-cancer would offer a new avenue for this research. The development of a 1,3-DCA reaction between nitrile oxides and unsymmetrical bicyclic alkenes could lead to the synthesis of 2-isoxazolines enantioselectively. The asymmetric 1,3-DCA methodology could be used for racemic C¹-substituted oxabicyclic alkenes for the synthesis of optically enriched 2-isoxazolines as proposed in Scheme 5.7. The unreacted C¹-substituted oxabicyclic alkene will also be obtained as an enantioenriched product.
The 2-isoxazolines fused to a bicyclic framework that were prepared from the asymmetric version of 1,3-DCA could be useful to generate pure diastereomers of 1,3-amino alcohols that may prove to be very useful as chiral ligands in asymmetric synthesis. For example a new class of bidentate ligand that was prepared from commercially available (+)-pulegone was used as a chiral auxiliary for the 1,3-DCA reaction of nitrile oxides (Scheme 5.8).\textsuperscript{172}

Scheme 5.8. Application of 1,3-amino alcohols in asymmetric 1,3-DCA reactions.

Chiral ligands, such as those derived from camphor, have been used in asymmetric Pd-catalyzed allylic alkylation and have shown to produce high yields and enantioselectivity (Scheme 5.9).\textsuperscript{173}
Scheme 5.9. Application of chiral ligands derived from 1,3-amino alcohols in asymmetric 1,3-DCA reactions.

The work demonstrated in this thesis suggests a much broader potential in future research, in areas as diverse as methodology development, preparation of medicinal chemistry libraries, as well as synthesis of chiral ligands and complex organic molecules.
Chapter 6

Experimental Sections

Appendix

References
6.1 Experimental Section

General considerations:

All reactions were performed in septum-sealed, flame-dried flasks under nitrogen. All commercial reagents were used as received from their respective suppliers. Column chromatography was performed on 230-400 mesh silica gel using flash column chromatography techniques. Analytical thin-layer chromatography (TLC) was performed on Merck pre-coated silica gel 60 F254 plates. ¹H NMR and ¹³C NMR spectra were recorded at 300/400 and 75/100 MHz, respectively. Chemical shifts are reported in parts per million (δ) using internal solvent signals as references and coupling constants are reported in hertz (Hz). Infrared spectra were taken on a Bomem MB-100 FTIR spectrophotometer. Unless stated otherwise, commercial reagents were used without purification. Solvents were purified by distillation under dry nitrogen: THF and Et₂O from potassium/benzophenone; DME from CaH₂; DMPU, DMSO, TMEDA and TEA from 4Å molecular sieves.

![Chemical reaction image]

**Preparation of 2-Bromofuran, 2-2:** A solution of NBS (20 g, 0.112 mol) in DMF (60 mL) was added via addition funnel to a solution of furan (15.3 g, 0.225 mol) in DMF (40 mL) in a 500 mL three-neck RBF over a period of 40-60 minutes, keeping the internal temperature between 25-35 °C under constant stirring. Addition of NBS solution to reaction mixture was found to be exothermic. During addition, the reaction mixture went from brown solution to dark green. After the addition was complete, the reaction mixture
was stirred at ambient temperature for an additional 2-4 h. The resulting clear brown solution was heated gradually to 100-110 °C, in order to distill out some of the unreacted furan. After maintaining at 100-110 °C temperature for 0.5-1 h, the reaction mixture was exposed to a constant jet of steam generated by heating distilled water to 100-120 °C in a separate two-neck RBF. Distillate consisting of water and bromofuran was collected in a receiver. The initial few drops contained mostly residual unreacted furan, and were therefore collected separately. Distillation was continued until no organic product was present in the distillate. The distillate was transferred to a separatory funnel along with water (20-30 mL). The suspension was shaken well to force traces of DMF to aqueous layer. After layer separation, the bromofuran 2-34 settled down as a colorless lower layer and was collected and stored in a dry bottle containing anhydrous K$_2$CO$_3$ (11.5 g, 70%).

**2-Bromofuran, 2-2**

Yield = 70% (11.5 g, 87.2 mmol); Colorless liquid; IR (CH$_2$Cl$_2$): 3140; 2930; 1679; 1472; 1386; 1161; 1052 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.28 (dd, $J = 3.3$, 2.3 Hz, 1H); 6.35 (dd, $J = 4.9$, 3.6Hz, 1H); 7.40 (dd, $J = 2.1$, 1.1 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): 141.3, 124.0, 114.0, 111.5; HRMS (EI) calcd. for C$_4$H$_4$BrO [M$^+$]: m/z 146.9446, found 146.9452.

**General procedure A: Palladium-Catalyzed Suzuki Coupling (Table 2.4):** Under nitrogen atmosphere arylboronic acid (1.0 mmol), was suspended in a DMF-Water (3 mL:1 mL), followed by the addition of bromofuran (1.7 mmol), PdCl$_2$(Ph$_3$P)$_2$ (0.02 mmol) and K$_2$CO$_3$ (2.5 equiv.). The mixture was heated to 75-85 °C for 16-20 h. After reaction completion the mixture was cooled to room temperature, followed by quenching by addition of 15-20 mL water. The obtained suspension was extracted with ether (10 mL
x 3), and then the combined organic layers was washed with water, dried over anhydrous sodium sulfate, and concentrated using rotary evaporation. The crude product was purified by column chromatography (EtOAc–hexanes mixtures) to give the product.

**General Procedure B: Iron-Catalyzed Coupling (Table 2.7):** To an oven-dried, nitrogen flushed flask equipped with a magnetic stir and rubber septum was charged with Fe(acac)$_3$ (24 mg, 20 mol %) and DMPU (2.5 mL). The flask was cooled to -25 °C and bromofuran 2-34 was added (584 mg, 4 mmol). RMgX (16 mmol, 400 mol %) was then added drop wise over a period of 20 minutes to provide a deep purple to brown solution. The solution was then stirred for 2.5 hours and water was added drop wise (2 mL) followed by saturated sodium bicarbonate (5 mL) and extracted with 3 x 10 mL Et$_2$O. The extract was dried over Na$_2$SO$_4$ and concentrated under rotary evaporation. The crude products were then purified by silica gel column chromatography with a mixture of ethyl acetate and hexanes or diethyl ether and pentane.

![Reaction scheme](image)

**2-Phenylfuran, 2-12a**

Following general procedure A: Yield = 62% (90 mg, 0.62 mmol); Colorless oil; Rf = 0.38 (Hexanes); IR (CH$_2$Cl$_2$): 3054, 1608, 1507, 1477, 1265, 1023 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): δ 6.45-6.57 (m, 1H), 6.66 (d, J = 3.4 Hz, 1H), 7.26 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.8 Hz, 2H), 7.47-7.48 (m, 1H), 7.69 (d, J = 7.8 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 75 MHz): 154.0, 142.0, 130.9, 128.6, 127.3, 123.8, 111.6, 104.9; HRMS (EI) calcd. for C$_{10}$H$_8$O [M]$^+$: m/z 144.0575, found 144.0579.$^{175}$
2-(4-Methoxyphenyl)furan, 2-12e

Following general procedure A: Yield = 57% (100mg, 0.57 mmol); White solid; R_f = 0.26 (EtOAc:hexanes = 5:95); IR (CH_2Cl_2): 2959; 2937; 1617; 1218; 1047 cm^{-1}; ^1H NMR (CDCl_3, 300 MHz): δ 3.82 (s, 3H); 6.42-6.45 (m, 1H, CH); 6.51 (d, J = 2.8 Hz, 1H, CH); 6.91 (d, J = 8.8 Hz, 2H, 2 × CH); 7.41 (d, J = 1.3 Hz, 1H, CH); 7.61-7.56 (m, 2H, 2 × CH); ^13C NMR (CDCl_3, 75 MHz): 159.0, 154.0, 141.3, 125.2, 124.0, 114.1, 111.5, 103.3, 55.2; HRMS (EI) calcd. for C_{11}H_{10}O_2 [M]^+: m/z 174.0681, found: 174.0686.

2-(2-Methoxyphenyl)furan, 2-12g

Following general procedure A: Yield = 63% (110mg, 0.63 mmol); Brown oil; R_f = 0.42 (EtOAc:hexanes = 10:90); IR (CH_2Cl_2): 3002, 2940, 2837, 1602, 1464, 1083 cm^{-1}; ^1H NMR (CDCl_3, 300 MHz): δ 3.93 (s, 3H), 6.48-6.50 (m, 1H, CH), 6.93-7.04 (m, 3H, CH), 7.20-7.27 (m, 1H, CH), 7.46 (d, J = 0.7 Hz, 1H, CH), 7.85 (dd, 7.7, 1.3 Hz, 1H, CH); ^13C NMR (CDCl_3, 75 MHz): δ 155.3, 150.3, 141.1, 128.0, 126.0, 120.7, 119.9, 111.6, 111.0, 109.8, 55.4; HRMS (EI) calcd. for C_{11}H_{10}O_2 [M]^+: m/z 174.0681, found: 174.0685.
2-(4-Chlorophenyl)furan, 2-12h

Following general procedure A: Yield = 70% (116 mg, 0.65 mmol); White solid; \( R_f = 0.29 \) (Hexanes = 100); IR (CH\(_2\)Cl\(_2\)): 3054, 2987, 1487, 1422, 1265, 1093, 1020 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta 6.42-6.49 \) (m, 1H), 6.62 (d, \( J = 2.9 \) Hz, 1H), 7.33 (d, \( J = 8.5 \) Hz, 2H), 7.45 (s, 1H), 7.58 (d, \( J = 8.5 \) Hz, 2H), \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \( \delta 153.0, 142.3, 133.0, 129.4, 128.9, 125.0, 111.8, 105.4 \); HRMS (EI) calcd. for C\(_{10}\)H\(_7\)ClO \([M]^+\): m/z 178.0185, found 178.0188.\(^{177}\)

2-(3-Chlorophenyl)furan, 2-12i

Following general procedure A: Yield = 67% (119 mg, 0.66 mmol); Colorless oil; \( R_f = 0.29 \) (Hexanes = 100); IR (CH\(_2\)Cl\(_2\)): 3371, 1603, 1582, 1282, 1013 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta 6.44 \) (dd, \( J = 3.42, 1.83 \) Hz, 1H), 6.63 (d, \( J = 3.4 \) Hz, 1H), 7.15-7.38 (m, 2H), 7.46 (d, \( J = 1.71 \) Hz, 1H), 7.49-7.52 (m, 1H), 7.64 (t, \( J = 1.77 \) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \( \delta 152.5, 142.5, 134.7, 132.5, 130.0, 127.2, 123.8, 121.8, 111.7, 106.0 \); HRMS (EI) calcd. for C\(_{10}\)H\(_7\)ClO \([M]^+\): m/z 178.0185, found 178.0182.
2-(2-Chlorophenyl)furan, 2-12j

Following general procedure A: Yield = 70% (70mg, 0.39 mmol); Colorless oil; R_f = 0.29 (EtOAc:hexanes = 100); IR (CH_2Cl_2): 3065, 1599, 1499, 1470, 1031, cm^{-1}; ^1H NMR (CDCl_3, 300 MHz): δ 6.53 (dd, J = 3.5, 1.8 Hz, 1 H), 7.14 (dd, J = 3.5, 0.6Hz, 1H), 7.19(dd, J = 7.4, 1.7Hz, 1 H), 7.31(td, J = 3.9, 1.4Hz , 1 H), 7.44(dd, J = 7.9, 1.2 Hz, 1H), 7.51 (dd, J = 1.8, 0.6Hz, 1 H), 7.87 (dd, J = 7.9, 1.7Hz, 1 H); ^13C NMR (CDCl_3, 75 MHz): δ 150.2, 142.1, 130.7, 130.1, 129.3, 128.0, 127.9, 126.9, 111.7, 110.9; HRMS (EI) calcd. for C_{10}H_{7.5}ClO [M]^+: m/z 178.0185, found 178.0188.

2-(4-Acetylphenyl)furan, 2-12l

Following general procedure A: Yield = 59% (110 mg, 0.59 mmol); White solid; R_f = 0.24 (EtOAc:hexanes = 20:80); IR (CH_2Cl_2): 1668, 1475, 1416, 1079, 1020 cm^{-1}; ^1H NMR (CDCl_3, 300 MHz): δ 2.59 (s, 3H); 6.46-6.54 (m, 1H), 6.78 (d, J = 3.3 Hz, 1H), 7.51 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.4Hz, 2H); ^13C NMR (CDCl_3, 75 MHz): δ 197.3, 152.8, 143.3, 135.5, 134.9, 128.9, 123.5, 112.1, 107.5, 26.5; HRMS (EI) calcd. for C_{12}H_{10}O_2 [M]^+: m/z 186.0681, found 186.0687.

168
**2-(4-Biphenyl)furan, 2-12m**

Following general procedure A: Yield = 77% (170 mg, 0.77 mmol); White Solid; R_f = 0.33 (EtOAc:hexanes =5:95); IR (CHCl_3): 3054, 2987, 1600, 1478, 1265, 1158 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 300 MHz): \(\delta\) 6.42-6.40 (m, 1H), 6.69 (d, J = 3.3 Hz, 1H), 7.32-7.37 (m, 1H), 7.33-7.50 (m, 3H), 7.62 (d, J = 8.4 Hz, 4H), 7.75 (d, J = 8.4Hz, 2H); \(^{13}\)C NMR (CDCl_3, 75 MHz): \(\delta\) 153.8, 142.1, 140.6, 140.0, 129.9, 128.8, 127.3, 126.9, 124.2, 111.7, 105.1; HRMS (EI) calcd. for C\(_{16}\)H\(_{12}\)O [M]+: m/z 220.0888, found 220.0885.\(^{178}\)

**2-Cyclohexylfuran, 2-12t**

Following general procedure B; yield = 56% (551 mg, 3.66 mmol); Colorless oil; R_f = 0.62 (EtOAc–hexanes, 10:90). \(^1\)H NMR (CDCl_3, 400 MHz): \(d\) = 1.20–1.41 (m, 6 H), 1.70–1.75 (m, 1 H), 1.75–1.82 (m, 2 H), 1.99–2.05 (m, 2 H), 2.56–2.65 (m, 1 H), 5.93 (d, \(J = 3.2\) Hz, 1 H), 6.27 (dd, \(J = 1.9, 3.2\) Hz, 1 H), 7.29 (d, \(J = 1.9\) Hz, 1 H). \(^{13}\)C NMR (CDCl_3, 100 MHz): 160.0, 140.1, 108.9, 101.5, 36.3, 30.51, 25.1, 24.9. All the data were in good agreement with previously reported data.\(^{179}\)
2-s-Butylfuran, 2-12q

Following general procedure B; yield = 55% (345 mg, 2.77 mmol); Orange liquid; $R_f$ = 0.64 (EtOAc–hexanes, 10:90). IR (CH$_2$Cl$_2$): 2967, 2870, 1539, 1457, 1378, 1111 cm$^{-1}$. $^1$H NMR (CDCl$_3$, 400 MHz): d = 0.81–0.86 (m, 3 H), 1.18 (d, $J = 7.0$ Hz, 3 H), 1.21–1.37 (m, 2 H), 2.68 (q, $J = 7.0$ Hz, 1 H), 5.91 (d, $J = 3.3$ Hz, 1 H), 6.20–6.22 (m, 1 H), 7.30–7.35 (m, 1 H); $^{13}$C NMR (CDCl$_3$, 100 MHz): 160.5, 141.6, 109.7, 104.9, 38.2, 28.5, 18.4, 11.4; HRMS (EI) calcd. for C$_8$H$_{12}$O [M]$^+$: m/z 124.0888, found 124.0893.

**General Procedure C: Diels-Alder Reaction Between 2-Substituted furans 2-12k, 2-12ac-ae and Maleic anhydride 2-39 (Table 2.6):** To an oven-dried flask equipped with a magnetic stir bar and reflux condenser, anhydrous diethyl ether (10 mL) and maleic anhydride (1.01 mmol) were added. The reaction mixture was heated to reflux and 2-substituted furan (1.01 mmol) was added in a drop-wise manner. The mixture was left to reflux for 2-3 h, cooled to room temperature, and stored at 0-5 °C overnight. The precipitated adduct was filtered and washed with diethyl ether (2 × 10mL). The collected product was then dried under high vacuum at room temperature.

**exo-1-Methyl-4,10-dioxatricyclo[5.2.1.0(2,6)]dec-8-ene-3,5-dione, 2-40a:** Following general procedure C; Yield = 61% (5.45g, 30.2 mmol); Off-white solid; mp: 75-77 °C; $R_f$ = 0.25 (EtOAc:hexanes = 30:70); IR (CH$_2$Cl$_2$): 2987, 1846, 1786, 1712, 1266, 1233, 736
cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.53 (d, $J = 1.0$ Hz, 1H), 6.52 (d, $J = 1.0$ Hz, 1H), 5.30 (s, 1H); 3.28 (d, $J = 6.7$ Hz, 1H), 3.01 (d, $J = 6.7$ Hz, 1H), 1.75 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.1, 168.6, 140.6, 137.4, 89.5, 81.8, 51.8, 50.9, 15.3; HRMS (ESI) calcd. for C$_9$H$_7$O$_4$ [M-H]: m/z 179.0344, found 179.0339.

**exo-1-Ethyl-4,10-dioxatricyclo[5.2.1.0(2,6)]dec-8-ene-3,5-dione, 2-40b:** Following general procedure C; Yield = 55% (0.55 g, 2.83 mmol); White solid; mp: 40-42 °C; $R_f$ = 0.37 (EtOAc:hexanes = 30:70); IR (CH$_2$Cl$_2$): 3095, 2974, 2946, 1843, 1778, 1230, 1086, 906 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.54 (dd, $J = 5.7$, 1.5 Hz, 1H), 6.41 (d, $J = 5.7$ Hz, 1H), 5.32 (d, $J = 1.7$ Hz, 1H), 3.28 (d, $J = 6.8$ Hz, 1H), 3.06 (d, $J = 6.8$ Hz, 1H), 2.11-2.03 (m, 2H), 1.12 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.2, 168.5, 138.8, 137.6, 93.8, 81.7, 51.8, 50.2, 22.4, 9.3; HRMS (EI) calcd. for C$_{10}$H$_{10}$O$_4$ [M$^+$]: m/z 194.0579, found 194.0586.

**exo-1-Hydroxymethyl-4,10-dioxatricyclo[5.2.1.0(2,6)]dec-8-ene-3,5-dione, 2-40c:** Following general procedure C; Yield = 53% (1.0 g, 5.1 mmol); White solid; mp: 83-85 °C; $R_f$ = 0.12 (EtOAc:hexanes = 50:50); IR (CH$_2$Cl$_2$): 3417, 1859, 1775, 1234, 1086, 927 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.63 (d, $J = 5.7$ Hz, 1H), 6.59 (dd, $J = 5.7$ Hz,
1.4 Hz, 1H), 5.42 (d, J = 1.6 Hz, 1H), 4.18 (m, 2H), 3.33 (d, J = 6.8 Hz, 1H), 3.24 (d, J = 6.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 169.5, 169.3, 138.4, 137.5, 92.6, 82.2, 60.2, 51.4, 48.6; HRMS (EI) calcd. for C$_9$H$_8$O$_5$ [M$^+$]: m/z 196.0372, found 196.0380.$^{181}$

![Chemical structure]

**exo-1-Methoxy-4,10-dioxatricyclo[5.2.1.0(2,6)]dec-8-ene-3,5-dione, 2-40d**: Following general procedure C; Yield = 45% (90 mg, 0.46 mmol); White solid; mp: 110-112 °C; R$_f$ = 0.2 (EtOAc:hexanes = 50:50); IR (CH$_2$Cl$_2$): 3095, 2999, 1868, 1791, 1322, 1091, 922 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 6.68 (dd, J = 5.8, 1.9 Hz, 1H), 6.50 (d, J = 5.8 Hz, 1H), 5.24 (d, J = 1.8 Hz, 1H), 3.60 (s, 3H), 3.34 (d, J = 6.7 Hz, 1H), 3.21(d, J = 6.7 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 169.7, 166.1, 139.8, 135.9, 115.4, 76.7, 55.7, 53.0, 49.0; HRMS (EI) calcd. for C$_9$H$_8$O$_5$ [M$^+$]: m/z 196.0372, found 196.0377.$^{182}$

**General Procedure D: Diels-Alder Reaction of 2-substituted furans 2-12k, 2-12ac-ag with N-phenylmaleimide 2-42 (Table 2.7)**: To an oven-dried flask equipped with a stir bar and fitted with reflux condenser, 2-alkylfuran (5.2 mmol), chloroform (5 mL) and N-phenylmaleimide (5.2 mmol) were added. The reaction mixture was brought to reflux and left for 24-72 h, after which it was allowed to cool to room temperature. The crude reaction mixture was purified by a silica-packed flash chromatography column using 10-70 % ethyl acetate in hexanes to obtain the cycloadduct as a solid.
exo-1-Methyl-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0(2,6)]dec-8-ene-3,5-dione,  2-43a:
Following general procedure D; Yield = 82% (0.6 g, 2.35 mmol); White solid; mp: 143-145 °C; R_f = 0.13 (EtOAc:hexanes = 30:70); IR (CH_2Cl_2): 2997, 1708, 1497, 1389, 1196, 716 cm⁻¹; ¹H NMR (400 MHz, CDCl_3): δ 7.46-7.42 (m, 2H), 7.38-7.35 (m, 1H), 7.26-7.24 (m, 2H), 6.53 (d, J = 5.3 Hz, 1H), 6.34 (d, J = 5.6 Hz, 1H), 5.28 (s, 1H), 3.10 (d, J = 6.4 Hz, 1H), 2.84 (d, J = 6.5 Hz, 1H), 1.77 (s, 3H); ¹³C NMR (100 MHz, CDCl_3): δ 175.3, 174.0, 140.7, 137.0, 131.7, 129.0, 128.7, 126.5, 88.6, 81.1, 50.6, 49.5, 15.7; HRMS (EI) calcd. for C₁₅H₁₃NO₃ [M⁺]: 255.0895, found 255.0888.

exo-1-Ethyl-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0(2,6)]dec-8-ene-3,5-dione,  2-43b:
Following general procedure D; Yield = 79% (1.1 g, 4.08 mmol); White solid; mp: 112-114 °C; R_f = 0.33 (EtOAc:hexanes = 30:70); IR (CH_2Cl_2): 2971, 2977, 1713, 1497, 1380, 1190, 716 cm⁻¹; ¹H NMR (400 MHz, CDCl_3): δ 7.45-7.42 (m, 2H), 7.38-7.35 (m, 1H), 7.26-7.24 (m, 2H), 6.53 (dd, J = 5.7, 1.5 Hz, 1H), 6.42 (d, J = 5.7 Hz, 1H), 5.30 (d, J = 1.6 Hz, 1H), 3.09 (d, J = 6.5 Hz, 1H), 2.89 (d, J = 6.5 Hz, 1H), 2.2-2.0 (m, 2H), 1.14 (t, J = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl_3): δ 175.3, 173.9, 138.8, 137.1, 131.7, 129.0,
m/z 269.1052, found 269.1055.

**exo-1-Hydroxymethyl-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0(2,6)]dec-8-ene-3,5-dione, 2-43c:** Following general procedure D; Yield = 40% (0.32 g, 1.17 mmol); White solid; mp: 157-158 °C; Rf = 0.2 (EtOAc:hexanes = 25:75); IR (CH2Cl2): 3055, 2987, 1699, 1390, 1265, 1212 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl3): δ 7.50-7.47 (m, 2H), 7.46-7.36 (m, 1H), 7.26-7.24 (m, 2H), 6.65 (d, J = 5.7 Hz, 1H), 6.58 (dd, J = 5.6, 1.3 Hz, 1H), 5.36 (d, J = 1.6 Hz, 1H), 4.15-4.11 (m, 2H), 3.13 (m, 2H), 2.74-2.70 (m, 1H); \(^13\)C NMR (100 MHz, CDCl3): δ 175.2, 175.0, 138.5; 137.1; 131.4; 129.2; 128.9; 126.4; 91.8; 81.4; 60.9; 50.0; 48.2; HRMS (ESI) calcd. for C\(_{16}\)H\(_{15}\)NO\(_3\) [M-H]: m/z 270.0766, found 270.0762.

**endo-1-Hydroxymethyl-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0(2,6)]dec-8-ene-3,5-dione, 2-44c:** Following general procedure D; Yield = 24% (0.19 g, 0.7 mmol); White solid; mp: 122-124 °C; Rf = 0.25 (EtOAc:hexanes = 25:75); IR (CH2Cl2): 2923, 1705, 1497, 1380, 1183, 725 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl3): δ 7.44-7.34 (m, 3H), 7.10-7.08 (m, 2H), 6.58 (dd, J = 5.8, 1.4 Hz, 1H), 6.48 (d, J = 5.8 Hz, 1H), 5.39 (dd, J = 5.5, 1.5 Hz, 1H), 4.25 (m, 2H), 3.79 (dd, J = 7.8, 5.5 Hz, 1H), 3.57 (d, J = 7.8 Hz, 1H), 2.32 (s, 1H); \(^13\)C NMR (100 MHz, CDCl3): δ 174.2, 173.8, 135.8, 134.9, 131.3, 129.2, 128.9,
126.3, 92.4, 79.9, 61.6, 48.0, 46.1; HRMS (ESI) calcd. for C_{15}H_{12}NO_4 [M-H]: m/z 270.0766, found 270.0760.

**exo-1-Acetyl-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0(2,6)]deca-8-ene-3,5-dione, 2-43e:**

Following general procedure D; Yield = 2% (40 mg, 0.141 mmol); Pale yellow solid; mp: 105-108 °C; R_f = 0.1 (EtOAc:hexanes = 30:70); IR (CH_2Cl_2): 2924, 1779, 1712, 1498, 1387, 1195, 714 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl_3): δ 7.47-7.42 (m, 2H), 7.40-7.36 (m, 1H), 7.25-7.22 (m, 2H); 6.63-6.59 (m, 2H), 5.44 (s, 1H), 3.33 (d, J = 6.6 Hz, 1H), 3.10 (d, J = 6.6 Hz, 1H), 2.29 (s, 3H); \(^13\)C NMR (100 MHz, CDCl_3): δ 203.1, 174.3, 173.0, 137.2, 136.7, 131.4, 129.2, 128.9, 126.3, 94.5, 81.8, 50.4, 49.1, 27.1; HRMS (ESI) calcd. for C_{16}H_{12}NO_4 [M-H]: m/z 282.0766, found 282.0760.

**exo-3,5-Dioxo-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0(2,6)]deca-8-ene-1-carboxylic acid methyl ester, 2-43f:** Following general procedure D; Yield = 3% (70 mg, 0.23 mmol); Off-white solid; mp: 130-132 °C; R_f = 0.13 (EtOAc:hexanes = 30:70); IR (CH_2Cl_2): 2957, 2924, 2854, 1716, 1497, 1387, 1194, 1068 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl_3): 7.46-7.41 (m, 2H), 7.38-7.34 (m, 1H), 7.26-7.24 (m, 2H), 6.66 (d, J = 5.6 Hz, 1H), 6.63 (dd, J = 5.6, 1.7 Hz, 1H), 5.44 (d, J = 1.6 Hz, 1H), 3.90 (s, 3H), 3.30 (d, J = 6.6 Hz, 1H),
3.11 (d, J = 6.6Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 174.2, 172.8, 166.8, 137.4, 136.7, 131.4, 129.2, 128.9, 126.4, 89.6, 81.8, 53.0, 50.3, 48.8; HRMS (ESI) calcd. for C$_{18}$H$_{12}$NO$_5$ [M-H]: m/z 298.0715, found 298.0725.

4-Methoxy-2-phenylisoindole-1,3-dione, 2-45: Following general procedure D; Yield = 10% (50 mg, 0.2 mmol); Off-white solid; mp: 182-184 °C; R$_f$ = 0.33 (EtOAc:hexanes = 30:70); IR (CH$_2$Cl$_2$): 3054, 2987, 1717, 1262, 1053, 896; 750 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.70 (dd, J = 8.4, 7.4 Hz 1H), 7.52-7.42 (m, 3H), 7.40-7.34 (m, 3H), 7.24 (d, J = 8.4 Hz, 1H), 4.0 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 166.9, 165.7, 157.0, 136.4, 133.9, 131.7, 129.0, 127.9, 126.6, 117.7, 117.0, 115.8, 56.4; HRMS (EI) calcd. for C$_{15}$H$_{11}$NO$_3$ [M$^+$]: m/z 253.0739, found 253.0742.

**General Procedure E: Furan-Benzzyne Diels–Alder Cycloaddition (Table 2.8):** To a round-bottom flask under an atmosphere of N$_2$ and equipped with a reflux condenser and addition funnel, was added 2-substituted furan (1 equiv) and THF (~0.5 M). To this solution was added isoamyl nitrite (2.5 equiv). Anthranilic acid (2 equiv) in THF (~0.5 M) was then added drop wise over a period of 20 min. The flask was then heated to 45–55 °C for 3 h. The reaction mixture was then poured into EtOAc (20 mL) and H$_2$O (10 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL),
dried over MgSO₄, and concentrated. The crude extract was then purified by flash chromatography over silica (EtOAc–hexanes).

**Oxabenzonorbornadiene, 2-49ac:** Following general procedure E; Yield = 55% (5.8 g, 40.2 mmol); Off-white solid, MP: 46-48 °C; Rf = 0.50 (EtOAc–hexanes, 20:80). IR (CH₂Cl₂): 3075, 3020, 1693, 1455, 1280, 1196, 1132, 909, 847, 837, 734 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ = 7.28-7.24 (m, 2H), 7.05-7.02 (m, 2H), 7.0-6.95 (m, 2H), 5.73 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 148.9, 143.0, 125.0, 120.2, 82.3. All data were in good agreement with previously reported data.₁⁸³

**1-Ethylxobenzonorbornadiene, 2-49g:** Following general procedure E; Yield = 80% (628 mg, 3.6 mmol); Amber coloured oil; Rf = 0.50 (EtOAc–hexanes, 1:4). IR (CH₂Cl₂): 2975, 2939, 1463, 1455, 1382, 1289, 1094, 908, 734, 650 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ = 7.22 (dd, J = 1.4, 5.8 Hz, 1H), 7.16 (d, J = 6.3 Hz, 1H), 7.04 (dd, J = 1.6, 5.4 Hz, 1H), 6.97 (d, J = 1.2 Hz, 2H), 6.79 (d, J = 5.5 Hz, 1H), 5.66 (d, J = 1.6 Hz, 1H), 2.44–2.25 (m, 2H), 1.18 (t, J = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 151.1, 150.5, 144.6, 144.4, 124.9, 124.7, 120.0, 119.2, 93.4, 81.7, 22.2, 9.0; HRMS (EI) calcd. for C₁₂H₁₂O [M]⁺: m/z 172.0888, found 172.0884.
1-Acetyloxabenzonorbornadiene, 2-49d: Following general procedure E; Yield = 59% (800 mg, 4.4 mmol); Light-yellow oil; \( R_f = 0.57 \) (EtOAc–hexanes, 20:80). IR (CH\(_2\)Cl\(_2\)): 2960 1718, 1460, 1417, 1365, 1286, 1244, 1097, 908, 731 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.29–7.24 \) (m, 2H), 7.07–6.96 (m, 4H), 5.81 (d, \( J = 2 \) Hz, 1H), 2.41 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 205.3, 148.0, 147.4, 143.4, 142.2, 125.6, 125.2, 120.6, 119.5, 95.7, 82.3, 26.8 \); HRMS (EI) calcd. for C\(_{13}\)H\(_{14}\)O \([\text{M}]^+\): m/z 186.1045, found 186.1040.

1-t-Butyloxabenzonorbornadiene, 2-49l: Following general procedure E; Yield = 66% (49 mg, 0.24 mmol); Bright yellow oil; \( R_f = 0.56 \) (EtOAc–hexanes, 1:4); IR (NaCl): 3082, 2977, 2874, 1481, 1465, 1367, 1283, 1176, 1142, 1034, 905, 730, 691, 650 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.44–7.42 \) (m, 1H), 7.24–7.22 (m, 1H), 7.05 (dd, \( J = 1.8, 5.6 \) Hz, 1H), 7.01 (d, \( J = 5.6 \) Hz, 1H), 6.99–6.97 (m, 2H), 5.67 (d, \( J = 1.7 \) Hz, 1H), 1.33 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 152.2, 149.2, 144.4, 142.9, 124.5, 124.4, 119.5, 95.7, 82.3, 26.8 \).
121.6, 119.9, 99.7, 81.4, 32.6, 26.6. HRMS (EI) calcd. for C_{14}H_{16}O [M]^+: m/z 200.1201, found 200.1203.

**General procedure F:** 1,3-dipolar cycloaddition of bicyclic alkenes 3-1, 3-2, 3-3, 3-4 and 3-6, with acetonitrile oxide 3-7a and benzonitrile oxide 3-7b (Tables 3.1, 3.2, 3.4, 3.5 and Scheme 3.6): A solution of nitroalkane (3.75 mmol) in toluene (5 mL) was added to a flame-dried flask containing bicyclic alkene (1.39 mmol), (Boc)$_2$O (505 mg, 2.32 mmol), DMAP (20.3 mg, 0.17 mmol) and toluene (10 mL) via a cannula over 10 minutes. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed by rotary evaporation, and the crude reaction mixture was purified by column chromatography (EtOAc:hexanes = 10:90-60:40) to give the corresponding cycloadduct.

**General procedure G:** 1,3-dipolar cycloaddition of bicyclic alkenes 3-5 with acetonitrile oxide (Table 3.3): A solution of nitroalkane (1.49 mmol) in toluene (2 mL) was added to a flame-dried flask containing (Boc)$_2$O (505 mg, 2.317 mmol), DMAP (20.3 mg, 0.166 mmol) and toluene (3 mL). Bicyclic alkene (1.388 mmol) was dissolved in THF (10mL) and added via a cannula over 10 minutes. The reaction mixture was stirred at 60 °C temperature for 18 h. Reaction mixture was cooled to room temperature and solvent was removed by rotary evaporation. Methanol (5 mL) was added to crude reaction mixture and resulting precipitate was filtered and dried under vacuum at room temperature to obtain corresponding cycloadduct.
3-Methyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-20aa: Following general procedure F; Yield = 90% (251 mg, 1.25 mmol); White solid; mp: 150-152 °C; Rf = 0.12 (EtOAc-hexanes, 2:8); IR (CH2Cl2): 3058, 3029, 2977, 2945, 1626, 1459, 1433, 1387, 1343, 1255, 1205, 1158, 1002, 966, 879, 864, 857, 763 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ: 7.32-7.25 (m, 2H), 7.24-7.18 (m, 2H), 5.52 (s, 1H), 5.41 (s, 1H), 4.82 (d, J = 7.7 Hz, 1H), 3.46 (d, J = 7.6 Hz, 1H), 2.07 (s, 3H); ¹³C NMR (100 MHz, CDCl3) δ: 152.3, 144.6, 141.4, 127.7, 127.5, 121.0, 119.7, 86.1, 85.7, 79.7, 61.9, 12.0; HRMS (ESI) calcd. for C12H12NO2 [M+H]⁺: m/z 202.0868, found 202.0876.

![Chemical Structure](image)

3-Phenyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-20ab: Following general procedure F; Yield = 93% (85 mg, 0.322 mmol); Pale yellow solid; mp: 155-159 °C; Rf = 0.5 (EtOAc-hexanes, 3:7); IR (CH2Cl2): 2959, 2925, 2854, 1460, 1446, 1358, 1261, 1157, 1025, 1003, 894, 867, 832, 772, 751 cm⁻¹; ¹H NMR (400MHz, CDCl3) δ: 7.77-7.74 (m, 2H), 7.46-7.42 (m, 3H), 7.37-7.34 (m, 2H), 7.26-7.22 (m, 2H), 5.63 (s, 1H), 5.50 (s, 1H), 5.05 (d, J = 7.7 Hz, 1H), 4.0 (d, J = 7.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl3) δ: 154.5, 145.3, 141.8, 130.6, 129.4, 129.1, 128.4, 128.1, 127.2, 121.6, 120.3, 88.1, 86.3, 81.5, 59.3, HRMS (ESI) calcd. for C17H14NO2 [M+H]⁺: m/z 264.1025, found 264.1020.
5,8-Dimethoxy-3-methyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-20ba: Following general procedure F; Yield = 68% (75 mg, 0.287 mmol); Off-white solid; mp: 132-134 °C; Rf = 0.14 (EtOAc-hexanes, 3:7); IR (CH2Cl2): 2954, 2835, 2360, 1500, 1261, 1084, 1007, 732 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 6.65 (s, 2H), 5.67 (s, 1H), 5.54 (s, 1H), 4.84 (d, J = 7.6 Hz, 1H), 3.77 (s, 6H), 3.47 (d, J = 7.6 Hz, 1H), 2.06 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 152.4, 147.7, 146.8, 133.6, 130.2, 111.9, 111.8, 85.7, 83.8, 77.6, 61.4, 55.9, 55.8, 11.9; HRMS (ESI) calcd. for C₁₄H₁₆NO₄ [M+H]⁺: m/z 262.1079, found 262.1088.

5,8-Dimethoxy-3-phenyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-20bb: Following general procedure F; Yield = 67% (76 mg, 0.235 mmol); Light brown solid; mp: 184-186 °C; Rf = 0.26 (EtOAc-hexanes, 30:70); IR (CH2Cl2): 3054, 2986, 1501, 1265, 1087, 897, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.78-7.76 (m, 2H), 7.46-7.42 (m, 3H), 6.71 (m, 2H), 5.78 (s, 1H), 5.66 (s, 1H), 5.06 (d, J = 7.6 Hz, 1H), 3.99 (d, J = 7.6 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ:
154.4, 148.3, 147.4, 134.4, 130.6, 130.5, 129.4, 129.2, 127.1, 112.6, 112.3, 87.8, 84.3, 79.5, 58.7, 56.5; HRMS (ESI) calcd. for C_{19}H_{18}NO_4 [M+H]^+: m/z 324.1236, found 324.1235.

6,7-Dimethoxy-3-methyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-20ca: Following general procedure F; Yield = 77% (80 mg, 0.306 mmol); Off-white solid; mp: 173-175 °C; R_f = 0.12 (EtOAc-hexanes, 1:1); IR (CH_2Cl_2): 3055, 2987, 2836, 1614, 1491, 1331, 1266, 1220, 1088, 895, 735; ^1H NMR (400 MHz, CDCl_3) δ: 6.89 (s, 1H), 6.86 (s, 1H), 5.46 (s, 1H); 5.35 (s, 1H), 4.78 (d, J = 7.6 Hz, 1H), 3.853 (s, 3H), 3.850 (s, 3H), 3.41 (d, J = 7.6 Hz, 1H), 2.04 (d, J = 0.6 Hz, 3H); ^13C NMR (100 MHz, CDCl_3) δ: 152.3, 148.7, 148.5, 137.0, 133.6, 105.3, 104.3, 86.5, 86.0, 80.0, 62.4, 56.27, 56.26, 12.0; HRMS (ESI) calcd. for C_{14}H_{15}NO_4Na [M+Na]^+: m/z 284.0899, found 284.0906.

6,7-Dimethoxy-3-phenyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-20cb: Following general procedure F; Yield = 95% (123 mg, 0.38 mmol); Orange-brown solid; mp: 169-171 °C; R_f = 0.33 (EtOAc-hexanes, 1:1); IR (CH_2Cl_2):
3,5,8-Trimethyl-3a,4,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct

3-20da: Following general procedure F; Yield = 98% (98 mg, 0.427 mmol); Off-white solid; mp: 152-154 °C; R_f = 0.12 (EtOAc-hexanes, 2:8); IR (CH_2Cl_2): 2962, 1499, 1439, 1328, 1261, 1026, 877, 727 cm⁻¹; ^1H NMR (300 MHz, CDCl_3) δ: 6.87 (s, 2H), 5.56 (s, 1H), 5.44 (s, 1H), 4.79 (d, J = 7.5 Hz, 1H), 3.41 (d, J = 7.5 Hz, 1H), 2.28 (s, 6H), 2.07 (d, J = 0.6 Hz, 3H); ^13C NMR (CDCl_3, 100 MHz): δ 152.5, 143.0, 139.7, 129.1, 128.8, 128.3, 126.9, 85.8, 84.9, 78.7, 61.4, 18.0, 17.8, 12.0; HRMS (ESI) calcd. for C_{14}H_{16}NO_2 [M+H]^+: m/z 252.1000, found 252.0989.
**5,8-Dimethyl-3-phenyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole,**

**Cycloadduct 3-20db:** Following general procedure F; Yield = 88% (100 mg, 0.343 mmol); Off-white solid; mp: 185-187 °C; Rf = 0.34 (EtOAc-hexanes, 2:8); IR (CH2Cl2): 3054, 2987, 1499, 1446, 1422, 1357, 1265, 897, 738 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ: 7.78-7.73 (m, 2H), 7.47-7.40 (m, 3H), 6.94-6.88 (m, 2H), 5.67 (s, 1H); 5.56 (s, 1H); 5.02 (d, J = 7.8 Hz, 1H), 3.97 (d, J = 7.8 Hz, 1H), 2.36 (s, 3H), 2.32 (s, 3H); ¹³C NMR (75 MHz, CDCl3) δ: 154.0, 143.3, 139.6, 130.2, 129.2, 129.1, 129.0, 128.9, 128.6, 126.8, 126.6, 87.3, 84.9, 80.0, 58.2, 18.07, 18.05; HRMS (ESI) calcd. for C₁₉H₁₸NO₂ [M+H]+: m/z 292.1338, found 292.1349.

**6,7-Dibromo-3-methyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole**

**Cycloadduct 3-20ea:** Following general procedure F; Yield = 68% (85 mg, 0.328 mmol); White solid; mp: 239-241 °C; Rf = 0.17 (EtOAc-hexanes, 2:8); IR (CH2Cl2): 3054, 2987, 2306, 1422, 1264, 896, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ: 7.57 (s, 1H), 7.54 (s, 1H), 5.48 (s, 1H), 5.37 (s, 1H), 4.82 (d, J = 7.6 Hz, 1H), 3.47 (d, J = 7.6 Hz, 1H), 2.06 (s, 3H); ¹³C NMR (100 MHz, CDCl3) δ (152.0, 145.5, 142.0, by HMBC), 184.
126.4, 126.6, 124.5, 123.0, 85.6, 85.2, 79.2, 61.7, 12.0; HRMS (ESI) calcd. for C_{12}H_{79}Br_2NO_2Na [M+Na]^+: m/z 379.8898, found 379.8888.

\[
\begin{array}{c}
\text{Ph} \rightleftharpoons \text{NO}_2
\end{array}
\xrightarrow{(Boc)_2O \text{ DMAP} \text{ Toluene} \text{ 25 °C}}
\begin{array}{c}
3-7b
\end{array}
\xrightarrow{3-8b}
\begin{array}{c}
3-20eb
\end{array}
\]

6,7-Dibromo-3-phenyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-20eb: Following general procedure F; Yield = 59% (86 mg, 0.204 mmol); Brown solid; mp: 194-196 °C; R_f = 0.43 (EtOAc-hexanes, 2:8); IR (CH_2Cl_2): 3054, 2987, 1446, 1265, 738 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) δ: 7.77-7.75 (m, 2H), 7.68 (s, 1H), 7.66 (s, 1H), 7.50-7.48 (m, 3H), 5.62 (s, 1H), 5.49 (s, 1H), 5.08 (d, J = 7.7 Hz, 1H), 4.05 (d, J = 7.7 Hz, 1H); \(^13\)C NMR (75 MHz, CDCl_3) δ: 153.6, 145.8, 142.4, 130.4, 129.4, 128.3, 126.7, 126.6, 125.3, 124.1, 123.8, 87.0, 85.3, 80.5, 58.6; HRMS (ESI) calcd. for C_{17}H_{117}Br_2NO_2Na [M+Na]^+: m/z 441.9056, found 441.9061.

\[
\begin{array}{c}
\text{Me} \rightleftharpoons \text{NO}_2
\end{array}
\xrightarrow{(Boc)_2O \text{ DMAP} \text{ Toluene} \text{ 25 °C}}
\begin{array}{c}
3-7a
\end{array}
\xrightarrow{3-8a}
\begin{array}{c}
3-20fa
\end{array}
\]

5,6,7,8-Tetrafluoro-3-methyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-20fa: Following general procedure F; Yield = 60% (57 mg, 0.207 mmol); White solid; mp: 160-162 °C; R_f = 0.35 (EtOAc-hexanes, 3:7); IR (CH_2Cl_2): 3033, 2962, 2924, 1505, 1488, 1330, 1295, 1129, 1076, 909, 813 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl_3) δ: 5.80 (s, 1H), 5.67 (s, 1H), 4.88 (d, J = 7.6 Hz, 1H), 3.55 (d, J
= 7.4 Hz, 1H), 2.07 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 151.4, 142.5, 141.5, 140.0, 139.0, 126.5, 123.5, 84.9, 83.3, 77.4, 61.4, 11.8; HRMS (ESI) calcd. for C$_{12}$H$_7$F$_4$NO$_2$Na [M+Na]$^+$: m/z 296.0311, found 296.0304.

![Chemical structure](image)

5,6,7,8-Tetrafluoro-3-phenyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 2-25fb: Following general procedure F; Yield = 60% (70 mg, 0.208 mmol); Pale yellow solid; mp: 164-166 °C; R$_f$ = 0.37 (EtOAc-hexanes, 1.5:8.5); IR (CH$_2$Cl$_2$): 3055, 2987, 1509, 1490, 1265, 739 cm$^{-1}$; $^{1}$H NMR (300 MHz, CDCl$_3$) δ: 7.73-7.70 (m, 2H), 7.50-7.40 (m, 3H), 5.89 (s, 1H), 5.77 (s, 1H), 5.09 (d, $J$ = 7.7 Hz, 1H), 4.08 (d, $J$ = 7.7 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 153.1, 143.0, 142.3, 140.0, 138.8, 130.6, 129.2, 127.9, 126.7, 125.5, 123.5, 86.3, 83.4, 78.6, 58.3; HRMS (ESI) calcd. for C$_{19}$H$_{10}$F$_4$NO$_2$ [M+H]$^+$: m/z 336.0648, found 336.0640.

![Chemical structure](image)

2,2-Dimethyl-1-(3-methyl-3a,4,9,9a-tetrahydro-4,9-epiminonaphtho[2,3-d]isoxazol-10-yl)propan-1-one, cycloadduct 3-21aa: Following general procedure F; Yield = 86% (85 mg, 0.298 mmol); White solid; mp: 172-173 °C; R$_f$ = 0.17 (EtOAc-hexanes, 3:7); IR
\((\text{CH}_2\text{Cl}_2): 2967, 1626, 1476, 1409, 1202, 1146, 983, 758 \text{ cm}^{-1}\); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\): 7.33-7.27 (m, 2H), 7.22-7.16 (m, 2H), 5.73 (s, 1H), 5.67 (s, 1H), 4.78 (d, \(J = 7.7 \text{ Hz}, 1\text{H}\)), 3.45 (d, \(J = 7.6 \text{ Hz}, 1\text{H}\)), 2.06 (s, 3H), 1.20 (s, 9H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\): 175.4, 152.9, 144.2, 140.9, 127.8, 127.2, 120.9, 120.6, 86.8, 67.0, 61.8, 60.5, 38.7, 27.9, 12.0; HRMS (ESI) calcd. for \(\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_2\) [M+H]\(^+\): \(m/z 285.1603\), found 285.1602.

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{(Boc)}_2\text{O}} \text{DMAP} \xrightarrow{\text{Toluene} \ 25 ^\circ \text{C}} \text{3-7b} \\
\text{3-8b} & \xrightarrow{\text{3-2a}} \text{3-21ab}
\end{align*}
\]

\text{2,2-Dimethyl-1-(3-phenyl-3a,4,9a-tetrahydro-4,9-epiminonaphtho[2,3-d]isoxazol-10-yl)propan-1-one, 3-21ab}: Following general procedure F; Yield = 62\% (63 mg, 0.181 mmol); White solid; mp: 166-168 \(^\circ\)C; \(R_f = 0.2\) (EtOAc-hexanes, 1:9); IR (CH\(_2\)Cl\(_2\)): 3054, 2986, 1703, 1422, 1266, 1170, 896, 746 cm\(^{-1}\); \(^1\text{H NMR}\) 400 MHz, CDCl\(_3\)): \(\delta\): 7.79-7.72 (m, 2H), 7.43-7.37 (m, 5H), 7.21-7.19 (m, 2H), 5.49 (m, 2H), 5.02 (br d, \(J = 7.8 \text{ Hz}, 1\text{H}\)), 3.94 (d, \(J = 7.8 \text{ Hz}, 1\text{H}\)), 1.28-1.05 (m, 9H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 100 MHz): \(\delta\) (171.0, 154.5, by HMBC), 144.0, 144.6, 141.1, 130.1, 128.9, 127.7, 127.3, 126.7, 121.6, 120.6, 88.7, 88.2, 63.0, (60.0 by HMBC), 59.6, 28.0; HRMS (EI) calcd. for \(\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2\) [M\(^+\)]: \(m/z 346.1681\), found 346.1671.
3-Methyl-10-tosyl-3a,4,9,9a-tetrahydro-4,9-epiminonaphtho[2,3-d]isoxazole,

cycloadduct 3-21ba: Following general procedure F; Yield = 52% (64 mg, 0.185 mmol);
Light brown solid; mp: 215-220 °C; Rf = 0.12 (EtOAc-hexanes, 2:8); IR (CH2Cl2): 2981, 1626, 1733, 1368, 1288, 1150, 1089, 744 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ: 7.44 (d, J = 8.2 Hz, 2H), 7.04-6.97 (m, 6H), 5.16 (s, 1H), 5.10 (s, 1H), 4.67 (d, J = 7.8 Hz, 1H), 3.44 (d, J = 7.8 Hz, 1H), 2.27 (s, 3H), 2.01 (s, 3H); ¹³C NMR (100 MHz, CDCl3) δ: 151.7, 143.4, 143.0, 139.7, 135.2, 129.1, 127.8, 127.7, 127.5, 121.9, 120.8, 85.9, 69.7, 64.2, 63.0, 21.4, 11.7; HRMS (ESI) calcd. for C19H19N2O3S [M+H]+: m/z 355.1116, found 355.1108.

3-Phenyl-10-tosyl-3a,4,9,9a-tetrahydro-4,9-epiminonaphtho[2,3-d]isoxazole,

cycloadduct 3-21bb: Following general procedure F; Yield = 95% (64 mg, 0.153 mmol);
Off-white solid; mp: 206-210 °C; Rf = 0.14 (EtOAc:hexanes = 20:80); IR (CH2Cl2): 3054, 2987, 1422, 1328, 1265, 1158, 1003, 896, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ: 7.67-7.65 (m, 2H), 7.44-7.40 (m, 5H), 7.15-7.11 (m, 2H), 7.07-7.03 (m, 2H), 6.97 (d, J
= 8.0 Hz, 2H), 5.29 (s, 1H), 5.17 (s, 1H), 4.90 (d, J = 8.0 Hz, 1H), 3.97 (d, J = 8.0 Hz, 1H), 2.26 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 153.5, 143.6, 143.4, 140.0, 135.6, 130.3, 129.1, 129.0, 128.2, 128.0, 127.7, 126.7, 122.1, 120.8, 87.2, 85.4, 60.1, 21.4; HRMS (ESI) calcd. for C$_{24}$H$_{20}$N$_2$O$_3$SNa [M+Na$^+$]: 439.1092, found 439.1093.

\[
\text{MeNO}_2 \quad 3-7a \quad \xrightarrow{\text{(Boc)$_2$O, DMAP, Toluene, 25°C}} \quad 3-8a \\
\text{Boc} \quad \text{N} \quad \text{Me} \\
\text{O}^\bullet \text{N}\text{N} \quad \text{Me} \\
\text{O}^\bullet \text{N}\text{N} \quad \text{Me}
\]

\[
\text{3-2c} \quad \xrightarrow{\text{MeNO}_2} \quad 3-21ca
\]

*tert*-Butyl-3-methyl-3a,4,9,9a-tetrahydro-4,9-epiminonaphtho[2,3-d]isoxazole-10-carboxylate, cycloadduct 3-21ca: Following general procedure F; Yield = 99% (120 mg, 0.399 mmol); Off-white solid; mp: 147-150 °C; R$_f$ = 0.34 (EtOAc-hexanes, 2:8); IR (v, cm$^{-1}$): 3050, 2979, 1705, 1460, 1367, 1347, 1153, 912, 738; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.32-7.24 (m, 2H), 7.18-7.14 (m, 2H), 5.5-5.18 (m, 2H), 4.71 (s, 1H), 3.41 (d, J = 7.8 Hz, 1H), 2.07 (s, 3H), 1.38 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 154.0, 152.7, 144.4, 141.0, 127.4, 127.0, 121.2, 120.3, 86.8, 80.5, 67.2, 62.6, 61.5, 27.9, 12.0; HRMS (ESI) calcd. for C$_{17}$H$_{21}$N$_2$O$_3$ [M+H$^+$]: m/z 301.1552, found 301.1562.

\[
\text{PhNO}_2 \quad 3-7b \quad \xrightarrow{\text{(Boc)$_2$O, DMAP, Toluene, 25°C}} \quad 3-8b \\
\text{Boc} \quad \text{N} \quad \text{Ph} \\
\text{O}^\bullet \text{N}\text{N} \quad \text{Ph} \\
\text{O}^\bullet \text{N}\text{N} \quad \text{Ph}
\]

\[
\text{3-2c} \quad \xrightarrow{\text{PhNO}_2} \quad 3-21cb
\]

*tert*-Butyl-3-phenyl-3a,4,9,9a-tetrahydro-4,9-epiminonaphtho[2,3-d]isoxazole-10-carboxylate, cycloadduct 3-21cb: Following general procedure F; Yield = 97% (140
mg, 0.386 mmol); Off-white solid; mp: 173-174 °C; $R_f = 0.25$ (EtOAc-hexanes, 2:8); IR (CH$_2$Cl$_2$): 3054, 2986, 1703, 1422, 1264, 1170, 896, 739 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.86 (br s, 2H), 7.55-7.45 (m, 5H), 7.27-7.19 (m, 2H), 5.5-5.2 (br s, 2H), 5.0 (d, $J = 7.6$ Hz, 1H), 4.16 (d, $J = 7.6$ Hz, 1H), 1.38-0.95 (m, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: (155.0 by HMBC), 145.0, 141.1, 130.1, 128.9, 128.5, 127.7, 127.3, 126.7, 121.6, 120.6, 88.7, 88.2, 80.7, 66.4, 63.0, 59.6, 28.0; HRMS (ESI) calcd. for C$_{22}$H$_{23}$N$_2$O$_3$ [M+H]$^+$: m/z 363.1709, found 363.1726.

8,9-Bis-methoxymethyl-5-methyl-3,10-dioxo-4-aza-tricyclo[5.2.1.0$^{2,6}$]dec-4-ene,

cycloadduct 3-22a: Following general procedure F; Yield = 79% (76 mg, 0.315 mmol); Off-white solid; mp: 67-69 °C; $R_f = 0.08$ (EtOAc-hexanes, 1:1); IR (CH$_2$Cl$_2$): 3055, 2987, 2930, 1718, 1438, 1422, 1266, 1228, 1099, 926, 738 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.66 (d, $J = 8.0$ Hz, 1H), 4.53 (s, 1H), 4.48 (s, 1H), 3.38-3.29 (m, 9H), 3.26-3.20 (m, 2H), 2.11-2.02 (m, 2H), 1.95 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 153.0, 85.0, 84.9, 79.1, 70.1, 70.0, 61.4, 58.8, 58.7, 44.0, 39.8, 11.8; HRMS (ESI) calcd. for C$_{12}$H$_{19}$NO$_4$ [M]$^+$: m/z 241.1314, found 241.1313.
8,9-Bis-methoxymethyl-5-phenyl-3,10-dioxa-4-aza-tricyclo[5.2.1.0^2,6]dec-4-ene, cycloadduct 3-22b: Following general procedure F; Yield = 96% (117 mg, 0.385 mmol); Off-white solid; mp: 164-166 °C; R_f = 0.16 (EtOAc-hexanes, 1:1); IR (CH_2Cl_2): 3055, 2987, 1717, 1684, 1265, 1127, 1099, 904, 738 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 7.68-7.66 (m, 2H), 7.4-7.38 (m, 3H), 4.88 (d, J = 8.4 Hz, 1H), 4.65 (s, 1H), 4.59 (s, 1H), 3.84 (d, J = 7.8 Hz, 1H), 3.39-3.19 (m, 10H), 2.26-2.23 (m, 1H), 2.14-2.12 (m, 1H); ^13C NMR (100 MHz, CDCl_3): δ 155.0, 133.5, 130.1, 130.0, 126.8, 86.7, 85.0, 80.5, 70.3, 70.2, 58.93, 58.90, 58.2, 44.5, 40.0; HRMS (ESI) calcd. for C_{17}H_{21}NO_4 [M]^+: m/z 303.1471, found 303.1465.

3,9-Dimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, 5aa and 3,4-dimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadducts 3-23aa and 3-24aa: Following general procedure F; Yield = 96% (82.6 mg, 0.383 mmol, 8a/9a = 85:15 measured by ^1H NMR); White solid; mp: 162-164 °C R_f = 0.15 (EtOAc-hexanes, 2:8); IR (CH_2Cl_2): 3054, 2987, 1461, 1437, 1265, 991, 893, 738 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 7.30-7.20 (m, 4H), 5.44 (s, 0.15H), 5.35 (s, 0.85H), 4.95 (d, J = 7.8 Hz, 0.15H), 4.58 (d, J = 7.6 Hz, 0.85H), 3.56 (d, J = 7.6 Hz, 0.85H), 3.29 (d, J = 7.7 Hz, 0.15H), 2.12 (s, 0.5H), 2.08 (s, 2.5H), 1.92 (s, 0.5Hz), 1.89 (s, 2.5H); ^13C NMR (100 MHz, CDCl_3) major isomer 3-23aa: δ 152.7, 145.7, 144.8, 127.7, 127.5, 120.0, 119.6,
91.2, 87.2, 78.7, 63.8, 12.5, 11.9. Visible peaks for minor isomer 3-24aa: δ 152.0, 148.3, 142.3, 127.9, 127.4, 120.8, 118.6, 89.5, 88.0, 83.9, 64.0, 15.5, 13.6; HRMS (ESI) calcd. for C_{13}H_{13}NO_{2} Na [M+Na]^+: m/z 238.0844, found 238.0836.

9-Methyl-3-phenyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-23ab: Following general procedure F; Yield = 79% (87 mg, 0.313 mmol); Brown solid; mp: 126-128 °C; R_f = 0.47 (EtOAc-hexanes, 2:8); IR (CH_2Cl_2): 3054, 2986, 1461, 1446, 1265, 897, 743 cm^{-1}; ^1H NMR (400 MHz, CDCl_3) δ: 7.68-7.66 (m, 2H), 7.38-7.34 (m, 3H), 7.26-7.23 (m, 1H), 7.17-7.14 (m, 3H), 5.31 (s, 1H), 4.70 (d, J = 7.7 Hz, 1H), 3.99 (d, J = 7.7 Hz, 1H), 1.84 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ 154.3, 145.8, 144.7, 130.2, 129.0, 128.7, 127.8, 127.6, 126.8, 120.2, 119.6, 91.4, 88.7, 80.0, 60.7, 12.6; HRMS (ESI) calcd. for C_{18}H_{16}NO_2 [M+H]^+: m/z 278.1181, found 278.1178.

4-Methyl-3-phenyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-24ab: Following general procedure F; Yield = 7 % (8 mg, 0.028 mmol); White solid; mp: 72-75 °C; R_f = 0.45 (EtOAc-hexanes, 2:8); IR (CH_2Cl_2): 3054, 2987, 1465, 1448, 1442, 1266, 896, 742 cm^{-1}; ^1H NMR (400 MHz, CDCl_3) δ: 7.69-7.66 (m, 2H), 7.44-7.39 (m, 3H), 7.34-7.32 (m, 1H), 7.27-7.18 (m, 3H), 5.51 (s, 1H), 5.15 (d, J = 7.8 Hz, 1H), 3.93 (d, J = 7.9 Hz, 1H), 1.55 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ
154.3, 148.2, 142.1, 130.0, 129.9, 128.7, 127.9, 127.4, 126.9, 121.0, 118.6, 90.6, 88.6, 83.5, 60.3, 16.2; HRMS (ESI) calcd. for C_{18}H_{16}NO_{2} [M+H]^+: m/z 278.1181, found 278.1168.

9-Ethyl-3-methyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-23ba and 4-ethyl-3-methyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-24ba: Following general procedure F; Yield = 92\% (122 mg, 0.532 mmol, 3-23ba/3-24ba = 92:8 measured by \textsuperscript{1}H NMR); Off white solid; mp: 128-130 °C; R\textsubscript{f} = 0.5 (EtOAc-hexanes, 3:7); IR (\nu, \text{cm}^{-1}): 3054, 2987, 1422, 1265, 896, 738; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \delta 7.35-7.20 (m, 4H), 5.5 (s, 0.08H), 5.39 (s, 0.92H), 4.96 (d, J = 7.6 Hz, 0.08H), 4.65 (d, J = 7.6 Hz, 0.92H), 3.56 (dd, J = 7.6 Hz, 0.8 Hz, 0.92H), 3.30 (m, 0.08H), 2.53-2.23 (m, 2H), 2.14 (s, 0.25H), 2.10 (s, 2.75H), 1.16 (t, J = 7.5 Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) major isomer 3-23ba: \delta 152.6, 146.1, 143.1, 127.5, 127.4, 120.7, 119.7, 95.0, 86.9, 78.5, 63.8, 19.7, 11.9, 8.8. Visible peaks for minor isomer 3-24ba: \delta 151.9, 145.8, 142.9, 127.6, 127.2, 121.0, 119.6, 92.4, 89.7, 64.2, 22.2, 13.9, 9.3; HRMS (ESI) calcd. for C_{14}H_{16}NO_{2} [M+H]^+: m/z 230.1175, found 230.1180.
(3-Methyl-3a,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazol-9(4H)-yl)methanol, cycloadduct 3-23ca and (3-methyl-9,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazol-4(3aH)-yl)methanol, cycloadduct 3-24ca: Following general procedure F; Yield = 53% (53 mg, 0.229 mmol, 3-23ca/3-24ca = 90:10 measured by \(^1\)H NMR); White solid; mp: 135-140 °C; \(R_f = 0.31\) (EtOAc-hexanes, 1:1); IR (CH\(_2\)Cl\(_2\)): 3054, 2984, 1461, 1435, 1265, 1034, 896, 739 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.38-7.35 (m, 1H), 7.27-7.18 (m, 3H), 5.48 (s, 0.1H), 5.40 (s, 0.9H), 4.93 (d, \(J = 7.8\) Hz, 0.1H), 4.78 (d, \(J = 7.6\) Hz, 0.9H), 4.49-4.40 (m, 2H), 3.58 (d, \(J = 7.5\) Hz, 0.9H), 3.39 (d, \(J = 7.8\) Hz, 0.1H), 2.43 (m, 1H), 2.07 (s, 0.4H) 2.06 (s, 2.6H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) major isomer 3-23ca: \(\delta\) 152.9, 145.5, 141.8, 127.9, 127.6, 121.0, 119.6, 93.6, 86.3, 79.0, 64.1, 59.5, 11.8. Visible peaks for minor isomer 3-24ca: \(\delta\) 151.8, 142.2, 127.5, 120.9, 119.7, 91.2, 89.1, 84.2, 62.6, 60.3, 13.3; HRMS (ESI) calcd. for C\(_{13}\)H\(_{14}\)NO\(_3\) [M+H]\(^+\): m/z 232.0968, found 232.0974.
1-(3-Methyl-3a,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazol-9(4H)-yl)ethan-1-one, cycloadduct 3-23da: Following general procedure F; Yield = 68% (95 mg, 0.39 mmol); Pale yellow solid; mp: 107-110 °C; Rf = 0.14 (EtOAc-hexanes, 2:8); IR (ν, cm⁻¹): 3054, 2987, 1718, 1460, 1422, 1265, 896, 739; ¹H NMR (400 MHz CDCl₃): δ 7.53-7.49 (m, 1H), 7.32-7.21 (m, 3H), 5.50 (s, 1H), 5.04 (d, J = 7.4 Hz, 1H), 3.54 (dd, J = 7.4 Hz, 0.8 Hz, 1H), 2.42 (s, 3H), 2.12 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 204.8, 152.6, 143.8, 139.9, 128.4, 127.8, 121.1, 119.8, 96.9, 88.1, 79.3, 63.1, 28.7, 12.0; HRMS (ESI) calcd. for C₁₄H₁₄NO₃ [M+H]^+: m/z 244.0973, found 244.0971.

1-(3-Methyl-9,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazol-4(3aH)-yl)ethan-1-one, cycloadduct 3-24da: Yield = 22% (32 mg, 0.1315 mmol); Light brown solid; mp: 123-125 °C; Rf = 0.3 (EtOAc-hexanes, 2:8); IR (ν, cm⁻¹): 3055, 2986, 1716, 1460, 1421, 1365, 1266, 897, 739; ¹H NMR (400 MHz, CDCl₃): δ 7.37-7.35 (m, 1H), 7.30-7.21 (m, 3H), 5.61 (s, 1H), 4.89 (d, J = 7.6 Hz, 1H), 3.76 (d, J = 7.6 Hz, 1H), 2.41 (s, 3H), 1.91 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 205.3, 151.1, 143.4, 140.8, 128.3, 128.0, 121.1, 119.5, 93.6, 87.9, 85.1, 63.8, 28.5, 13.0; HRMS (ESI) calcd. for C₁₄H₁₃NO₃ [M]^+: m/z 243.0895, found 243.0904.
Methyl-3-methyl-3a,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazole-9(4H)-
carboxylate, cycloadduct 3-23ea: Following general procedure F; Yield = 63% (65 mg, 0.25 mmol); Brown solid; mp: 143-147 °C; R_f = 0.21 (EtOAc-hexanes, 4:6); IR (CH_2Cl_2): 3055, 2987, 1767, 1741, 1483, 1266, 895, 739 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.40 (m, 1H), 7.26-7.15 (m, 3H), 5.44 (s, 1H), 4.96 (d, J = 7.5 Hz, 1H), 3.91 (s, 3H), 3.52 (d, J = 7.4 Hz, 1H), 2.0 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ 166.4, 152.2, 143.5, 139.7, 128.5, 127.7, 120.8, 120.0, 92.9, 87.5, 78.3, 63.0, 52.9, 11.7; HRMS (ESI) calcd. for C_{14}H_{14}NO_4[M+H]^+: m/z 260.0923, found 260.0919.

Methyl-3-methyl-9,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazole-4(3aH)-
carboxylate, cycloadduct 3-24ea: Yield = 35% (37.1 mg, 0.143 mmol); Brown solid; mp: 128-130 °C; R_f = 0.36 (EtOAc-hexanes, 4:6); IR (CH_2Cl_2): 3056, 2957, 1762, 1738, 1460, 1438, 1318, 1271, 1111, 1072, 893, 735, 663 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 7.40-7.37 (m, 1H), 7.30-7.26 (m, 1H), 7.23-7.17 (m, 2H), 5.54 (s, 1H), 4.83 (d, J = 7.7 Hz, 1H), 3.92 (s, 3H), 3.71 (d, J = 7.6 Hz, 1H), 1.86 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ 167.3, 150.4, 143.1, 140.7, 128.5, 128.2, 121.1, 120.0, 88.2, 87.7, 85.3, 64.5, 52.9, 12.1; HRMS (ESI) calcd. for C_{14}H_{14}NO_4[M+H]^+: m/z 260.0923, found 260.0917.
Methyl-3-phenyl-3a,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazole-9(4H)-carboxylate, cycloadduct 3-23eb: Following general procedure F; Yield = 48% (60.6 mg, 0.188 mmol); Pale yellow liquid; R_f = 0.11 (EtOAc-hexanes, 2:8); IR (CH_2Cl_2): 3054, 2987, 1767, 1422, 1264, 896, 747 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 7.75-7.72 (m, 2H), 7.53-7.25 (m, 7H), 5.56 (s, 1H), 5.25 (d, J = 7.6 Hz, 1H), 4.10 (d, J = 7.6 Hz, 1H), 4.0 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ 166.5, 154.0, 143.8, 139.9, 130.4, 129.0, 128.8, 128.2, 128.0, 126.8, 121.2, 120.0, 93.1, 88.9, 80.7, 60.1, 53.0; HRMS (ESI) calcd. for C_{19}H_{16}NO_4 [M+H]^+: m/z 322.1079, found 322.1069.

Methyl-3-phenyl-9,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazole-4(3aH)-carboxylate, cycloadduct 3-24eb: Yield = 49% (64.4 mg, 0.2 mmol); Pale yellow solid; mp: 133-136 °C; R_f = 0.2 (EtOAc-hexanes, 2:8); IR (CH_2Cl_2): 1762, 1741, 1458, 1351, 1326, 900 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 7.75-7.25 (m, 9H), 5.68 (s, 1H), 5.13 (d, J = 7.7 Hz, 1H), 4.35 (d, J = 7.7 Hz, 1H), 3.16 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ 166.9, 153.1, 142.7, 140.7, 130.1, 128.6, 128.4, 128.3, 127.2, 126.9, 121.1, 120.9, 88.9, 88.4, 85.1, 61.7, 52.0; HRMS (ESI) calcd. for C_{19}H_{16}NO_4 [M+H]^+: m/z 322.1079, found 322.1073.
3-Methyl-9-(trimethylsilyl)-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-23fa: Following general procedure F; Yield = 65% (123 mg, 0.45 mmol); Pale yellow solid; mp: 70-74 °C; Rf = 0.3 (EtOAc-hexanes, 3:7); IR (CH2Cl2): 3054, 2987, 1615, 1456, 1266, 845, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 7.25-7.13 (m, 4H), 5.40 (s, 1H), 4.81 (d, J = 7.7 Hz, 1H), 3.43 (d, J = 7.6 Hz, 1H), 2.03 (s, 3H), 0.31 (s, 9H); ¹³C NMR (100 MHz, CDCl3): δ 152.4, 146.0, 145.1, 127.1, 126.9, 121.0, 119.6, 89.8, 88.9, 80.4, 62.3, 12.2, -2.4; HRMS (ESI) calcd. for C₁₅H₂₀NO₂Si [M+H]⁺: m/z 274.1258, found 274.1263.

5,8-Dimethoxy-3,9-dimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-23ga and 5,8-dimethoxy-3,4-dimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-24ga: Following general procedure F; Yield = 96% (91.3 mg, 0.331 mmol, 3-23ga/3-24ga = 89:11 measured by ¹H NMR); Off-white solid; mp: 162-165 °C; Rf = 0.15 (EtOAc-hexanes, 2:8); IR (CH2Cl2): 3054, 2987,
1499, 1438, 1421, 1265, 896, 740, 704 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.65 (s, 2H), 5.55 (s, 0.11H), 5.41 (s, 0.89H), 4.92 (d, J = 8 Hz, 0.11H), 4.62 (d, J = 7.6 Hz, 0.89H), 3.77 (s, 3H), 3.75 (s, 3H), 3.52 (d, J = 7.5 Hz, 0.89H), 3.33 (d, J = 8 Hz, 0.11H), 2.09 (s, 0.33H), 2.04 (s, 2.67H), 1.93 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) major isomer 3-23ga: δ 152.7, 148.6, 146.5, 135.1, 132.4, 111.84, 111.80, 92.1, 86.9, 76.1, 63.3, 55.95, 55.90, 13.8, 11.9. Visible peaks for minor isomer 3-24ga: δ 152.0, 14.3, 126.9, 112.0, 111.6, 89.1, 88.6, 63.9, 55.9, 17.0, 13.5; HRMS (ESI) calcd. for C₁₅H₁₈NO₄ [M+H]+: m/z 276.1236, found 276.1236.

5,8-Dimethoxy-9-methyl-3-phenyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-23gb and 5,8-dimethoxy-4-methyl-3-phenyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole, cycloadduct 3-24gb: Following general procedure F; Yield = 91% (105 mg, 0.311 mmol, 3-23gb/3-24gb = 90:10 measured by ¹H NMR); Pale yellow solid, mp: 158-160 °C; R_f = 0.42 (EtOAc:hexanes = 30:70); IR (CH₂Cl₂): 2930, 2854, 1499, 1264, 1026, 740 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.77-7.74 (m, 2H), 7.46-7.34 (m, 3H), 6.72-6.67 (m, 2H), 5.66 (s, 0.1H), 5.56 (s, 0.9H), 5.16 (d, J = 7.5 Hz, 0.1H), 4.87 (d, J = 7.7 Hz, 0.9H), 4.06 (d, J = 7.7 Hz, 0.9H), 4.0 (d, J = 8 Hz, 0.1H), 3.85 (s, 3H), 3.79 (s, 3H), 2.03 (s, 2.7H), 1.65 (s, 0.3H); ¹³C NMR (75 MHz, CDCl₃) major isomer 3-23gb: δ 154.1, 148.6, 146.6, 135.2, 132.2, 130.1, 128.8, 128.7,
Visible peaks for minor isomer 3-24gb: δ 153.1, 147.5, 135.8, 129.7, 128.6, 126.9, 112.3, 111.7, 90.3, 81.0, 60.2, 17.8; HRMS (ESI) calcd. for C_{20}H_{20}NO_4 [M+H]^+: m/z 338.1392, found 338.1346.

3,8-Dimethyl-6-phenyl-3a,4,4a,7a,8,8a-hexahydro-5H-4,8-epoxyisoxazolo[4,5-f]isoindole-5,7(6H)-dione, cycloadduct 3-25a: Following general procedure G; Yield = 52% (90 mg, 0.288 mmol); White solid, mp: 287-288 °C; Rf = 0.13 (EtOAc-hexanes, 1:1); IR (CH_2Cl_2): 3054, 2987, 1718, 1652, 1422, 126, 896, 739 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 7.46-7.20 (m, 5H), 5.28 (s, 1H), 4.56 (d, J = 7.9 Hz, 1H), 3.60 (d, J = 7.8 Hz, 1H), 3.19 (d, J = 6.9 Hz, 1H), 2.84 (d, J = 6.9 Hz, 1H), 2.01 (s, 3H), 1.69 (s, 3H); ^13C NMR (100 MHz, DMSO-d6): δ 175.9, 174.4, 153.5, 132.2, 129.0, 128.5, 126.9, 89.9, 85.2, 78.1, 61.2, 50.1, 47.6, 12.4, 11.1; HRMS (ESI) calcd. for C_{17}H_{17}N_2O_4 [M+H]^+: m/z 313.1183, found 313.1188.
8-Ethyl-3-methyl-6-phenyl-3a,4,4a,7a,8,8a-hexahydro-5H-4,8-epoxyisoxazolo[4,5-f]isoindole-5,7(6H)-dione, cycloadduct 3-25b: Following general procedure G; Yield = 63% (118 mg, 0.361 mmol); White solid; mp: 283-284 °C; Rf = 0.1 (EtOAc-hexanes, 1:1); IR (CH₂Cl₂): 3054, 2988, 1716, 1394, 1265, 1196, 739 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 7.50-7.39 (m, 3H), 7.18 (d, J = 7.4 Hz, 2H), 4.89 (s, 1H), 4.80 (d, J = 8.3 Hz, 1H), 3.85 (d, J = 8.2 Hz, 1H), 3.38 (d, J = 7.1 Hz, 1H), 3.20 (d, J = 7.0 Hz, 1H), 2.03-1.96 (m, 1H), 1.94 (s, 3H), 1.77-1.68 (m, 1H), 1.09 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 175.8, 174.3, 153.5, 132.1, 129.0, 128.5, 126.8, 93.9, 83.5, 77.8, 60.8, 50.0, 45.9, 20.0, 11.1, 8.8; HRMS (ESI) calcd. for C₁₈H₁₉N₂O₄ [M+H]⁺: m/z 327.1339, found 327.1344.
8-Acetyl-3-methyl-6-phenyl-3a,4,4a,7a,8,8a-hexahydro-5H-4,8-epoxyisoazololo[4,5-f]isoindole-5,7(6H)-dione, cycloadduct 3-25d: Following general procedure G; Yield = 14% (5 mg, 0.0147 mmol); White solid; mp: 295-296 °C; R_f = 0.25 (100% EtOAc); IR (CH_2Cl_2): 3054, 2987, 1780, 1717, 1652, 1422, 1265, 1197, 739 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.50-7.40 (m, 3H), 7.16 (d, J = 7.5 Hz, 2H), 5.28 (d, J = 8 Hz, 1H), 5.12 (s, 1H), 3.99 (d, J = 7.9 Hz, 1H), 3.70 (d, J = 7.1 Hz, 1H), 3.45 (d, J = 7.1 Hz, 1H), 2.25 (s, 3H), 1.97 (s, 3H); ^13C NMR (100 MHz, DMSO-d_6): δ 200.4, 175.1, 173.8, 153.7, 131.8, 129.0, 128.6, 126.7, 96.9, 84.6, 78.7, 61.2, 49.0, 47.6, 28.1, 11.0; HRMS (EI) calcd. for C_{18}H_{16}N_{2}O_{5} [M]^+: m/z 340.1059, found 340.1072.

5-Methyl-3,8-dioxo-4,9-diaza-tricyclo[5.2.1.0^{2,6}]dec-4-ene-9-carboxylic acid tert-butyl ester, cycloadduct 3-27aa: Following general procedure F; Yield = 13% (5 mg, 0.019 mmol); White solid; mp: 103-105 °C; R_f = 0.34 (EtOAc:hexanes = 40:60); IR
(CH$_2$Cl$_2$): 2976, 2925, 1738, 1706, 1448, 1370, 1326, 1250, 1160, 1061, 1035, 925 cm$^{-1}$; 
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 4.81 (d, J = 8.2Hz, 1H), 4.73 (s, 1H), 4.7 (s, 1H), 3.55 (d, J = 8.2Hz, 1H), 1.93 (s, 3H), 1.90-1.83 (m, 2H), 1.47 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.4, 153.4, 83.0, 81.7, 78.4, 62.3, 60.5, 32.1, 28.1, 11.9; HRMS (ESI) calcd. for C$_{12}$H$_{18}$N$_2$O$_4$Na $[M+Na]^+$: m/z 277.1164, found 277.1164.

5-Methyl-3,9-dioxa-4,8-diaza-tricyclo[5.2.1.0$^{2,6}$]dec-4-ene-8-carboxylic acid tert-butyl ester, cycloadduct 3-28aa: White solid; Yield = 39% (15 mg, 0.059 mmol); mp: 139-141 °C; R$_f$ = 0.57 (EtOAc:hexanes = 40:60); IR (CH$_2$Cl$_2$): 2984, 1694, 1375, 1348, 1327, 1255, 1157, 1037, 939, 855, 776 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 4.76 (d, J = 6.8Hz, 1H, this doublet is merged with singlet at $\delta$ 4.75), 4.75 (s, 1H), 4.62 (s, 1H), 3.57 (d, J = 8.4Hz, 1H), 1.97 (s, 3H), 1.85-1.77 (m, 2H), 1.48 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.2, 153.7, 83.1, 81.7, 78.4, 60.1, 59.2, 32.1, 28.0, 11.7; HRMS (ESI) calcd. for C$_{12}$H$_{18}$N$_2$O$_4$Na $[M+Na]^+$: m/z 277.1164, found 277.1158.

5-Phenyl-3,8-dioxa-4,9-diaza-tricyclo[5.2.1.0$^{2,6}$]dec-4-ene-9-carboxylic acid tert-butyl ester, cycloadduct 3-27ab and 5-Phenyl-3,9-dioxa-4,8-diaza-tricyclo[5.2.1.0(2,6)]dec-4-ene-8-carboxylic acid tert-butyl ester, cycloadduct 3-28ab:

Following general procedure F; Yield = 78% (86 mg, 0.27 mmol, 3-27ab/3-28ab = 50:50 measured by $^1$H NMR); White solid; MP: 120-125 °C (partial melting), 150-153 °C; R$_f$ = 0.55 (EtOAc:hexanes = 30:70); IR (CH$_2$Cl$_2$): 2963, 2926, 1741, 1706, 1446, 1393,
1369, 1251, 1157, 1055, 887, 763 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.75-7.73 (m, 2H), 7.69-7.67 (m, 2H), 7.43-7.38 (m, 6H), 5.02 (dd, J₁ = 8.4Hz, J₂ = 1.1Hz, 1H), 4.96 (dd, J₁ = 8.4Hz, J₂ = 1.1Hz, 1H), 4.89 (s, 1H); 4.84 (s, 1H), 4.80 (s, 1H); 4.75 (s, 1H), 4.11 (d, J = 8.3Hz, 2H), 2.02-1.86 (m, 4H), 1.52 (s, 18H), 1.50 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 156.7, 156.2, 155.1, 154.9, 130.5, 128.9, 127.7, 127.6, 126.6, 126.5, 83.0, 82.9, 82.7, 80.1, 79.1, 62.2, 59.9, 57.1, 55.3, 32.4, 32.2, 28.0; HRMS (ESI) calcd. for C₁₇H₂₁N₂O₄[M+H]⁺: m/z 317.1501, found 317.1515.

(5-Methyl-3,8-dioxa-4,9-diaza-tricyclo[5.2.1.0²,⁶]dec-4-en-9-yl)-phenyl-methanone 3-27ba: Following general procedure F; Yield = 26% (23 mg, 0.089 mmol); Pale yellow solid; mp: 125-128 °C; Rₛ = 0.19 (EtOAc:hexanes = 40:60); IR (CH₂Cl₂): 2959, 1663, 1448, 1077, 924, 861, 704 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.69 (d, J = 7.4Hz, 2H), 7.50-7.47 (m, 1H), 7.42-7.38 (m, 2H), 4.97 (s, 1H), 4.96 (d, J = 8.4Hz, 1H) 4.87 (s, 1H), 4.84 (s, 1H), 3.67 (d, J = 8.0Hz, 1H), 2.02-1.93 (m, 2H), 1.95 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.0, 153.3, 132.8, 131.9, 128.6, 128.3, 85.4, 79.1, 62.0, 60.6, 32.4, 11.9; HRMS (EI) calcd. for C₁₄H₁₄N₂O₃ [M⁺]: m/z 258.1004, found 258.1001.

(5-Methyl-3,9-dioxa-4,8-diaza-tricyclo[5.2.1.0²,⁶]dec-4-en-8-yl)-phenyl-methanone, 3-28ba: Yield = 61% (55 mg, 0.21 mmol); Pale yellow solid; mp: 48-50 °C; Rₛ = 0.3 (EtOAc:hexanes = 40:60); IR (CH₂Cl₂): 2963, 1660, 1448, 1179, 941, 861, 703 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.76 (d, J = 7.4Hz, 2H), 7.52-7.48 (m, 1H), 7.42-7.38 (m,
Phenyl-(5-phenyl-3,8-dioxa-4,9-diaza-tricyclo[5.2.1.0²⁶]dec-4-en-9-yl)-methanone, 3-27bb: Following general procedure F; Yield =47% (52.2 mg, 0.16 mmol); Pale yellow solid; mp:120-123 °C; Rf = 0.38 (EtOAc:hexanes = 30:70); IR (CH₂Cl₂): 2924, 2854, 1719, 1712, 1597, 1498, 1387, 1196, 891, 714 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.75-7.62 (m, 4H); 7.54-7.41 (m, 6H), 5.20 (d, J = 11.4Hz, 1H), 5.10 (s, 1H), 5.0 (s, 1H), 4.22 (d, J = 8.3Hz, 1H), 2.05 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 172, 153.8, 132.4, 132.0, 129.1, 128.0, 81.5, 80.9, 58.7, 32.4, 11.7; HRMS (ESI) calcd. for C₁₄H₁₅N₂O₃ [M+H]⁺: m/z 259.1083, found 259.1081.

Phenyl-(5-phenyl-3,8-dioxa-4,9-diaza-tricyclo[5.2.1.0²⁶]dec-4-en-9-yl)-methanone, 3-28bb:  Yield = 31% (34.8 mg, 0.11 mmol); Yellow solid; mp: 172-174 °C; Rf = 0.28 (EtOAc:hexanes = 30:70); IR (CH₂Cl₂): 3055, 2986, 1668, 1448, 1422, 1354, 1265, 938, 895, 739 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.81 (d, J = 7.6Hz, 2H), 7.76-7.68 (m, 6H), 7.55-7.48 (m, 6H), 5.10 (s, 1H), 5.0 (d, J = 8.3Hz, 1H), 4.91 (s, 1H), 4.31 d, J = 8.4Hz, 1H), 2.1-2.0 (m, 2H); ¹³C NMR (CDCl₃): δ 171.1, 155.3, 132.8, 132.2,
130.8, 129.2, 129.1, 128.2, 127.6, 126.9, 82.7, 81.2, 59.0, 55.5, 32.7; HRMS (ESI) calcd. for C\textsubscript{19}H\textsubscript{17}N\textsubscript{2}O\textsubscript{3} [M+H]\textsuperscript{+}: m/z 321.1239, found 321.1223.

**General Procedure H:** Cleavage of Symmetrical 2-isoxazolines 4-9, 4-36 (Table 4.1, and 4.4) and 4-30 (Scheme 4.13):

A solution of methanol (25.0 mL) and deionized water (5.0mL) was added to an oven-dried flask containing the isoxazoline (102 mg, 0.5 mmol), and the mixture was cooled to 0-5 °C. AlCl\textsubscript{3} (200 mg, 1.5 mmol) was added to the cold solution in one portion and maintained for 15 minutes. Raney-nickel (1.2 g) was added and the reaction was stirred for 4 hours. The solution was filtered through a pad of celite, the filter cake was washed with methanol and the solvent was then removed by rotary evaporation. The organic mixture was extracted with dichloromethane, dried over sodium sulphate and concentrated by rotary evaporation. Following addition of hexanes (3-5 mL), the crude product was allowed to stir at room temperature for 30 minutes and was then filtered to afford pure β-hydroxyketone (95 mg, 0.465 mmol, 93%) as a white solid.

**General Procedure I:** Cleavage of Unsymmetrical 2-isoxazolines 4-32 and 4-34 (Table 4.2, 4.3):

Following General Procedure H (above), THF was added as a co-solvent of varying quantities: For every 0.15 mmol of isoxazoline 6g-l, the relative solvent ratio was modified to 5:5:2 (THF:MeOH:water) using THF (5 mL), MeOH (5 mL), and distilled water (2 mL). For every 0.15 mmol of isoxazolines 10a-b, the solvent ratio was modified to 15:5:2 using THF (15 mL), MeOH (5 mL) and distilled water (2 mL).
1-(3-hydroxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one, 3-27aa:

Following general procedure H; Yield = 93% (95 mg, 0.465 mmol); Off-white solid; mp: 137-140 °C; R_f = 0.2 (EtOAc-hexanes, 4:6); IR (CH_2Cl_2): 3055, 2987, 1712, 1442, 1265, 738 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 7.32-7.30 (m, 1H), 7.18-7.14 (m, 3H), 5.54 (s, 1H), 5.17 (s, 1H); 4.39 (dd, J = 10.8 Hz, 7.0 Hz, 1H), 2.95 (d, J = 6.8 Hz, 1H), 2.72 (d, J = 10.8 Hz, 1H), 2.25 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ 207.3, 145.7, 141.6, 127.8, 127.1, 121.1, 118.9, 85.8, 79.7, 73.8, 58.1, 31.6; HRMS (ESI) calcd. for C_{12}H_{11}O_3 [M-H]^-: m/z 203.0708, found 303.0701.

1-(3-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one, 4-27ba:

Following general procedure H; Yield = 94% (38 mg, 0.143); Off-white solid; mp: 126-128 °C; R_f = 0.2 (EtOAc-hexanes, 4:6); IR (CH_2Cl_2): 3054, 2987, 1716, 1501, 1265, 739 cm^{-1}; ^1H NMR (400 MHz, CDCl_3): δ 6.66-6.61 (m, 2H), 5.66 (s, 1H), 5.31 (s, 1H), 4.39(dd, J = 10.6 Hz, 6.9 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.96 (d, J = 6.7 Hz, 1H), 2.56 (d, J = 10.7 Hz, 1H), 2.25 (s, 3H); ^13C NMR (100 MHz, CDCl_3): δ 207.5, 147.9, 146.2, 134.8, 130.5, 112.1, 111.4, 83.8, 77.8, 73.5, 57.3, 56.0, 31.5; HRMS (EI) calcd. for C_{13}H_{16}O_5 [M-H]: m/z 263.0919, found 263.0913.
1-\((\text{-3-Hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl})\)ethan-1-one, \textbf{4-27ca}: \hspace{1em} Following general procedure \(\text{H}\); Yield = 87\% (60 mg, 0.227 mmol); Off-white solid; mp: 144-145 °C; \(R_f = 0.12\) (EtOAc-hexanes, 6:4); IR (CH\(_2\)Cl\(_2\)): 3055, 2987, 1712, 1492, 1266, 1090, 739 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.90 (s, 1H), 6.80 (s, 1H), 5.47 (s, 1H), 5.10 (s, 1H), 4.33 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.90 (d, \(J = 6.7\) Hz, 1H), 2.61 (br s, 1H), 2.24 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 207.5, 148.8, 148.2, 138.1, 133.7, 105.5, 103.5, 86.0, 80.0, 74.1, 58.5, 56.4, 56.3, 31.5; HRMS (ESI) calcd. for C\(_{14}\)H\(_{16}\)O\(_5\) [M-H]: m/z 263.0925, found 263.0928.

1-\((\text{-3-Hydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl})\)ethan-1-one, \textbf{4-27da}: \hspace{1em} Following general procedure \(\text{H}\); Yield = 76\% (35 mg, 0.15 mmol); White solid; mp: 155-157 °C; \(R_f = 0.25\) (EtOAc-hexanes, 4:6); IR (CH\(_2\)Cl\(_2\)): 3054, 2987, 1713, 1422, 1265, 896, 740 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.88-6.83 (m, 2H), 5.58 (s, 1H), 5.21 (s, 1H), 4.36 (dd, \(J = 11.1\) Hz, 6.6 Hz, 1H), 2.92 (d, \(J = 6.8\) Hz, 1H), 2.70 (d, \(J = 11.1\) Hz, 1H), 2.29 (s, 3H), 2.26 (s, 3H), 2.25 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 207.5, 143.9, 139.7, 129.0, 128.4, 128.3, 126.0, 84.8, 78.5, 73.4, 57.4, 31.5, 18.0, 17.8; HRMS (ESI) calcd. for C\(_{14}\)H\(_{15}\)O\(_3\) [M-H]: m/z 231.1027, found 231.1030.
1-(6,7-Dibromo-3-hydroxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one, 4-27ea: Following general procedure H; Yield = 71% (30 mg, 0.082 mmol); Pale yellow solid; mp: 162-164 °C; Rf = 0.22 (EtOAc-hexanes, 4:6); IR (CH2Cl2): 3054, 2986, 1715, 1422, 1265, 1026, 896, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 7.57 (s, 1H), 7.47 (s, 1H), 5.51 (s, 1H), 5.12 (s, 1H), 4.39 (dd, J = 10.9 Hz, 6.6 Hz, 1H), 2.96 (d, J = 6.5 Hz, 1H), 2.46 (d, J = 10.9 Hz, 1H), 2.25 (s, 3H); ¹³C NMR (100 MHz, CDCl3): δ 206.3, 146.7, 142.7, 126.4, 124.4, 123.9, 123.1, 85.1, 79.2, 73.3, 57.6, 31.5; HRMS (ESI) calcd. for C₁₂H₉⁷⁹Br₂O₃ [M-H]⁻: m/z 358.8918, found 358.8911.

1-(3-Hydroxy-4-methyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one, 4-33a: Following general procedure I; Yield = 80% (25 mg, 0.114 mmol); White solid; mp: 161-163 °C; Rf = 0.12 (EtOAc-hexanes, 3:7) IR (CH₂Cl₂): 3420, 3055, 2987, 1710, 1422, 1265, 896, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.22-7.14 (m, 4H), 5.42 (s, 1H), 4.13 (dd, J = 10.7 Hz, 6.9 Hz, 1H), 3.05 (d, J = 6.9 Hz, 1H), 2.50 (d, J = 10.9 Hz, 1H), 2.26 (s, 3H), 1.76 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 207.8, 146.6, 145.0, 127.3, 127.1, 120.0, 118.5, 89.1, 78.7, 75.2, 59.2, 31.6, 12.9; HRMS (ESI) calcd. for C₁₃H₁₅O₃ [M+H]⁺: m/z 219.1016, found 219.1021.
1-(4-Ethyl-3-hydroxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one, 4-33b: Following general procedure I; Yield = 95% (38 mg, 0.163 mmol); White solid; mp: 171-173 °C; Rf = 0.3 (EtOAc-hexanes, 3:7); IR (CH2Cl2): 3419, 3054, 2987, 1701, 1635, 1422, 1265, 896, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 7.25-7.18 (m, 4H), 5.43 (s, 1H), 4.17 (dd, J = 11.1 Hz, 6.8 Hz, 1H), 3.03 (d, J = 6.8 Hz, 1H), 2.44 (d, J = 11.2 Hz, 1H), 2.33-2.24 (m, 1H), 2.25 (s, 3H), 2.19-2.09 (m, 1H), 1.09 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl3): δ 207.9, 147.2, 143.3, 127.5, 127.0, 120.8, 118.7, 92.7, 78.6, 74.9, 59.3, 31.6, 19.8, 8.72; HRMS (ESI) calcd. for C₁₄H₁₇O₃ [M+H]⁺: m/z 233.1172, found 233.1168.

1-(3-Hydroxy-4-(hydroxymethyl)-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one, 4-33d: Following general procedure I; Yield = 85% (35 mg, 0.15 mmol); White solid; mp: 160-163 °C; Rf = 0.12 (EtOAc-hexanes, 1:1); IR (CH₂Cl₂): 3054, 2987, 1705, 1422, 1265, 896, 739 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): 7.34-7.32 (m, 1H), 7.20-7.18 (m, 3H), 5.53 (s, 1H), 4.50-4.40 (m, 3H), 3.04 (d, J = 6.9 Hz, 1H), 2.27 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 205.8, 147.3, 144.5, 126.7, 126.1, 121.0, 118.7, 90.9, 77.5, 73.0, 59.0, 58.1, 30.4; HRMS (ESI) calcd. for C₁₃H₁₅O₄ [M+H]⁺: m/z 235.0970, found 235.0972.
1,1'-(2-Hydroxy-3,4-dihydro-1,4-epoxynaphthalene-1,3(2H)-diyl)bis(ethan-1-one), 4-33e: Following general procedure I; Yield = 69% (9 mg, 0.036 mmol); White solid; mp: 105-110 °C; R_f = 0.29 (EtOAc-hexanes, 3:7, 2 elutions); IR (CH_2Cl_2): 3054, 2987, 1715, 1635, 1422, 1265, 896, 742 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl_3): δ 7.34 (d, \(J = 7.2\) Hz, 1H), 7.23-7.15 (m, 3H), 5.62 (s, 1H), 4.60 (dd, \(J = 7.2\) Hz, 6.8 Hz, 1H), 2.98-2.95 (m, 2H), 2.38 (s, 3H), 2.27 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl_3): δ 206.7, 206.0, 145.0, 140.7, 128.4, 127.3, 120.5, 119.1, 96.0, 79.1, 75.4, 58.0, 31.3, 28.8; HRMS (EI) calcd. for \(C_{14}H_{14}O_4\)[M]^+: m/z 246.0892, found 246.0887.

Methyl-3-acetyl-2-hydroxy-3,4-dihydro-1,4-epoxynaphthalene-1(2H)-carboxylate, 4-33f: Following general procedure I; Yield = 85% (25 mg, 0.095 mmol); White solid; mp: 92-95 °C; R_f = 0.29 (EtOAc-hexanes, 1:1); IR (CH_2Cl_2): 3054, 2987, 1763, 1716, 1442, 1265, 896, 735 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl_3): δ 7.51 (d, \(J = 6.4\) Hz, 1H), 7.25-7.19 (m, 3H), 5.60 (s, 1H), 4.56 (dd, \(J = 10.0\) Hz, 6.8 Hz, 1H), 3.95 (s, 3H), 3.0(d, \(J = 7.2\) Hz, 1H), 2.95 (d, \(J = 10.0\) Hz, 1H), 2.27 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl_3): δ 206.2,
167.2, 144.8, 139.9, 128.6, 127.3, 121.2, 119.0, 91.8, 79.2, 75.5, 57.9, 52.8, 31.4; HRMS (ESI) calcd. for C_{14}H_{15}O_5 [M+H]^+: m/z 263.0919, found 263.0915.

1-(3-Hydroxy-5,8-dimethoxy-4-methyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one, 4-33g: Following general procedure I; Yield = 86% (52 mg, 0.187 mmol); White solid; mp: 130-132 °C; R_f = 0.24 (EtOAc-hexanes, 3:7); IR (CH_2Cl_2): 3055, 2987, 1712, 1500, 1442, 1265, 896, 736 cm^{-1}; \(^1\)H NMR (400 MHz, CDCl_3): δ 6.64 (s, 2H), 5.51 (s, 1H), 4.18 (dd, J = 10.8 Hz, 6.8 Hz, 1H), 3.74 (s, 6H), 3.02 (d, J = 6.8 Hz, 1H), 2.55 (m, 1H), 2.25 (s, 3H), 1.83 (s, 3H); \(^13\)C NMR (100 MHz, CDCl_3): δ 208.2, 148.5, 145.8, 136.0, 132.7, 111.9, 111.5, 89.9, 76.4, 75.0, 58.4, 56.0, 55.9, 31.5, 14.0; HRMS (ESI) calcd. for C_{15}H_{19}O_5 [M+H]^+: m/z 279.1232, found 279.1228.

6-Acetyl-5-hydroxy-4-methyl-2-phenylhexahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione, 4-35a: Following general procedure I; Yield = 80% (40 mg, 0.126 mmol); Off-white solid; mp: 252-253 °C; R_f = 0.4 (EtOAc, 100 %); IR (CH_2Cl_2): 3054, 2987, 1713, 1422, 1265, 896, 746 cm^{-1}; \(^1\)H NMR (300 MHz, DMSO-d_6): δ 7.50-7.38 (m, 3H), 7.19 (d, J = 7.2 Hz, 2H), 5.64 (d, J = 6.2 Hz, 1H), 4.82 (s, 1H), 4.26-4.22 (m, 1H), 3.23-3.16
(m, 2H), 2.97 (d, J = 6.9 Hz, 1H), 2.07 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ 204.2, 176.3, 175.0, 132.2, 128.9, 128.3, 126.8, 88.0, 77.0, 75.2, 60.1, 50.7, 48.5, 30.4, 12.7; HRMS (ESI) calcd. for C$_{17}$H$_{18}$NO$_5$ [M+H]$^+$: m/z 316.1179, found 316.1185.

6-Acetyl-4-ethyl-5-hydroxy-2-phenylhexahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione, 4-35b: Following general procedure I; Yield = 70% (35 mg, 0.106 mmol); Off-white solid; mp: 238-240 °C; R$_f$ = 0.4 (EtOAc, 100%); IR (CH$_2$Cl$_2$): 3054, 2987, 1716, 1422, 1265, 896 cm$^{-1}$; $^{1}$H NMR (300 MHz, DMSO-d$_6$): δ 7.55-7.35 (m, 3H), 7.25-7.10 (m, 2H), 5.61 (d, J = 5.3 Hz, 1H), 4.83(s, 1H), 4.5-4.3 (m, 1H), 3.25-3.05 (m, 3H), 2.2-1.95 (m, 4H), 1.65-1.45 (m, 1H), 1.15-0.95(bs , 3H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ 204.2, 176.2, 174.9, 132.2, 128.9, 128.3, 126.8, 91.7, 76.9, 73.2, 59.9, 50.4, 47.0, 30.4, 20.1, 8.3; HRMS (EI) calcd. for C$_{18}$H$_{19}$NO$_5$ [M]$^+$: m/z 329.1263, found 329.1277.

1-(2-Acetyl-3-hydroxy-1,2,3,4-tetrahydro-1,4-epiminonaphthalen-9-yl)-2,2-dimethylpropan-1-one, 4-37a: Following general procedure H; Yield = 66% (40 mg, 0.139 mmol); Light brown solid; mp: 162-164 °C; R$_f$ = 0.34 (EtOAc-hexanes, 1:1); IR
(CH₂Cl₂): 3054, 2987, 1715, 1422, 1265, 896, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.30 (m, 1H), 7.22-7.14 (m, 3H), 5.69 (s, 1H), 5.42 (s, 1H), 4.33 (dd, J₁ = 9 Hz, J₂ = 7.1 Hz, 1H), 3.4 (br s, 1H); 2.85 (d, J = 6.9 Hz, 1H), 2.26 (s, 3H), 1.2 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 207 (C=O, from HMBC), 179 (N-C=O, from HMBC) 145.5, 141.6, 127.6, 127.0, 121.6, 119.4, 78.0 (C-H from HMBC), 74.0 (C-H, from HSQC), 68.7, 61.8, 39.5, 31.1, 27.7; HRMS (ESI) calcd. for C₁₇H₂₂NO₃ [M+H]⁺: m/z 288.1599, found 2888.1610

1-(3-Hydroxy-5,6-bis(methoxymethyl)-7-oxabicyclo[2.2.1]heptan-2-yl)ethan-1-one, 4-31: Following general procedure H; Yield = 82 % (40 mg, 0.163 mmol); White solid; mp: 72-74 °C; Rᵣ = 0.13 (EtOAc, 100 %); IR (CH₂Cl₂): 3054, 2987, 1714, 1422, 1265, 896, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 4.68 (d, J = 0.9 Hz, 1H), 4.29 (dd, J₁ = 9.6 Hz, J₂ = 7 Hz, 1H), 4.19 (d, J = 0.9 Hz, 1H), 3.36-3.19 (m, 10H), 2.94 (d, J = 6.9 Hz, 1H), 2.38 (d, J = 10.1 Hz, 1H), 2.19 (s, 3H), 2.0-1.94 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 206.2, 84.9, 79.1, 75.6, 70.4, 60.7, 58.9, 58.8, 44.8, 40.5, 31.3; HRMS (ESI) calcd. for C₁₁H₂₀O₅ [M-H]⁻: m/z 243.1232, found 243.1237.
6.2 Appendix
$^1$H NMR of exo-1-ethyl-4,10-dioxatricyclo[5.2.1.0$^{2,6}$]dec-8-ene-3,5-dione
13C NMR of 1-ethyl-4,10-dioxatricyclo[5.2.1.0^2,6]dec-8-ene-3,5-dione in CDCl3 on 400MHz.

Quaternary and CH2 up, CH3 and CH down.

 NMRCENTRE
 UNIVERSITY OF GUELPH

NAME: JN-31-1
PROCNO: 1
DATE: 20120508
TIME: 14:26
INSTRUM:
spect
POWDER: 5 mm PAAMM BR
PULPROG: jmod
T2: 65536
SOLVENT: CDCl3
NS: 156
DS: 0
SNH: 22058.624 Hz
FIDRES: 0.33859 Hz
AQ: 1.4855326 sec
AQ: 203
DM: 22.667 usec
DE: 6.50 usec
TR: 296.6 K
CHST2: 145.0000000
CHST1: 1.0000000
DI: 5.00000000 sec
DD: 0.00683655 sec
TO: 1

----- CHANNEL F1 -----  
NC1: 13C
P1: 9.00 usec
P2: 18.00 usec
P3: 3.00 dB
P12: 72.6724666 MHz
SP1: 100.6233333 MHz

----- CHANNEL F2 -----  
NC2: 1H
P12: 80.00 usec
P2: -1.20 dB
P12: 14.00 dB
PL12: 13.4281947 MHz
PL12: 0.40500000 MHz
SP2: 400.1316055 MHz
SI: 32768
SF: 100.6127953 MHz
MV: 0
SSB: 0
LB: 1.00 Hz
GB: 0
PC: 1.40
\[^{1}\text{H}\text{ NMR of exo-1-ethyl-4-phenyl-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione}^\]
JN-86-2 in CDCl$_3$ on 100MHz
Jmod 256 scans
Quaternary and CH2 up, CH3 and CH down
$^1$H NMR of 3,5,8-trimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole
13C NMR of 3,5,8-trimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole

**C NMR of 3,5,8-trimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole**

**NMR CENTRE**
**UNIVERSITY OF GUELPH**

**NMR**
- **Sample:** JN-135
- **Experiment:** 1
- **Run:** 1
- **Date:** 20101026
- **Time:** 13:12
- **Instrument:** spect.
- **Probes:** 8 mm PABBO BB.
- **Software:** jmod
- **TD:** 6536
- **Solvent:** CDCl3
- **NS:** 112
- **DS:** 0
- **SW:** 22058.824 Hz
- **FIDRES:** 0.336591 Hz
- **AQ:** 1.4855326 sec
- **RG:** 203
- **DM:** 22.667 usec
- **DE:** 6.50 usec
- **TE:** 297.7 K
- **CHST:** 145.000000
- **CHST1:** 1.000000
- **D1:** 5.00000000 sec
- **D0:** 0.00089655 sec

**CHANNEL C1**
- **NOC1:** 13C
- **P1:** 9.60 usec
- **P2:** 18.00 usec
- **P12:** -3.00 dB
- **PL1W:** 72.6724966 W
- **ST01:** 100.6233333 MHz

**CHANNEL C2**
- **CPD**
- **P1:** 80.00 usec
- **P2:** -1.20 dB
- **P12:** 14.00 dB
- **PL1W:** 13.4308347 W
- **PL12W:** 0.4000000 W
- **SFO2:** 400.1314005 MHz
- **S1:** 12768
- **SF:** 100.6177690 MHz
- **MW:** 0
- **SSB:** 0
- **BG:** 1.00 usec
- **FC:** 1.40
$^1$H NMR of 8,9-bis-methoxymethyl-5-methyl-3,10-dioxo-4-aza-tricyclo[5.2.1.0$^{2,6}$]dec-4-ene
\[^{13}\text{C} \text{NMR of 8,9-bis-methoxymethyl-5-methyl-3,10-dioxa-4-aza-tricyclo[5.2.1.0^2,6]} \text{dec-4-ene}\]
$^1$H NMR of methyl-3-methyl-3a,9a-dihydro-4,9-epoxynaphtho[2,3-d]isoxazole-9(4H)-carboxylate
$^{13}$C NMR of methyl-3-methyl-3,9-dihydro-4,9-epoxynaphtho[2,3-d]isoxazole-9(4H)-carboxylate
$^1$H NMR of 5,8-dimethoxy-3,9-dimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole
$^{13}$C NMR of 5,8-dimethoxy-3,9-dimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-

JN-218 in CDCl$_3$ on 100 MHZ (imod)
Quaternary and CH$_2$ up, CH$_3$ and CH down
Molecular structure of 5,8-dimethoxy-3,9-dimethyl-3a,4,9,9a-tetrahydro-4,9-epoxynaphtho[2,3-d]isoxazole from X-Ray Diffraction analysis
$^1$H NMR of 3,8-dimethyl-6-phenyl-3a,4,4a,7a,8,8a-hexahydro-5H-4,8-
epoxyisoxazolo[4,5-f]isoindole-5,7(6H)-dione
\( ^{13}\text{C} \) NMR of 3,8-dimethyl-6-phenyl-3a,4,4a,7a,8,8a-hexahydro-5H-4,8-epoxyisoxazolo[4,5-f]isoindole-5,7(6H)-dione
H NMR of (5-methyl-3,8-dioxa-4,9-diaza-tricyclo[5.2.1.0\(^2,6\)]dec-4-en-9-yl)-phenyl-methanone
$^{13}$C NMR of (5-methyl-3,8-dioxo-4,9-diaza-tricyclo[5.2.1.0$^{2,6}$]dec-4-en-9-yl)-phenyl-methanone
H NMR of (5-methyl-3,9-dioxaocta-4,8-diaza-tricyclo[5.2.1.0²,6]dec-4-en-8-y1)phenyl-methanone
$^{13}C$ NMR of (5-methyl-3,9-dioxa-4,8-diaza-tricyclo[5.2.1.0$^{2,6}$]dec-4-en-8-yl)phenyl-methanone

**JN-23-1 in CDCl$_3$ (100MHz)**

CH2 and quaternary up, CH3 and CH down

<table>
<thead>
<tr>
<th>Peak</th>
<th>v(F1) [ppm]</th>
<th>v(F1) [Hz]</th>
<th>Intensity [abs]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>153.7755</td>
<td>15472.082</td>
<td>19169035.51</td>
</tr>
<tr>
<td>2</td>
<td>132.4361</td>
<td>13324.764</td>
<td>1527137.19</td>
</tr>
<tr>
<td>3</td>
<td>132.045</td>
<td>13285.414</td>
<td>758355.69</td>
</tr>
<tr>
<td>4</td>
<td>129.0539</td>
<td>12987.48</td>
<td>-10491452.81</td>
</tr>
<tr>
<td>5</td>
<td>128.0578</td>
<td>12884.211</td>
<td>-11529683.34</td>
</tr>
<tr>
<td>6</td>
<td>81.5638</td>
<td>8206.3404</td>
<td>-7040396.66</td>
</tr>
<tr>
<td>7</td>
<td>80.538</td>
<td>8143.4775</td>
<td>-5208330.19</td>
</tr>
<tr>
<td>8</td>
<td>77.3207</td>
<td>7779.4504</td>
<td>4553306.44</td>
</tr>
<tr>
<td>9</td>
<td>77.0024</td>
<td>7747.4254</td>
<td>5451014.44</td>
</tr>
<tr>
<td>10</td>
<td>75.5847</td>
<td>7715.6007</td>
<td>5002203.75</td>
</tr>
<tr>
<td>11</td>
<td>58.7459</td>
<td>5910.6888</td>
<td>5526658.03</td>
</tr>
<tr>
<td>12</td>
<td>57.4896</td>
<td>5785.0239</td>
<td>-618287.75</td>
</tr>
<tr>
<td>13</td>
<td>32.4441</td>
<td>3284.291</td>
<td>9252548.84</td>
</tr>
<tr>
<td>14</td>
<td>11.6794</td>
<td>1175.9898</td>
<td>-6052825.62</td>
</tr>
</tbody>
</table>

ppm
Molecular structure of (5-methyl-3,9-dioxa-4,8-diaza-tricyclo[5.2.1.0²⁶]dec-4-en-8-yl)-phenyl-methanone from X-Ray Diffraction analysis
\[^1\text{H}\text{ NMR of } 1-(3\text{-hydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl})\text{ethan-1-one} \]
C NMR of 13-hydroxy-5,8-dimethyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-one

JN-196 in CDCl3 on 100MHz
Quaternary and CH2 up, CH3 and CH down

---

**NMRCENTRE UNIVERSITY OF GUELPH**

**NAME** JN-196

**SEIRHO** 3

**PROCNO** 1

**Date** 20110605

**Time** 18:04

**INSTRUM** spect

**PROBHD** 5 mm PARBO BB

**POLPROG** nmod

**TD** 65536

**SOLVENT** CDCl3

**NS** 211

**DS**

**SNR** 22058.824 Hz

**PIDRES** 0.336591 Hz

**A0** 1.4855326 sec

**NQ** 204

**DW** 22.467 usec

**D0** 6.50 usec

**TE** 297.1 K

**CETU2** 145.0000000

**CETU1** 1.0000000

**DI** 5.000000000 sec

**D20** 0.00689655 sec

**TD0** 1

---------- CHANNEL F1 ----------

**MUC2** 13C

**DI** 9.00 usec

**D1** 18.00 usec

**PL** 3.00 dB

**PLW** 72.67214966 W

**BFO1** 100.6233333 MHz

---------- CHANNEL F2 ----------

**CFBFRG2** 18t16

**MUC2** 1R

**PCF52** 80.00 usec

**PL2** -1.20 dB

**PL12** 14.00 dB

**PL2W** 13.41081047 W

**PL12W** 0.40400000 W

**BFO2** 400.131605 MHz

**SI** 32768

**CR** 100.6197699 MHz

**MDM** EM

**SEB** 0

**LS** 1.00 Hz

**DG** 0

**PC** 1.40
$^1$H NMR of 1-(3-hydroxy-5,8-dimethoxy-4-methyl-1,2,3,4-tetrahydro-1,4-
epoxynaphthalen-2-yl)ethan-1-one
$^{13}$C NMR of 13-hydroxy-5,8-dimethoxy-4-methyl-1,2,3,4-tetrahydro-1,4-
epoxynaphthalen-2-yl)ethan-1-one

NMR CENTRE
UNIVERSITY OF GUELPH

**NMR Parameters**

- **Sample**: JN-222
- **Set/Mode**: 2
- **Date**: 20111001
- **Time**: 14:33
- **Instrument**: spect
- **Pulse Program**: 5 mm PARBO 8B
- **T0**: 65.516
- **Solvent**: CDCl$_3$
- **DS**: 350
- **SNR**: 22058.824 Hz
- **FID RES**: 0.336591 Hz
- **AQ**: 1.4850436 sec
- **BG**: 203
- **DW**: 22.677 usec
- **DT**: 5.000000000 sec
- **DD**: 0.00689655 sec
- **TD**: 1

**Channel 1**

- **NUC**: 13C
- **P1**: 9.00 usec
- **P2**: 18.00 usec
- **PL**: -3.00 db
- **PL1**: 72.672048466 W
- **SF01**: 100.623333 MHz

**Channel 2**

- **NUC**: 1H
- **PCD2**: 80.00 usec
- **PL2**: -1.20 db
- **PL12**: 14.00 db
- **PL1N**: 33.41081047 W
- **PL1W**: 0.40000000 W
- **SF02**: 401.131600 MHz
- **SI**: 37748
- **SF**: 100.6127719 MHz
- **H1W**: 1.40 Hz
- **SSB**: 0
- **LB**: 1.00 Hz
- **GB**: 0
- **FC**: 1.40
Molecular structure of 1-(3-hydroxy-5,8-dimethoxy-4-methyl-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)ethan-1-one from X-Ray Diffraction analysis
6.3 References


(a) Quadrelli, P.; Piccanello, A.; Martinez, V. N.; Bovio, B.; Mella, M.; Caramella, P. *Tetrahedron* 2006, 62, 7370.


Pelter, A.; Rowlands, M.; Clements. G. *Synthesis* **1987**, *1*, *51*.


128 Tyrell, E.; Brookes, P. *Synthesis* 2004, 4, 469.


