Preparation of Aminoalcohols and Their Application for the Synthesis of Heterocycles and as Potential Sensors for Nerve Agents

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PREPARATION OF AMINOALCOHOLS AND THEIR APPLICATION FOR THE SYNTHESIS OF HETEROCYCLES AND AS POTENTIAL SENSORS FOR NERVE AGENTS

by

David L. Sellers

A dissertation submitted to the Graduate College
in partial fulfillment of the requirements
for the Degree of Doctor of Philosophy
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Dissertation Committee:

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Oxazoles and oxazolines are important heterocyclic scaffolds commonly used in pharmaceuticals and optoelectronic materials. Traditionally these heterocyclic compounds are prepared by condensation methodology that suffers from poor reactivity when using electron deficient or sterically crowded reaction partners. Condensation methods also exhibit low tolerance of many functional groups as the reactions typically use strong acids and high temperatures. This dissertation describes an alternate strategy for the formation of these compounds by employing an epoxide opening followed by oxidation to form these heterocyclic compounds.

Epoxide opening reactions with primary aliphatic, allylic, and benzylic amines, aminolysis reactions, often achieve high yields regardless of the sterics and electronics of the reaction partners. The aminoalcohol produced by these reactions serves as an easily diversifiable intermediate. Using mild oxidants such as manganese dioxide or N-bromosuccinimide the aminoalcohol intermediate can form a substituted oxazole or oxazoline. This method offers one of the highest atom economies of any reported syntheses.

We investigated styrene oxide in addition to 1,10-phenanthroline epoxide as substrates. The former served as an interesting substrate to explore the regioselectivity of these aminolysis reactions. Many syntheses have been developed that favor the epoxide opening on the less hindered
side using aliphatic and benzylic amines, while no reaction is reported to give a high yield of the other regioisomer. Magnesium perchlorate as a Lewis acid catalyst gave unique selectivity for the regioisomer formed by the opening on the more hindered side of styrene oxide. This regioselectivity, however, is eroded by the presence of even stoichiometric amounts of water.

The reactivity of phenanthroline and phenanthrene aminoalcohols was further explored in the optical sensing of chemical warfare agents. As alcohols readily react with phosphorus halides, these aminoalcohols show potential as sensors for organophosphorus nerve agents such as Soman. This was explored for the reaction between the aminoalcohols and a nerve agents mimics by both optical spectroscopy and nuclear magnetic resonance spectroscopy.
ACKNOWLEDGEMENTS

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David L. Sellers
# CHAPTER 1: SYNTHESIS OF B-AMINOALCOHOLS BY THE AMINOLYSIS OF EPOXIDES

## 1.1 Introduction

### 1.1.1 The role of epoxides in synthesis

### 1.1.2 The importance of aminoalcohol compounds

### 1.1.3 Methodology for the aminolysis of epoxides

### 1.1.4 Scope of the investigation of the aminolysis of epoxides

## 1.2 Results and Discussion

### 1.2.1 Synthesis of epoxide starting materials

### 1.2.2 Synthesis of phenanthroline aminoalcohols

### 1.2.3 Synthesis of 2,9-dimethylphenanthroline aminoalcohols

### 1.2.4 Synthesis of phenanthrene aminoalcohols
Table of Contents—Continued

1.2.5 Synthesis of aminoalcohols derived from stilbene oxide ................................................................. 28
1.2.6 Synthesis of aminoalcohols from cyclohexene oxide ................................................................. 29
1.2.7 Regioselective synthesis of aminoalcohols derived from styrene oxide .............................. 30
   1.2.7.1 Investigation of the parameters affecting regioselectivity ....................................................... 30
   1.2.7.2 Scope of the synthesis of aminoalcohols derived from styrene oxide ................................. 37
   1.2.7.3 Comparative investigation in the role of amine on regioselectivity ......................................... 39
   1.2.7.4 Regioselectivity in the synthesis of aminoalcohols via a bromohydrin ............................... 46
1.3 Conclusion ................................................................................................................................................. 48
1.4 References .................................................................................................................................................. 49

CHAPTER 2: SYNTHESIS OF 1,10-PHENANTHROLINE AND PHENANTHRENE OXAZOLES. 53

2.1 Introduction ............................................................................................................................................... 53
   2.1.1 Importance of the oxazole functional group in materials ............................................................ 54
   2.1.2 Methods for synthesizing benzoazole-like compounds ............................................................. 57
   2.1.3 The Japp oxazole synthesis and other methods for the synthesis oxazoles .............................. 57
2.2 Results and Discussion ........................................................................................................58

2.2.1 Synthesis of phenanthroline oxazoles ........................................................................58

2.2.2 Synthesis of phenanthrene oxazoles ..........................................................................61

2.2.3 Efforts at probing the mechanism of the oxidation .........................................................62

2.2.4 Evaluation of the effectiveness of a one-pot reaction ....................................................64

2.3 Conclusion .........................................................................................................................65

2.4 References .........................................................................................................................65

CHAPTER 3: SYNTHESIS OF OXAZOLES FROM AMINOALCOHOLS VIA OTHER OXIDANTS .. 68

3.1 Introduction .........................................................................................................................68

3.1.1 Bioactivity of oxazole and oxazoline containing compounds ......................................68

3.1.2 Other uses for oxazoline compounds ..........................................................................71

3.1.3 Synthesis of oxazoline compounds ..............................................................................72

3.1.4 Synthesis of oxazole compounds ................................................................................73

3.2 Results and Discussion ......................................................................................................76

3.2.1 Screening of oxidants ..................................................................................................76
3.2.2 Oxidation of dimethylphenanthroline aminoalcohols .............................................. 81
3.2.3 Oxidation of stilbene aminoalcohols ........................................................................ 82
3.2.4 Oxidation of styrene aminoalcohols ........................................................................ 84
3.2.5 Oxidation of cyclohexene aminoalcohols ............................................................... 89
3.2.6 Attempts at extending to one-pot methodology ...................................................... 89
3.3 Conclusion .................................................................................................................. 89
3.4 References ................................................................................................................ 90

CHAPTER 4: APPLICATION OF AMINOALCOHOLS TO THE DETECTION OF NERVE AGENTS .... 95

4.1 Introduction ................................................................................................................ 95
4.1.1 Nerve agents ......................................................................................................... 95
4.1.2 Methods for detecting suspected nerve agents in the field ........................................ 96
4.1.3 Colorimetric chemosensors for nerve agents ......................................................... 97
4.2 Results and Discussion ............................................................................................. 98
4.3 Future Aims for these Sensors .................................................................................. 104
4.4 Conclusion ................................................................................................................ 104
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5 References</td>
<td>104</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td>107</td>
</tr>
<tr>
<td>APPENDIX</td>
<td>171</td>
</tr>
</tbody>
</table>
LIST OF TABLES

1.1 Evaluation of solvent and counter ion effects on the epoxide opening of epoxide 2 .............. 18
1.2 Evaluation of solvent on the regioselectivity during opening of epoxide 6 .......................... 34
1.3 Evaluation of concentration on the regioselectivity during opening of epoxide 6 ..................... 35
1.4 Evaluation of water content on the regioselectivity during opening of epoxide 6 ..................... 35
1.5 Evaluation of additives on the regioselectivity during opening of epoxide 6 ......................... 36
1.6 Comparison of regioselective openings of epoxide 6 with aniline ...................................... 40
1.7 Comparison of regioselective openings of epoxide 6 with 4-chloroaniline ............................. 41
1.8 Comparison of regioselective openings of epoxide 6 with amine 7 ...................................... 42
1.9 Comparison of regioselective openings of epoxide 6 with morpholine ................................. 43
1.10 Comparison of regioselective openings of epoxide 6 with imidazole ................................. 44
1.11 Comparison of regioselective openings of epoxide 6 with butylamine ............................... 45
1.12 Evaluation of boron compounds on the regioselectivity during opening of epoxide 6 ............. 47
2.1 Effects of acidity on the oxidation of aminoalcohols with MnO₂ ........................................... 63
3.1 Evaluation of alternative oxidants ......................................................................................... 78
3.2 Optimization for the synthesis of oxazoline 4 from aminoalcohol 3 ..................................... 79
LIST OF FIGURES

1.1 Yessotoxin, an example polyether ................................................................. 2
1.2 Templating for the formation of the six membered ring by hydrogen-bonded waters .......... 4
1.3 Aminoalcohol containing natural products ...................................................... 6
1.4 Naturally occurring β-receptor agonists .......................................................... 7
1.5 Synthetic antagonists of β-receptor antagonists .............................................. 8
1.6 Many other pharmaceutical drugs also contain the aminoalcohol group ................ 9
1.7 Aminoalcohols are used in organocatalysts and in ligands for chelating a catalytic metal ... 10
1.8 The magnesium perchlorate catalyzed reactions form a thick gel ...................... 33
2.1 Andersson biarylphosphite ligand ...................................................................... 55
2.2 Fihri’s complex for hydrogen production ........................................................ 56
2.3 Karlsson’s complex for hydrogen production .................................................. 56
3.1 Oxazole and oxazoline containing natural products ......................................... 69
3.2 Oxazole-containing drugs ................................................................................ 70
3.3 Oxazoline-containing drugs ............................................................................ 70
3.4 BOX ligand ........................................................................................................ 72
4.1 G-series nerve agents ..................................................................................... 95
4.2 Fluorescence titrations of compounds 1, 3, 5 .................................................. 100
List of Figures—Continued

4.3 Fluorescence titrations of compounds 2, 4, 6 ................................................................. 101
4.4 Species of inorganic phosphate found in cells ................................................................. 102
4.5 Fluorescence imaging of hydrogen peroxide in cells ..................................................... 103
LIST OF SCHEMES

1.1 Reaction of an epoxide with a nucleophile ................................................................. 1
1.2 Epoxide-opening cascade in the synthesis of glabrescol .................................................. 3
1.3 Jamison synthesis of polyether motif .............................................................................. 4
1.4 Synthesis of ascididemin ................................................................................................... 5
1.5 The dissertation hypothesis for the preparation of heterocyclic compounds ................. 5
1.6 The uncatalyzed aminolysis of styrene oxide by benzyl amine ........................................ 11
1.7 Lewis acid catalysis of an epoxide-opening reaction .......................................................... 12
1.8 A non-Lewis acid catalyzed aminolysis ............................................................................ 13
1.9 Epoxidation of 1,10-phenanthroline .................................................................................. 14
1.10 Epoxidation of phenanthrene .......................................................................................... 15
1.11 Epoxidation of 2,9-dimethyl-1,10-phenanthroline .......................................................... 15
1.12 Aminolysis of epoxide 2 by ammonium hydroxide .......................................................... 17
1.13 Reactions of epoxide 2 with aliphatic amines ................................................................ 19
1.14 Reactions of epoxide 2 with hexylamine catalyzed by magnesium perchlorate .......... 20
1.15 Reactions of epoxide 2 with benzylic amines .................................................................. 21
1.16 Reactions of epoxide 2 with ortho-substituted benzylic amines ....................................... 22
1.17 Reactions of epoxide 2 with ammonium chloride salts ................................................... 23
1.18 Reaction of epoxide 2 with t-butylglycine ...................................................................... 23
1.19 Reaction of epoxide 2 with 4-aminomethylbenzoic acid ................................................... 24
List of Schemes—Continued

1.20 Reactions of epoxide 13 with primary amines .......................................................... 26
1.21 Reactions of epoxide 11 with primary amines .......................................................... 27
1.22 Reactions of epoxide 18 with primary amines .......................................................... 28
1.23 Reaction of epoxide 20 with benzylamine ................................................................. 29
1.24 Reactions of epoxide 24 with primary amines .......................................................... 30
1.25 Reactions of epoxide 6 with primary amines catalyzed by magnesium perchlorate .... 38
1.26 Reactions of epoxide 6 with primary amines catalyzed by calcium perchlorate .......... 38
1.27 Formation of aminoalcohol 9c through a purported bromohydrin intermediate ......... 47
1.28 The Meinwald rearrangement of epoxides ................................................................. 47
2.1 Preparation of an iminoquinone from an aminoalcohols ........................................... 53
2.2 Kohler synthesis of an oxazole from an aminoalcohol ................................................. 54
2.3 Dissertation hypothesis that heterocyclic compounds can be formed from epoxides .... 54
2.4 Bourgin synthesis of substituted 2-phenylbenzoxazole ............................................. 57
2.5 Japp synthesis of oxazoles ......................................................................................... 58
2.6 Oxidation of aminoalcohols 1a-w ................................................................................ 59
2.7 Oxidation of aminoalcohols 3a-e ................................................................................ 61
2.8 Proposed mechanism for the formation of oxazole .................................................... 62
2.9 One-pot synthesis of a phenanthroline oxazole ......................................................... 64
List of Schemes—Continued

3.1 Methods for the synthesis of oxazolines................................................................. 73
3.2 Nicolau synthesis of diazonamide A........................................................................ 74
3.3 Wipf synthesis of muscoride A.................................................................................. 75
3.4 Methods for the synthesis of oxazoles...................................................................... 76
3.5 Oxidation products for the reaction of aminoalcohol 3 with NBS ................................ 77
3.6 Oxidation of aminoalcohols 9a-f with manganese dioxide ....................................... 81
3.7 Oxidation of aminoalcohols 11a-f with manganese dioxide ..................................... 82
3.8 Oxidation of aminoalcohol 11a with manganese dioxide ......................................... 83
3.9 Oxidation of aminoalcohols 11a-f with NBS .......................................................... 84
3.10 Oxidation of aminoalcohols 16a-f with manganese dioxide ..................................... 86
3.11 Oxidation of aminoalcohols 18a-f with manganese dioxide ..................................... 86
3.12 Oxidation of aminoalcohols 16a-f with NBS .......................................................... 87
3.13 Oxidation of aminoalcohols 18a-f with NBS .......................................................... 87
3.14 Oxidation of aminoalcohols 16a-f with DBDMH .................................................... 88
3.15 Oxidation of aminoalcohols 18a-f with DBDMH .................................................... 88
4.1 Zhang and Swager mechanism for the detection of DCP ......................................... 97
4.2 Phenanthroline aminoalcohols for the detection of DCP ......................................... 98
4.3 Synthesis of aminoalcohols 1-6 ................................................................................. 99
4.4 Degradation products of DCP................................................................................... 102
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABq</td>
<td>AB quartet in $^1$H NMR</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Ad</td>
<td>adamantyl</td>
</tr>
<tr>
<td>ACN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>app</td>
<td>apparent (NMR peak description)</td>
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<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Boc</td>
<td><em>tert</em>-butyloxycarbonyl</td>
</tr>
<tr>
<td>BOX</td>
<td>bis-oxazoline ligand</td>
</tr>
<tr>
<td>br</td>
<td>broad signal in $^1$H NMR</td>
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<tr>
<td>Bz</td>
<td>benzoyl</td>
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<tr>
<td>cat.</td>
<td>catalyst</td>
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<tr>
<td>conv.</td>
<td>conversion</td>
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<tr>
<td>COX</td>
<td>cyclooxygenase</td>
</tr>
<tr>
<td>δ (NMR)</td>
<td>chemical shift in NMR</td>
</tr>
<tr>
<td>d (NMR)</td>
<td>doublet in $^1$H NMR</td>
</tr>
<tr>
<td>d (time)</td>
<td>days</td>
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<tr>
<td>DBDMH</td>
<td>1,3-dibromo-5,5-dimethylhydantoin</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicycloundec-7-ene</td>
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List of Abbreviations—Continued

DCDMH  1,3-dichloro-5,5-dimethylhydantoin
DCE   dichloroethane
DCM   dichloromethane
DCP   diethylchlorophosphate
dd   doublet of doublets in $^1$H NMR
ddd  doublet of doublet of doublets in $^1$H NMR
DMF   $N,N$-dimethylformamide
DMP   Dess-Martin periodinane
DMSO  dimethylsulfoxide
ESI   electrospray ionization
ESI-MS electrospray ionization mass spectrometry
Et    ethyl
eq or equiv. equivalents
FT-IR Fourier transform infrared spectroscopy
GC-MS gas chromatography mass spectrometry
h or hr (time) hours
HMTA  hexamethylenetetramine
HRMS  high resolution mass spectrum
IR    infrared
List of Abbreviations—Continued

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<tr>
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<tr>
<td>LC-MS</td>
<td>liquid chromatography mass spectrometry</td>
</tr>
<tr>
<td>mCPBA</td>
<td>3-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>m (NMR)</td>
<td>multiplet in $^1$H NMR</td>
</tr>
<tr>
<td>m or min (time)</td>
<td>minutes</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
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</tr>
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<td>N/A</td>
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<tr>
<td>NBS</td>
<td>$N$-bromosuccinimide</td>
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<tr>
<td>nBu</td>
<td>$n$-butyl</td>
</tr>
<tr>
<td>NCS</td>
<td>$N$-chlorosuccinimide</td>
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<td>NMR</td>
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<td>NR</td>
<td>not reported</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
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<tr>
<td>Nu</td>
<td>nucleophile</td>
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<tr>
<td>[O] or ox.</td>
<td>oxidation</td>
</tr>
<tr>
<td>p</td>
<td>pentet in $^1$H NMR</td>
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<td>PCC</td>
<td>pyridinium chlorochromate</td>
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</table>
List of Abbreviations—Continued

Ph  phenyl
pH  \(-\log[H^+]\)
PP\textsubscript{i}  inorganic pyrophosphate
PTC  phase transfer catalyst
q  quartet in \(^{1}\text{H}\) NMR
R  organic substituent
Rf  retardation factor
rt or r.t.  room temperature
s (NMR)  singlet
sat.  saturated
t  triplet in \(^{1}\text{H}\) NMR
TBHP  \textit{tert}-butyl hydroperoxide
tBu  \textit{tert}-butyl
TEA  triethylamine
Temp.  temperature
THF  tetrahydrofuran
TLC  thin layer chromatography
X  heteroatom
XPOR\textsubscript{2}  nerve agents
CHAPTER 1: SYNTHESIS OF B-AMINOALCOHOLS BY THE AMINOLYSIS OF EPOXIDES

1.1 Introduction

1.1.1 The role of epoxides in synthesis

Epoxides, also referred to as oxiranes, serve as crucial building blocks in the synthesis of complex organic compounds. While the epoxide has a C-O-C linkage similar to an ether, it often is classified separately because it possesses far different reactivity. The highly strained three-membered ring of the epoxide allows it to serve as a good electrophile as the ring strain decreases upon reaction with a nucleophile (Scheme 1.1). This ease of reactivity makes the epoxide useful for building molecules that have an oxygen atom placed two carbons away from a group that can be installed by nucleophilic substitution. The resulting alcohol is useful because it is

![Scheme 1.1 Reaction of an epoxide with a nucleophile](image_url)
arguably the most versatile functional group. Therefore, the products of the epoxide-opening reaction can be further modified to form a host of new structures.

The most dramatic uses of epoxides in synthesis are the epoxide opening cascades to form polyether compounds such as yessotoxin (Figure 1.1). The natural product is formed by the organisms that cause harmful algal blooms. The Nakanishi hypothesis, developed in the 1980’s, states that the biosynthesis of these compounds begins with a polyene that is epoxidized and then the rings are closed in a cascade reaction. The first notable instance using such a cascade reaction comes from the Corey synthesis of glabrescol (Scheme 1.2). It employed a novel dual epoxide opening cascade to form four of the five tetrahydrofuran rings of the final product. The cascade starts from the two alcohols at the ends of the chain attacking the adjacent epoxide and closing the

Figure 1.1 Yessotoxin, an example polyether
first two rings and causing a second set of openings to close the second set of rings. The final ring, found to be unable to be closed in a cascade, was closed by a multistep reaction where the alcohol derived from the blue epoxide attacked the alcohol derived from the red epoxide. As has been witnessed in many other cascade syntheses, the reaction achieved very high selectivity for the five-membered tetrahydrofuran rings. Further, the regiocontrol in this reaction was easier to achieve as the subsequent openings require the first ring to form as a five-membered ring.

Scheme 1.2 Epoxide-opening cascade in the synthesis of glabrescol

Much more difficult than the synthesis of the tetrahydrofuran polyethers are the syntheses of the tetrahydropyran polyethers. Timothy Jamison’s work with synthesis of ladder polyether compounds greatly opened this field by investigating the role of water in the regioselective formation of the tetrahydropyran polyethers (ladder polyethers) (Scheme 1.3). Previous attempts at the formation of these compounds in organic solvents formed the more favorable five-membered rings. Counter to most organic methodology, water was a critical component in the reaction as it templated the formation of the six-membered ring. While the role of water was not fully understood, it was hypothesized that a hydrogen bond network stabilizes a conformation of the epoxide-alcohol precursor in which the formation of the tetrahydropyran ring becomes more
favorable (Figure 1.2). Epoxides find use beyond cascade reactions; epoxides are used in the synthesis of other complex heterocyclic structures such as in the synthesis of ascididemin (5).

Moody et al., in their first reported synthesis of the marine alkaloid 5, showed the power of using an epoxide as the starting point of a complex synthesis (Scheme 1.4). While the formation of the iminoquinone intermediate 4 was originally attempted by a more traditional condensation between a ketone and amine, the step proved to suffer from low yields (10-50%). Starting instead with epoxide 2, intermediate 4 was formed in a high yield over two steps. This strategy of epoxide opening followed by oxidation could be useful to the formation of heterocyclic compounds as it avoids many steric and electronic effects that are problematic in traditional condensation reactions. Further, the reagents employed in these transformations are relatively mild and should allow for a wide degree of functional group tolerance. This body of work takes advantage of this special
reactivity of epoxides to form aminoalcohols and then oxidize them to produce oxazoles and related heterocyclic compounds (*vide infra*) (Scheme 1.5).

Scheme 1.4 Synthesis of ascididemin

Scheme 1.5 The dissertation hypothesis for the preparation of heterocyclic compounds
1.1.2 The importance of aminoalcohol compounds

The β-aminoalcohol functional group can be found in many natural products, pharmaceuticals, and other useful materials. The simplest aminoalcohol, ethanolamine is produced endogenously by humans in the biosynthesis of phosphatidylethanolamine, and is purported to have an anti-aging effect on cells by increasing the production of the latter compound. More structurally diverse aminoalcohols can be found in a wide variety of natural products including sphingosine and choline, which are precursors to the powerful signaling molecules 1-phosphatidylsphingosine and acetylcholine, respectively (Figure 1.3). Aminoalcohols can also be incorporated in highly complex structures such as in the neurotoxin veratridine where the nitrogen atom is part of the fused rings of the steroid (Figure 1.3).

Figure 1.3 Aminoalcohol containing natural products
The best-studied bioactive aminoalcohols are epinephrine (adrenalin), norepinephrine (noradrenaline) and their related pharmaceutical products (Figure 1.4). Epinephrine and norepinephrine are signaling molecules that affect a host of physiological changes in the human body. Many of these effects come from their binding to α- and β-receptors on cell surfaces. As these compounds cause the receptor to take action when they bind, they are referred to as agonists. Other naturally produced agonists of these receptors, such as ephedrine, also have the aminoalcohol functional group to allow them to bind to the receptor. Antagonists, like β-blockers, belong to an important and diverse class of pharmaceutical compounds. These compounds are synthetic drugs which block action of the β-receptor and have many effects on the heart and circulatory system. Professional performers, like ballet dancers and musicians, have made these drugs famous by using them to reduce their heartbeat and hand tremors when performing. These drugs have even made their way into pop culture having been referenced on the television show

![Native Adrenergic Receptor Agonists](image1)

![Natural Adrenergic Receptor Partial Agonist](image2)

Figure 1.4 Naturally occurring β-receptor agonists
Bones where Agent Booth suspects a professional mini-golfer of being a trained sniper since he was taking β-blockers. There are well over two-dozen β-blockers, many of which are approved for prescription, some of which are shown in Figure 1.5. Nearly all of these compounds maintain the aminoalcohol functional group so they can bind in the same receptor pocket as the native ligands.

**Synthetic Adrenergic Receptor Antagonists (β-blockers)**

propanolol (Inderal)  
atenol (Tenormin)  
butazamine

Figure 1.5 Synthetic antagonists of β-receptor antagonists

While the aminoalcohol group would never be described as a privileged structure in the pharmaceutical industry, it is found in many drugs because it interacts strongly with polar amino acids and also gives good solubility properties to the drug. It can be found in compounds used to treat different types of diseases and disorders (Figure 1.6). The aminobenzonitrile derivative was found to have good selectivity for one key androgen receptor to reverse and prevent muscle atrophy in monkeys. Another aminoalcohol drug is the famed antimalarial Mefloquin, which was developed by the US Army to combat malaria gaining resistance to quinine (another
aminoalcohol). Other compounds such as WAY-315193 and fingolimod contain the aminoalcohol to mimic a native substrate such as norepinephrine and sphingosine, respectively.

Due to the ability of β-aminoalcohols to hydrogen bond to other molecules or chelate to metal cations, compounds using this motif are used in the field of catalysis. One particular reaction that needs a catalytic cycle is the destruction and remediation of nerve agent stockpiles. Typically, the reaction is carried out at a very high pH and requires the use of stoichiometric amounts of caustic reagents. To make the process less hazardous the reaction should be carried out in water at a near neutral pH; to affect this the Costero group developed an aminoalcohol organocatalyst that allows water to react with the nerve agents at pH values closer to neutral (Figure 1.7). Another major challenge for catalysis lies in carrying out reactions stereoselectively without using stoichiometric amounts of an enantiopure compound. The Chauvin group developed the ligand shown below as the controlling element of an asymmetric carbonyl transfer reaction using an iron
catalyst and carbon monoxide (Figure 1.7). The Saluzzo organocatalyst shown above can mediate asymmetric hydrogen transfer reactions and replace costly metals and their often expensive chiral ligands (Figure 1.7). The main reason aminoalcohols were chosen to develop these catalysts is because they are easily accessed by reacting an amine with an epoxide, an aminolysis reaction, the methodology for which has been studied in detail.
1.1.3 Methodology for the aminolysis of epoxides

The term aminolysis means “to split using an amine” just as hydrolysis means “to split using water.” In the nucleophilic addition of amines to epoxides, one of the oxygen-carbon bonds is cleaved which is why the term aminolysis is applied. While the addition of nucleophiles to epoxides can be quite fast when using strong nucleophiles, the reaction is much slower using poor nucleophiles such as amines. When uncatalyzed, the reaction is quite slow, for example styrene oxide (6) and benzylamine (7) can take over seven days to reach equilibrium (Scheme 1.6). Such reaction times are not practical for bench chemists and are not economically feasible for a production facility. These inefficiencies have led to great exploration of Lewis acid catalyst methodology for carrying out these reactions. Lewis acids by definition are atoms or compounds that can accept a lone pair of electrons. Metal cations and compounds of Group 13 elements (B, Al) fit this definition quite well. The Lewis acid binds to one of the lone pairs of the oxygen atom of the epoxide which causes the bonds between oxygen and carbon to lengthen and weaken (Scheme 1.7). This makes the carbons more susceptible to nucleophilic attack and leads to a faster reaction.

Scheme 1.6 The uncatalyzed aminolysis of styrene oxide by benzyl amine
The methodology in this area recently had an excellent review conducted by Saddique et al. covering the recent developments in these aminolysis reactions. Much work has gone into making these reactions more environmentally benign by employing either easily recycled heterogeneous catalysts or by using Lewis acid catalysts that can be employed in solvent free conditions. Notable heterogeneous catalysts include alumina, graphene oxide, amino acids anchored to silica, montmorillonite clay, and sulfated zirconia. Metal salts using elements from across the periodic table have been employed, of particular note to this body of work are salts using metals from Group 1 (Li, Na, Ca), Group 2 (Mg, Ca), Group 13 (Al), and the lanthanide metals. Boron based compounds have been employed including BF$_3$, B$_2$O$_3$ on alumina, and B(OH)$_3$ in glycerol. The Chimni group reported an example using a modified thiourea as a hydrogen-bonding catalyst, but few other examples exist for this catalytic mode. Another interesting non-Lewis acid catalyst is cyanuric chloride. It is hypothesized that a cyanuric acid adduct is formed as an intermediate (Scheme 1.8).
Catalyst-free reactions with fast reaction times are also worth noting. Saidi *et al.* found that water is an excellent promoter of the reaction, provided the reactants are moderately soluble.\textsuperscript{51} This report appeared at a time when organic chemists (who traditionally feared water in a reaction) were discovering that water can be a crucial additive to achieve a desired reaction. However, these reactions often do not perform well in simple batch heating methods. Thus, they have been accelerated using either microwaving or ultrasound.\textsuperscript{52} The latter is particularly useful as it helps to break up materials that may have clumped together due to poor solubility. The aminolysis reaction has also been operated in a continuous flow system without catalyst.\textsuperscript{53} The reaction was sufficiently fast using high pressures and temperatures. As noted by both the Jamison group and the Lindsay group, conducting these reactions without catalyst at such high temperatures will erode the regioselectivity of the reaction if multiple regioisomers can be formed.\textsuperscript{53,54}

Scheme 1.8 A non-Lewis acid catalyzed aminolysis
1.1.4 Scope of the investigation of the aminolysis of epoxides

With the hypothesis that aminoalcohols may serve as excellent intermediates in the formation of heterocycles, it is important first to understand the role of substrate, catalyst and solvent were not previously understood in the literature. This work looked first at the formation of epoxides derived from 1,10-phenanthroline, phenanthrene, stilbene and cyclohexene compounds to understand the substrate scope of aminolysis reactions. Then the role of catalyst and solvent was investigated by the aminolysis of styrene oxide with a particular emphasis on the regioselectivity of the reaction.

1.2 Results and Discussion

1.2.1 Synthesis of epoxide starting materials

While many simple epoxides are commercially available, compounds such as epoxides 2, 11, and 13 (Schemes 1.9-11) are best synthesized in house. Many epoxidation reactions are at the disposal of synthetic chemists with peracid and peroxide oxidants seeing the greatest use. These oxidants however are often incompatible with substrates containing nitrogen. N-oxides can often

![Scheme 1.9 Epoxidation of 1,10-phenanthroline](image-url)
be formed as a byproduct of the reaction. Bleach (aqueous NaOCl) functions as an excellent alternative oxidant in epoxidation reaction and avoids the problematic formation of byproducts related to the nitrogen content of the substrate. Bleach, however, is not perfect as it is capable of forming chlorination products in addition to epoxides. This problem has been well studied by Ankowiak et al. They found that adjusting the pH of commercial bleach to 8.6 favored the formation of the epoxide. The reaction works well for 1,10-phenanthroline (1, Scheme 1.9) and phenanthrene (10, Scheme 1.10) as has been reported. It also extends well to 2,9-dimethyl-1,10-phenanthroline (13). Having employed the reaction numerous times, a wide degree of variability in the reaction has been observed.

Based on experience, the age of the bleach is a major contributor to whether or not the reaction will favor the epoxide. The use of older bleach affords less epoxide (~20%) and isolation becomes difficult. Fresh bleach typically gives good epoxide yields (75-90%). Our baseline for the
performance of fresh bleach comes from when 8.25% bleach was first sold in the United States. At this time the commercial bleach at many grocery stores had not been warehoused long before sale.

Bleach can follow two major degradation pathways and forms sodium chloride and sodium chlorate as major products. It is unknown which of these have the bigger effect on the reaction. In Ankowiak’s original study the pH was adjusted using hydrochloric acid, suggesting that the chloride anion, while problematic, may not influence the outcome in any major way. This would leave the chlorate anion as the likely culprit. Production or purification of sodium hypochlorite is not feasible in a typical synthesis lab, making the chemist dependent on the quality of commonly available bleach. We found that bleach purchased from a laboratory supply company did not perform better than the bleach bought from the grocery store shelf.

Given the issues using bleach, we briefly explored other possible reactions for the epoxidation of 1,10-phenanthroline. Calcium hypochlorite as an oxidizing agent seemed a good choice; however, solubility proved a major issue when attempting to adapt it to the Antkowiak epoxidation procedure. Epoxide 2 did not form. The calcium hypochlorite used was several years old and used without purification so it is possible that given better conditions it may still function in the reaction. Also a reaction using crystalline urea-hydrogen peroxide was employed with the hope that the presence of urea may reduce the formation of N-oxides. The reaction was disappointing because epoxide 2 was not formed. Given these results we still choose to employ commercial bleach with of yields between 40-60%. If a bottle of bleach is not able to achieve a 40% isolated yield of the epoxide, we discontinue use of that bottle and purchase another. In summary, this epoxidation reaction is excellent with new bleach, but still can be conducted with old bleach.
1.2.2 Synthesis of phenanthroline aminoalcohols

The epoxide opening of 5,6-dihydro-1,10-phenanthroline-5,6-epoxide (2) serves as an excellent starting point for studying the scope of the formation of aminoalcohols and their subsequent oxidation to form novel substituted heterocyclic compounds. The Schoffers group has demonstrated that many methods can be used to form phenanthrolines that are substituted at positions 5 and 6, and much of the following work is based on the work of Lars Kohler in his dissertation.\textsuperscript{37, 55-58} As phenanthroline compounds make excellent ligands for metal catalysis, this reaction was investigated with a broad scope to make a compound library for future projects. To form the simplest aminoalcohol in this class, ammonia in the form of ammonium hydroxide serves as an excellent nucleophile (Scheme 1.12). Whether in acetonitrile or neat, the reaction is highly chemoselective for the formation of the aminoalcohol. Ammonia is a strong nucleophile and can accomplish the reaction in the absence of a catalyst, compared to the addition of primary amines which require a catalyst to activate the epoxide.
Our lab previously explored several amines for the opening of epoxide 2 and found magnesium perchlorate to be the most effective catalyst for the reaction. Solvent effects were not investigated at that time.\textsuperscript{37, 58} It was necessary to determine the effects of the reaction medium before preparing a large chemical library. Looking at a range of polar protic to nonpolar solvents, we find acetonitrile (ACN) functions as the best reaction medium (Table 1.1). While reactions in methanol and chloroform show a higher yield, the former has issue with a competing alcoholyis reaction while the latter is virtually heterogenous in character and will likely suffer problems on a

Table 1.1 Evaluation of solvent and counter ion effects on the epoxide opening of epoxide 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst\textsuperscript{a}</th>
<th>Solvent</th>
<th>% Yield\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mg(ClO\textsubscript{4})\textsubscript{2}</td>
<td>Water</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Mg(ClO\textsubscript{4})\textsubscript{2}</td>
<td>Acetonitrile</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>Mg(ClO\textsubscript{4})\textsubscript{2}</td>
<td>MeOH</td>
<td>93\textsuperscript{c}</td>
</tr>
<tr>
<td>4</td>
<td>Mg(ClO\textsubscript{4})\textsubscript{2}</td>
<td>CHCl\textsubscript{3}</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>Mg(ClO\textsubscript{4})\textsubscript{2}</td>
<td>DCM</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>MgSO\textsubscript{4}</td>
<td>Acetonitrile</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>MgSO\textsubscript{4}</td>
<td>MeOH</td>
<td>58\textsuperscript{c}</td>
</tr>
<tr>
<td>8</td>
<td>CaSO\textsubscript{4}</td>
<td>Acetonitrile</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>CaCl\textsubscript{2}</td>
<td>Acetonitrile</td>
<td>27</td>
</tr>
<tr>
<td>10</td>
<td>MgCl\textsubscript{2}</td>
<td>Acetonitrile</td>
<td>33</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Epoxide 2 50 mg (0.25 mmol), catalyst (0.31 mmol)  
\textsuperscript{b} Isolated yield  
\textsuperscript{c} Includes weight of alcoholyis product
larger scale. Other chemically related salts cannot outperform magnesium perchlorate in terms of yield and ease of isolation of the product. It should be noted, for phenanthroline based epoxides magnesium perchlorate must be used in super-stoichiometric amounts even though its role is catalytic. This is likely due to the substrate binding to the metal making much of it less active. This is a common problem when using metal catalysts with substrates that contain Lewis basic sites.

Exploration of the reaction scope begins first with the reaction between epoxide 2 and aliphatic amines. For low boiling point nucleophiles, such as methyl and ethyl amine, using a heterogeneous Lewis acid allows for work-up by filtration and evaporation. Alumina was chosen as the catalyst based on Moody’s original work with the aminolysis of epoxide 2. This reaction affords aminoalcohols 15a and 15b in 55% and 99% yields, respectively (Scheme 1.13). It turns out

![Reaction diagram](image)

Scheme 1.13 Reactions of epoxide 2 with aliphatic amines

<table>
<thead>
<tr>
<th>R</th>
<th>15a Yield, Time</th>
<th>15b Yield, Time</th>
<th>15c Yield, Time</th>
<th>15d Yield, Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>55%, 96h</td>
<td>99%, 72h</td>
<td>72%, 24h</td>
<td>93%, 12h</td>
</tr>
<tr>
<td>CH₂CH₂CH₃</td>
<td>62%, 18h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₂(CH₂)₃CH₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

15e 62%, 18h
15f 72%, 45h
out that alumina was a serendipitous choice for the reaction with aliphatic amines because magnesium perchlorate tends to catalyze the subsequent dehydration of the aminoalcohol. Evidence of this comes from the isolation of enamine 16 from the reaction between epoxide 2 and hexylamine (Scheme 1.14). Alumina is the ideal catalyst to form aminoalcohols 15e and 15f from allylamine and picolylamine, respectively. In the latter case it is likely due to picolylamine needing a Lewis acid that will not be deactivated by chelation.

Alumina is not necessary for the reaction with all aliphatic amines. The cycloalkane derivative 15g forms readily when catalyzed by magnesium perchlorate as does the phenethylamine derivative 15h without any noticeable dehydration product (Scheme 1.15). As is to be expected from the original screening, meta- and para-substituted benzyl amines open the epoxide without issue, giving yields between 56-99%. For ortho-methoxy substituted benzyl amines, however, the magnesium ion is not an effective Lewis acid, likely due to the cation being chelated by the amine and methoxy oxygen thereby deactivating it. Instead ytterbium triflate can
Scheme 1.15 Reactions of epoxide 2 with benzylic amines

RCH$_2$NH$_2$ $\xrightarrow{Mg(ClO_4)_2,}$ ACN, reflux

2 $\rightarrow$ 15 $+$ en.

15g, 72%, 24 h
15h, 70%, 24 h
15i, 92%, 48 h
15j, 77%, 44 h
15k, 87%, 24 h
15l, 76%, 40 h
15m, 61%, 40 h
15n, 78%, 24 h
15o, 56%, 24 h
15p, 99%, 24 h
be used effectively and provides the products in near quantitative yields except for trimethoxy derivative 15s (Scheme 1.16). The yield for 15s is much lower because the amine was added as an unneutralized hydrochloric acid salt. Ytterbium triflate greatly speeds up the reaction time compared to magnesium perchlorate. The ytterbium salt, however, requires precipitation with sodium hydroxide to effectively remove it from phenanthroline compounds. This can cause problems for work-up, especially if the product is predisposed to dehydration such as compounds 15a-e. For reactions where the starting amine is sold as a hydrochloric acid salt, Hüning’s base allows for in situ neutralization of the reactant provided alumina was used as a catalyst (Scheme 1.17). This allows for the formation of nitro-substituted derivatives 15t-v to be formed in moderate yields. Even an amino acid such as glycine can be employed using lithium perchlorate as the catalyst if the carboxylic acid is protected as the t-butylo ester (Scheme 1.18). 4-Aminomethylbenzoic acid is

![Scheme 1.16 Reactions of epoxide 2 with ortho-substituted benzylic amines](image-url)
a more difficult substrate to work with. It failed to open the epoxide as either a free carboxylic acid or as an adamantyl ester using any of the catalysts mentioned above (Scheme 1.19). Eventually derivative 17 was abandoned because we were unable to synthesize it despite using several different methods.
Isolation of aminoalcohols 15d-15w was difficult because all derivatives are oils, foams, or glassy solids at room temperature. Early attempts at isolating the compounds as acid salts met with only marginal success. All derivatives were instead isolated by column chromatography. Two main problems persist throughout the chromatography of these derivatives: column streaking and the high degree of similarity between aminoalcohol and unreacted starting amine. Column streaking is quite common for compounds containing amines. Adding 1% ammonium hydroxide or triethyl amine helps to reduce the problem but nothing eliminates it. Also, the aminoalcohol product and unreacted starting amine elute close to one another across a wide range of solvent polarities. Often for reactions using three or more equivalents of amine, two columns are necessary in order to isolate the target compound in a high yield. The column inefficiencies likely represent the largest loss of yield in the mass balance of the reaction. If more ideal isolation conditions are found, many of these products could be isolated in near quantitative yields.

Considering reaction scope, these reactions tolerate a wide variety of electronic conditions from nitro- to methoxy groups by any one catalyst. However not all catalysts will tolerate sterically crowded nucleophiles. For ortho-substituted benzyl amines, lanthanide metal catalysts are often
necessary to achieve a high yield. Generally, if a subsequent dehydration is not an issue, magnesium perchlorate and alumina can be used interchangeably, each providing its own benefits. Alumina is ideal for reactions where a reactant can be removed from the product by evaporation and when no aqueous work up is required for purification. However, alumina requires a large excess of amine nucleophile making isolation by column chromatography quite difficult. Magnesium offers the advantage of using a low excess of amine and easier reaction set up; however, it requires purification by aqueous work up. This rules out using this catalyst in cases where the product is quite hydrophilic because the yield will be eroded upon washing. Filtration through packing material such as silica gel will successfully remove the metal salt catalyst. Much product can be lost to the packing material in the case of phenanthroline derivatives disallowing for purification by this method. Overall the aminolysis reaction has proven to have a wide substrate tolerance for the formation of aminoalcohols 15a-w with the main exception being amino benzoic acids.

1.2.3 Synthesis of 2,9-dimethylphenanthroline aminoalcohols

The reactions of the previous section prove that a diverse suite of primary amines can be used with few problems coming from steric or electronic effects. To simplify the following experiments, only a subset of amines was used to explore the role of epoxides during aminolysis. The amines chosen cover a broad range of electronic properties so as to maintain good insight as to these effects on the hypothesis. Synthesis of the 2,9-dimethylphenanthroline analogues of compound 15 gave results very similar to the previous library (Scheme 1.20). Similarly, while magnesium perchlorate was ideal for the benzylic amines, alumina proved a far better catalyst for aminolysis with butyl amine and allyl amine. An interesting observation is that when the reaction was attempted with magnesium perchlorate, no conversion to the aminoalcohol products 18a or
18b was observed by TLC, nor was any product isolated after the reaction. Also, the dehydration products were neither observed nor isolated. A further interesting observation is the opening with 2-nitrobenzyl amine functions well when it is catalyzed by magnesium perchlorate, suggesting that the use of ytterbium triflate for ortho-substituted benzyl amines may only be necessary for ortho-alkoxy and ortho-hydroxy nucleophiles. The reaction does suffer from relatively low isolated yields, but based on TLC evidence, this is not likely due to reaction inefficiencies. Instead, aminoalcohols 18a-f are much more difficult to isolate by column chromatography than their phenanthroline counterparts. Addition of triethyl amine does not solve the problem. One final

![Scheme 1.20 Reactions of epoxide 13 with primary amines](image)

18a 42%, 16 h  
Al₂O₃

18b 20%, 16 h  
Al₂O₃

18c 31%, 16 h  
Mg(ClO₄)₂

18d 15%, 16 h  
Mg(ClO₄)₂

18e 18%, 16 h  
Mg(ClO₄)₂

18f 45%, 16 h  
Mg(ClO₄)₂
observation is that heterocyclic compound 18f demonstrates the aminolysis also tolerates oxygen-containing heterocycles as reaction partners which was not explored in the previous section.

1.2.4 Synthesis of phenanthrene aminoalcohols

Synthesis of phenanthrene aminoalcohols was expected to be more difficult because the starting epoxide 11 is significantly less stable than its phenanthroline analogue (Scheme 1.21). Further the aminoalcohols are also less stable than their phenanthroline analogues. For this reason, the reaction was performed with magnesium perchlorate as the catalyst in order to allow for easier purification. This way aminoalcohols 19a-e were less likely to degrade when undergoing difficult chromatographic isolations. Washing the organic phase was also made easier because the catalyst is used at sub-stoichiometric amounts. Interestingly the magnesium perchlorate effectively catalyzed the aminolysis with butyl amine and allyl amine to form 19a and 19b without any

Scheme 1.21 Reactions of epoxide 11 with primary amines

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>Reaction Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>19a</td>
<td>46%</td>
<td>16 h</td>
</tr>
<tr>
<td>19b</td>
<td>58%</td>
<td>16 h</td>
</tr>
<tr>
<td>19c</td>
<td>94%</td>
<td>16 h</td>
</tr>
<tr>
<td>19d</td>
<td>72%</td>
<td>16 h</td>
</tr>
<tr>
<td>19e</td>
<td>61%</td>
<td>16 h</td>
</tr>
</tbody>
</table>
detectable dehydration. Lacking the diimino moiety, the phenanthrene aminoalcohols were far more easily isolated by column chromatography and subsequently all stored at -10°C to prevent degradation.

1.2.5 Synthesis of aminoalcohols derived from stilbene oxide

Aminolysis of trans-stilbene oxide 20 demonstrated that this reaction also succeeds with more sterically hindered epoxides (Scheme 1.22). Calcium perchlorate tetrahydrate, which is also a Group 2 metal salt, functions better than magnesium perchlorate. One key problem of magnesium perchlorate not previously mentioned is how it degrades the amine starting material, which is part of the reason 1.5 equivalents of the amine is often necessary. Amine degradation products are often

\[
\begin{align*}
20 & \quad \text{RCH}_2\text{NH}_2, \quad \text{Ca(ClO}_4\text{)}_2, \quad \text{ACN, reflux} \\
& \quad \text{ HO} \quad \text{NH} \\
& \quad \text{21} \\
& \quad \text{+ en.}
\end{align*}
\]

\[
\begin{align*}
21\text{a} & \quad \text{CH}_2\text{CH}_2\text{CH}_3 \quad 76\%, \quad 12\ h \\
21\text{b} & \quad \text{82\%, \quad 12\ h} \\
21\text{c} & \quad \text{68\%, \quad 6\ h} \\
21\text{d} & \quad \text{69\%, \quad 6\ h} \\
21\text{e} & \quad \text{89\%, \quad 8\ h} \\
21\text{f} & \quad \text{80\%, \quad 8\ h}
\end{align*}
\]

Scheme 1.22 Reactions of epoxide 18 with primary amines
observed on GC-MS analysis of these reactions. Calcium perchlorate on the other hand avoids this side reaction and results a much cleaner product. Only 1.1 equivalents of amine are necessary to achieve a good yield. This catalyst tolerates a wide variety of amine nucleophiles. It is possible that the calcium perchlorate may also be a better catalyst for the preparation of phenanthroline aminoalcohols; however, its usefulness was discovered after the original library had already been prepared. All aminoalcohols 21a-f were isolated as crystalline solids, avoiding the need for purification by column chromatography. cis-Stilbene oxide was also studied for this reaction. It is a far more expensive reagent and was therefore limited to the reaction with benzyl amine. That said, the epoxide 22 is structurally similar to epoxide 11 and likely the full range of amines would still serve in the aminolysis reaction.

![Scheme 1.23 Reaction of epoxide 20 with benzylamine](image)

1.2.6 Synthesis of aminoalcohols from cyclohexene oxide

Aminoalcohols 25a-f are very interesting substrates for the preparation of heterocyclic compounds by a strategy of epoxide openings followed by subsequent oxidations (Scheme 1.24). The structures possess the least oxidizable carbon-hydrogen bonds on any compounds in this work. All other substrates are largely activated in the benzylic or allylic positions unlike compound 25a
which is largely aliphatic in character. The synthesis of aminoalcohols 25a-f is similar to those previously mentioned. The chief problems come from the lack of a chromophore, making monitoring of the reaction and purification much more difficult, especially as the compounds are also largely unreactive with stains. These transformations gave moderate to high yields (56-95% isolated yield).

1.2.7 Regioselective synthesis of aminoalcohols derived from styrene oxide

1.2.7.1 Investigation of the parameters affecting regioselectivity

Regioselectivity is a common challenge in organic synthesis. It has been well studied in asymmetric epoxides, particularly with the aminolysis of styrene oxide (6).\textsuperscript{21, 22, 25-30, 32, 33, 35, 38, 49, 50, 54, 59-65} These studies found that the regioselectivity is largely influenced by the nucleophilicity
and steric effects of the amine and somewhat by the choice of solvent. For the most part catalyst choice appears to have little influence over the outcome of the reaction (*vide infra*). The finding of magnesium perchlorate as an effective catalyst in the previous reactions comes as a serendipitously good choice in the regioselective opening of epoxide 6 by aliphatic and benzylic amines. Preliminary results for the aminolysis of epoxide 6 by benzyl amine (7) showed that both regioisomers 8 and 9 were obtained from the reaction in good proportions. Based on literature results, this is counter to nearly all examples of metal salt catalysts for these specific substrates (*vide infra*). Thus, we hypothesized that by a thorough investigation of reaction variables, we could influence the equilibrium to favor the far less common regioisomer 9. Formation of aminoalcohol 8 was favored when alkali or lanthanide metals were employed (Table 1.2, Entries 1-8). When other alkaline earth (Group 2) perchlorate salts are employed they also favor compound 8 (Table 1.2, Entries 10-13). Not only is magnesium unique to the formation of regioisomer 9, the reaction must be performed in acetonitrile (Table 1.2, Entries 14-17). Even other polar aprotic solvents like *N*,*N*-dimethylformamide (DMF) or tetrahydrofuran (THF) favor opening on the less hindered side of the epoxide to form aminoalcohol 8. In terms of stoichiometry, lower catalyst loadings (Table 1.3, Entries 1-3) and higher equivalents of amine (Table 1.3, Entries 4-6) tend to favor the formation of regioisomer 9. However, further reactions in this experiment do not use low catalyst loadings as they seem to favor Meinwald rearrangement products where the epoxide isomerizes to a ketone or aldehyde. This topic is discussed at the end of the chapter. Higher amine loadings give a small increase in regioselectivity but are not worth the difficulty in purification as a trade-off. Further investigation suggests that these changes to the equilibrium are not due to concentration effects (Table 1.3, entries 7-8).
Originally the reaction was thought to have a degree of variability that seemed to come from using acetonitrile as solvent. Acetonitrile can easily take up water. We developed a hypothesis that the reaction may be sensitive to moisture effects in the reaction. Indeed, with magnesium perchlorate as a catalyst, water steadily eroded the selectivity for isomer 9 (Table 1.4, Entries 1-7). This effect, however, did not persist for the other alkaline earth salt catalysts (Table 1.4, Entries 8-11). Unique to magnesium perchlorate and acetonitrile in the reaction was the formation of a thick gel upon the mixing of all reagents, which persisted throughout the reaction (Figure 1.8). This gel is evidence of a loosely-ordered hydrogen-bonded network. The consistency of the gel fell apart when the water content was increased suggesting that the matrix becomes more disordered. Understanding the nature of this gel might help us understand what gives rise to the unique regioselectivity of this reaction.
Figure 1.8 The magnesium perchlorate catalyzed reactions form a thick gel
Table 1.2 Evaluation of solvent and counter ion effects on the regioselectivity during opening of epoxide 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Loading</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>% Yield</th>
<th>Ratio 8:9c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>6 days</td>
<td>72%</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>Acetonitrile</td>
<td>reflux</td>
<td>72 hr</td>
<td>41%</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>Nitromethane</td>
<td>r.t.</td>
<td>24 hr</td>
<td>78%</td>
<td>71:29</td>
</tr>
<tr>
<td>4</td>
<td>LiClO₄</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>6 hr</td>
<td>72%</td>
<td>77:23</td>
</tr>
<tr>
<td>5</td>
<td>LiClO₄</td>
<td>4000%</td>
<td>Diethyl ether</td>
<td>r.t.</td>
<td>48 hr</td>
<td>65%</td>
<td>57:43</td>
</tr>
<tr>
<td>6</td>
<td>NaClO₄</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>6 hr</td>
<td>25%</td>
<td>76:24</td>
</tr>
<tr>
<td>7</td>
<td>Yb(OTf)₃</td>
<td>25%</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>NR</td>
<td>98%</td>
<td>55:45</td>
</tr>
<tr>
<td>8</td>
<td>Ca(BF₄)₂</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>24 hr</td>
<td>-d</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Ca(ClO₄)₂·4H₂O</td>
<td>50%</td>
<td>DMF</td>
<td>70°C</td>
<td>6 hr</td>
<td>62%</td>
<td>81:19</td>
</tr>
<tr>
<td>10</td>
<td>Ca(ClO₄)₂·4H₂O</td>
<td>50%</td>
<td>THF</td>
<td>70°C</td>
<td>6 hr</td>
<td>69%</td>
<td>78:22</td>
</tr>
<tr>
<td>11</td>
<td>Ca(ClO₄)₂·4H₂O</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>6 hr</td>
<td>75%</td>
<td>79:21</td>
</tr>
<tr>
<td>12</td>
<td>Ca(ClO₄)₂·4H₂O</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>6 hr</td>
<td>76%</td>
<td>78:22</td>
</tr>
<tr>
<td>13</td>
<td>Mg(OTf)₂</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>24 hr</td>
<td>6%</td>
<td>33:67</td>
</tr>
<tr>
<td>14</td>
<td>Mg(OTf)₂</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>6 hr</td>
<td>39%</td>
<td>35:65</td>
</tr>
<tr>
<td>15</td>
<td>Mg(ClO₄)₂</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>6 hr</td>
<td>67%</td>
<td>81:19</td>
</tr>
<tr>
<td>16</td>
<td>Mg(ClO₄)₂</td>
<td>50%</td>
<td>DMF</td>
<td>70°C</td>
<td>6 hr</td>
<td>62%</td>
<td>73:27</td>
</tr>
</tbody>
</table>

a Epoxide 6 500 mg (4.2 mmol), amine 7 500 mg (4.6 mmol), volume 10 mL
b Isolated after washing
c Ratio of peak areas from GC-MS chromatogram
d Evidence of Meinwald rearrangement products
Table 1.3 Evaluation of stoichiometry and concentration on the regioselectivity during opening of epoxide 6

\[
\begin{array}{ccccccc}
\text{Entry} & \text{Eq. Amine} & \text{Eq. Catalyst} & \text{Volume} & \% \text{ Yield}^{b} & \text{Ratio 8:9}^{c} \\
1 & 1.1 & .25 & 10 \text{ mL} & 42\% & 21:79 \\
2 & 1.1 & .50 & 10 \text{ mL} & 39\% & 35:65 \\
3 & 1.1 & 1.0 & 10 \text{ mL} & 59\% & 40:60 \\
4 & 0.5 & .50 & 10 \text{ mL} & 95\%^{d} & 42:58 \\
5 & 2 & .50 & 10 \text{ mL} & 78\% & 21:79 \\
6 & 3 & .50 & 10 \text{ mL} & 81\% & 30:70 \\
7 & 1.1 & .50 & 20 \text{ mL} & 54\% & 22:78 \\
8 & 1.1 & .50 & 5 \text{ mL} & 48\% & 19:81 \\
\end{array}
\]

\(^{a}\) Epoxide 2 500 mg (4.2 mmol), Mg(ClO\(_4\))\(_2\) (2.1 mmol), temp. 70°C

\(^{b}\) Isolated after washing

\(^{c}\) Ratio of peak areas from GC-MS chromatogram

\(^{d}\) Yield based on 2.1 mmol theoretical yield

Table 1.4 Evaluation of water content on the regioselectivity during opening of epoxide 6

\[
\begin{array}{cccc}
\text{Entry} & \text{Lewis Acid} & \% \text{ Yield}^{b} & \text{Ratio 8:9}^{c} \\
1 & \text{Mg(ClO}_4\text{)}\text{2} & 93\% & 33:67 \\
2 & \text{Mg(ClO}_4\text{)}\text{2·1H}_2\text{O} & 89\% & 24:76 \\
3 & \text{Mg(ClO}_4\text{)}\text{2·5H}_2\text{O} & 96\% & 50:50 \\
4 & \text{Mg(ClO}_4\text{)}\text{2·6H}_2\text{O} & 41\% & 58:42 \\
5 & \text{Mg(ClO}_4\text{)}\text{2·20H}_2\text{O} & 76\% & 64:36 \\
6 & \text{Mg(ClO}_4\text{)}\text{2·xH}_2\text{O} & 39\% & 65:35 \\
7 & \text{Ca(ClO}_4\text{)}\text{2} & 92\% & 71:29 \\
8 & \text{Ca(ClO}_4\text{)}\text{2·4H}_2\text{O} & 75\% & 72:28 \\
9 & \text{Ba(ClO}_4\text{)}\text{2} & 94\% & 81:19 \\
10 & \text{Ba(ClO}_4\text{)}\text{2·4H}_2\text{O} & 76\% & 78:22 \\
\end{array}
\]

\(^{a}\) Epoxide 6 500 mg (4.2 mmol), amine 7 (4.6 mmol), Mg(ClO\(_4\))\(_2\) (2.1 mmol), ACN 10mL, temp. 70°C

\(^{b}\) Isolated after washing

\(^{c}\) Ratio of peak areas from GC-MS chromatogram
We were aware of the fact that magnesium chelators may influence the selectivity. Early results suggested this may be the case, as seen in Table 1.5, Entry 1. Across many reactions, however, no clear trend of additive effects could be observed (Table 1.5, Entries 1-10). Acidic additives likely favor Meinwald products, however none were isolated to prove this. What may appear as a regioselectivity effect of an additive may actually be due to modulation of available water content in the reaction matrix.

Table 1.5 Evaluation of additives on the regioselectivity during opening of epoxide 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ratio 8:9&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Trisodium citrate dihydrate</td>
<td>Acetonitrile</td>
<td>41%</td>
<td>21:79</td>
</tr>
<tr>
<td>2</td>
<td>Mg(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Trisodium citrate dihydrate</td>
<td>Acetonitrile</td>
<td>6%</td>
<td>32:68</td>
</tr>
<tr>
<td>3</td>
<td>NaClO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Trisodium citrate dihydrate</td>
<td>Acetonitrile</td>
<td>5%</td>
<td>60:40</td>
</tr>
<tr>
<td>4</td>
<td>Yb(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Trisodium citrate dihydrate</td>
<td>Acetonitrile</td>
<td>30%</td>
<td>53:47</td>
</tr>
<tr>
<td>5</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Trisodium citrate dihydrate</td>
<td>Methanol</td>
<td>51%</td>
<td>61:39</td>
</tr>
<tr>
<td>6</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Trisodium citrate dihydrate</td>
<td>DMF</td>
<td>25%</td>
<td>82:18</td>
</tr>
<tr>
<td>7</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>EDTA</td>
<td>Acetonitrile</td>
<td>2%</td>
<td>24:76</td>
</tr>
<tr>
<td>8</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Jacobsen Ligand</td>
<td>Acetonitrile</td>
<td>10%</td>
<td>33:67</td>
</tr>
<tr>
<td>9</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>N-acyl tryptophan</td>
<td>Acetonitrile</td>
<td>27%</td>
<td>62:38</td>
</tr>
<tr>
<td>10</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Phenylalanine benzyl ester</td>
<td>Acetonitrile</td>
<td>7%</td>
<td>50:50</td>
</tr>
<tr>
<td>11</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Succinic acid</td>
<td>Acetonitrile</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Citric acid</td>
<td>Acetonitrile</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Citric acid</td>
<td>Methanol</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Citric acid</td>
<td>Acetic acid</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Epoxide 6 500 mg (4.2 mmol), amine 7 (4.6 mmol), catalyst and additive (2.1 mmol), volume 10mL, r.t.

<sup>b</sup> Isolated after washing

<sup>c</sup> Ratio of peak areas from GC-MS chromatogram
1.2.7.2 Scope of the synthesis of aminoalcohols derived from styrene oxide

The above optimization tables affirm that the discovery of magnesium perchlorate in anhydrous acetonitrile was not only useful for many symmetrical epoxides, but also gave interesting regioselectivity for the aminolysis of styrene oxide. The reaction scope was even better when compared to the phenanthroline library. Aliphatic and allylic amines were used without issue of a competing dehydration (Scheme 1.25). Based on the amines tolerated, which cover a wide range of electronic and steric effects, it is likely that epoxide 6 may serve as a substrate for most primary amines. Good regioselectivity for isomer 9 was maintained across all amines. The lower
yields are partially due to amine degradation and the magnesium-catalyzed rearrangement of the epoxide.

To access the more common regioisomer 8, many catalysts could be employed. Reactions with calcium perchlorate gave clean reactions and was an excellent choice for producing aminoalcohols 8a-f (Scheme 1.26). The reaction afforded products in >90% yield for compounds

![Reaction Scheme](image)

Scheme 1.26 Reactions of epoxide 6 with primary amines catalyzed by calcium perchlorate

8a-9f. It also worked for the ortho-nitro derivative, which was obtained in only at 68% yield. The lower yield may be due to the amine having suffered some degradation after neutralization ex situ and due to the steric of the amine.
1.2.7.3 Comparative investigation in the role of amine on regioselectivity

Many studies have looked at catalyst influence on the regioselectivity in the formation of aminoalcohols 8 and 9 which provides an excellent baseline for the comparison of the current study and future studies. For the aminolysis of styrene oxide (6) by aniline to afford products 8 and 9g, the regioselectivity, while a bit poorer, is in line with all other results (Table 1.6) Similar results were also obtained for the aminolysis by p-chloroaniline (Table 1.7). For both compounds the regioselectivity is likely most controlled by the electronics of the amine conjugated with benzene ring. This makes the nitrogen much less nucleophilic. It would prefer reacting at the more hindered site because the epoxide opens likely first in an $S_N1$ like reaction. The aminolysis using benzyl amine shows the true uniqueness of magnesium perchlorate in acetonitrile (Table 1.8). The only results similar are those obtained Chini$^{32}$ (Entry 9) and Reedjik$^{65}$ (Entry 14). They used acetonitrile is again the solvent but the catalysts are a lithium and zinc salt respectively. In neither case does the selectivity approach our result (Entry 1). For the use of morpholine in the reaction, where steric is likely the major influence our results line up with those of other reports (Table 1.9). The aminolysis with imidazole stands out as an interesting example (Table 1.10). While there are few reports about the formation of compound 9j, none have been able to achieve a selectivity higher than $\sim$4:1 in favor of 9j. Only isomer 9j was the product when magnesium perchlorate was employed in the presence of
Table 1.6 Comparison of regioselective openings of epoxide $\text{6}$ with aniline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield</th>
<th>Ratio 8:9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>Mg(ClO$_4$)$_2$</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>2 hr</td>
<td>98</td>
<td>26:74$^b$</td>
</tr>
<tr>
<td>2$^5$</td>
<td>Graphene oxide</td>
<td>-</td>
<td>r.t.</td>
<td>16 h</td>
<td>95</td>
<td>4:96</td>
</tr>
<tr>
<td>3$^6$</td>
<td>Proline on silica</td>
<td>-</td>
<td>microwave</td>
<td>15 m</td>
<td>96</td>
<td>3:97</td>
</tr>
<tr>
<td>4$^7$</td>
<td>Tryptophan on silica</td>
<td>-</td>
<td>microwave</td>
<td>3 m</td>
<td>100</td>
<td>2:98</td>
</tr>
<tr>
<td>5$^9$</td>
<td>Y(NO$_3$)$_3$·6H$_2$O</td>
<td>-</td>
<td>r.t.</td>
<td>1 h</td>
<td>81</td>
<td>16:84</td>
</tr>
<tr>
<td>6$^{10}$</td>
<td>Zn(BF$_4$)$_2$·xH$_2$O</td>
<td>-</td>
<td>r.t.</td>
<td>1 h</td>
<td>96</td>
<td>1:99</td>
</tr>
<tr>
<td>7$^{11}$</td>
<td>ZrCl$_4$</td>
<td>-</td>
<td>r.t.</td>
<td>15 m</td>
<td>98</td>
<td>8:92</td>
</tr>
<tr>
<td>8$^{12}$</td>
<td>LiBr</td>
<td>-</td>
<td>r.t.</td>
<td>5 h</td>
<td>98</td>
<td>2:92</td>
</tr>
<tr>
<td>9$^{13}$</td>
<td>Montmorillonite clay</td>
<td>-</td>
<td>r.t.</td>
<td>90 m</td>
<td>93</td>
<td>7:93</td>
</tr>
<tr>
<td>10$^{14}$</td>
<td>Organothiourea</td>
<td>-</td>
<td>60°C</td>
<td>2.75 h</td>
<td>96</td>
<td>15:85</td>
</tr>
<tr>
<td>11$^{15}$</td>
<td>LiClO$_4$</td>
<td>-</td>
<td>r.t.</td>
<td>3.5 h</td>
<td>95</td>
<td>8:92</td>
</tr>
<tr>
<td>12$^{16}$</td>
<td>Sc(OTf)$_3$</td>
<td>-</td>
<td>r.t.</td>
<td>2 h</td>
<td>95</td>
<td>5:95</td>
</tr>
<tr>
<td>13$^{17}$</td>
<td>Mg(ClO$_4$)$_2$</td>
<td>-</td>
<td>r.t.</td>
<td>8 m</td>
<td>99</td>
<td>2:98</td>
</tr>
<tr>
<td>14$^{18}$</td>
<td>Cu(BF$_4$)$_2$·xH$_2$O</td>
<td>-</td>
<td>r.t.</td>
<td>5 m</td>
<td>97</td>
<td>0:100</td>
</tr>
<tr>
<td>15$^{19}$</td>
<td>Cyanuric chloride</td>
<td>-</td>
<td>r.t.</td>
<td>15 m</td>
<td>99</td>
<td>3:97</td>
</tr>
<tr>
<td>16$^{20}$</td>
<td>-</td>
<td>Acetonitrile</td>
<td>172°C microwave</td>
<td>60 m</td>
<td>82</td>
<td>68:32</td>
</tr>
<tr>
<td>17$^{21}$</td>
<td>-</td>
<td>Methanol</td>
<td>152°C microwave</td>
<td>15 m</td>
<td>79</td>
<td>45:55</td>
</tr>
<tr>
<td>18$^{22}$</td>
<td>-</td>
<td>Water</td>
<td>60°C</td>
<td>8 h</td>
<td>95</td>
<td>15:85</td>
</tr>
<tr>
<td>19$^{23}$</td>
<td>ZnCl$_2$</td>
<td>Acetonitrile</td>
<td>82°C</td>
<td>12 h</td>
<td>100</td>
<td>7:93</td>
</tr>
<tr>
<td>20$^{24}$</td>
<td>Modified montmorillonite clay</td>
<td>-</td>
<td>r.t.</td>
<td>30 m</td>
<td>94</td>
<td>5:95</td>
</tr>
<tr>
<td>21$^{25}$</td>
<td>Sulfated zirconia</td>
<td>-</td>
<td>60°C</td>
<td>1 h</td>
<td>96</td>
<td>0:100</td>
</tr>
</tbody>
</table>

$^a$ Epoxide $\text{6}$ 500 mg (4.2 mmol), amine $\text{7}$ (4.6 mmol), catalyst loading (2.1 mmol); $^b$ GC-MS ratio
Table 1.7 Comparison of regioselective openings of epoxide 6 with 4-chloroaniline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>% Yield</th>
<th>Ratio 8:9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Mg(ClO₄)₂</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>4 hr</td>
<td>97⁵⁶</td>
<td>23:77⁵⁶</td>
</tr>
<tr>
<td>2²⁵</td>
<td>Graphene oxide</td>
<td>-</td>
<td>r.t.</td>
<td>16 h</td>
<td>96</td>
<td>5:95</td>
</tr>
<tr>
<td>3²⁶</td>
<td>Proline on silica</td>
<td>-</td>
<td>microwave</td>
<td>15 m</td>
<td>75</td>
<td>4:96</td>
</tr>
<tr>
<td>4²⁷</td>
<td>Tryptophan on silica</td>
<td>-</td>
<td>microwave</td>
<td>3 m</td>
<td>95</td>
<td>2:98</td>
</tr>
<tr>
<td>5⁶⁰</td>
<td>Zn(BF₄)ₓ·xH₂O</td>
<td>-</td>
<td>r.t.</td>
<td>30 m</td>
<td>92</td>
<td>13:87</td>
</tr>
<tr>
<td>6⁸¹</td>
<td>ZrCl₄</td>
<td>-</td>
<td>r.t.</td>
<td>15 m</td>
<td>95</td>
<td>0:100</td>
</tr>
<tr>
<td>7³⁵</td>
<td>LiBr</td>
<td>-</td>
<td>r.t.</td>
<td>5 h</td>
<td>100</td>
<td>0:100</td>
</tr>
<tr>
<td>8²⁸</td>
<td>Montmorillonite clay</td>
<td>-</td>
<td>r.t.</td>
<td>90 m</td>
<td>100</td>
<td>0:100</td>
</tr>
<tr>
<td>9⁴⁰</td>
<td>Organothiourea</td>
<td>-</td>
<td>60°C</td>
<td>3 h</td>
<td>87</td>
<td>13:87</td>
</tr>
<tr>
<td>10⁶³</td>
<td>Cu(BF₄)ₓ·xH₂O</td>
<td>-</td>
<td>r.t.</td>
<td>5 m</td>
<td>97</td>
<td>0:100</td>
</tr>
<tr>
<td>11⁵⁰</td>
<td>Cynuric chloride</td>
<td>-</td>
<td>r.t.</td>
<td>20 m</td>
<td>97</td>
<td>3:97</td>
</tr>
<tr>
<td>12⁶⁴</td>
<td></td>
<td>Water</td>
<td>60°C</td>
<td>8 h</td>
<td>94</td>
<td>5:95</td>
</tr>
<tr>
<td>13³⁹</td>
<td>Modified montmorillonite clay</td>
<td>-</td>
<td>r.t.</td>
<td>3 h</td>
<td>95</td>
<td>5:95</td>
</tr>
</tbody>
</table>

² Epoxide 6 500 mg (4.2 mmol), amine 7 (4.6 mmol), catalyst loading (2.1 mmol)
⁵ Isolated after washing
⁶ Ratio of peak areas from GC-MS chromatogram
Table 1.8 Comparison of regioselective openings of epoxide 6 with amine 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>% Yield</th>
<th>Ratio 8:9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mg(ClO₄)₂</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>4 h</td>
<td>83&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24:76&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Graphene oxide</td>
<td>-</td>
<td>r.t.</td>
<td>48 h</td>
<td>97</td>
<td>80:20</td>
</tr>
<tr>
<td>3&lt;sup&gt;33&lt;/sup&gt;</td>
<td>LiOTf</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>3.5 h</td>
<td>83</td>
<td>60:40</td>
</tr>
<tr>
<td>4&lt;sup&gt;21&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>r.t.</td>
<td>7 d</td>
<td>66</td>
<td>94:6</td>
</tr>
<tr>
<td>5&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Benzylamine HCl</td>
<td>-</td>
<td>r.t.</td>
<td>2 d</td>
<td>65</td>
<td>88:12</td>
</tr>
<tr>
<td>6&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Zn(BF₄)₂·xH₂O</td>
<td>-</td>
<td>r.t.</td>
<td>4 h</td>
<td>86</td>
<td>75:25</td>
</tr>
<tr>
<td>7&lt;sup&gt;61&lt;/sup&gt;</td>
<td>ZrCl₄</td>
<td>-</td>
<td>r.t.</td>
<td>15 m</td>
<td>96</td>
<td>78:22</td>
</tr>
<tr>
<td>8&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Montmorillonite clay</td>
<td>-</td>
<td>r.t.</td>
<td>90 m</td>
<td>89</td>
<td>82:18</td>
</tr>
<tr>
<td>9&lt;sup&gt;32&lt;/sup&gt;</td>
<td>LiClO₄</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>1.5 h</td>
<td>98</td>
<td>42:58</td>
</tr>
<tr>
<td>10&lt;sup&gt;92&lt;/sup&gt;</td>
<td>Sc(OTf)₃</td>
<td>-</td>
<td>r.t.</td>
<td>2 h</td>
<td>89</td>
<td>85:15</td>
</tr>
<tr>
<td>11&lt;sup&gt;50&lt;/sup&gt;</td>
<td>cyanuric chloride</td>
<td>-</td>
<td>r.t.</td>
<td>15 m</td>
<td>96</td>
<td>93:3</td>
</tr>
<tr>
<td>12&lt;sup&gt;54&lt;/sup&gt;</td>
<td>-</td>
<td>Acetonitrile</td>
<td>138°C microwave</td>
<td>15 m</td>
<td>84</td>
<td>82:18</td>
</tr>
<tr>
<td>13&lt;sup&gt;64&lt;/sup&gt;</td>
<td>-</td>
<td>Water</td>
<td>60°C</td>
<td>2.5 h</td>
<td>90</td>
<td>75:25</td>
</tr>
<tr>
<td>14&lt;sup&gt;65&lt;/sup&gt;</td>
<td>ZnCl₂</td>
<td>Acetonitrile</td>
<td>82°C</td>
<td>12 h</td>
<td>40</td>
<td>41:59</td>
</tr>
<tr>
<td>15&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Modified montmorillonite clay</td>
<td>-</td>
<td>r.t.</td>
<td>3 h</td>
<td>93</td>
<td>92:8</td>
</tr>
<tr>
<td>16&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Sulfated zirconia</td>
<td>-</td>
<td>60°C</td>
<td>6 h</td>
<td>84</td>
<td>53:31</td>
</tr>
</tbody>
</table>

<sup>a</sup> Epoxide 6 500 mg (4.2 mmol), amine 7 (4.6 mmol), catalyst loading (2.1 mmol)

<sup>b</sup> Isolated after washing

<sup>c</sup> Ratio of peak areas from GC-MS chromatogram
Table 1.9 Comparison of regioselective openings of epoxide 6 with morpholine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>% Yield</th>
<th>Ratio 8:9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Mg(ClO₄)₂</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>3 hr</td>
<td>76b</td>
<td>91:9c</td>
</tr>
<tr>
<td>2b</td>
<td>Graphene oxide</td>
<td>-</td>
<td>r.t.</td>
<td>16 h</td>
<td>82</td>
<td>99:0</td>
</tr>
<tr>
<td>3c</td>
<td>LiOTf</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>1 h</td>
<td>88</td>
<td>58:42</td>
</tr>
<tr>
<td>4d</td>
<td>Zn(BF₄)₂·xH₂O</td>
<td>-</td>
<td>r.t.</td>
<td>60 m</td>
<td>100</td>
<td>91:9</td>
</tr>
<tr>
<td>4e</td>
<td>ZrCl₄</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>15 m</td>
<td>94</td>
<td>55:45</td>
</tr>
<tr>
<td>5f</td>
<td>LiBr</td>
<td>-</td>
<td>r.t.</td>
<td>5 h</td>
<td>94</td>
<td>52:48</td>
</tr>
<tr>
<td>6g</td>
<td>Montmorillonite clay</td>
<td>-</td>
<td>r.t.</td>
<td>90 m</td>
<td>83</td>
<td>100:0</td>
</tr>
<tr>
<td>7h</td>
<td>Sc(OTf)₃</td>
<td>-</td>
<td>r.t.</td>
<td>3 h</td>
<td>92</td>
<td>70:30</td>
</tr>
<tr>
<td>8i</td>
<td>Mg(ClO₄)₂</td>
<td>-</td>
<td>r.t.</td>
<td>180 m</td>
<td>97</td>
<td>54:46</td>
</tr>
<tr>
<td>9j</td>
<td>Cu(BF₄)₂·xH₂O</td>
<td>-</td>
<td>r.t.</td>
<td>10 m</td>
<td>96</td>
<td>84:16</td>
</tr>
<tr>
<td>10k</td>
<td>Cyanuric chloride</td>
<td>-</td>
<td>r.t.</td>
<td>25 m</td>
<td>96</td>
<td>96:4</td>
</tr>
<tr>
<td>11l</td>
<td>Modified montmorillonite clay</td>
<td>Water</td>
<td>60°C</td>
<td>2 h</td>
<td>95</td>
<td>96:4</td>
</tr>
<tr>
<td>12m</td>
<td>-</td>
<td>Water</td>
<td>60°C</td>
<td>2 h</td>
<td>98</td>
<td>100:0</td>
</tr>
<tr>
<td>13n</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Epoxide 6 500 mg (4.2 mmol), amine 7 (4.6 mmol), catalyst loading (2.1 mmol)
* Isolated after washing
* Ratio of peak areas from GC-MS chromatogram
Table 1.10 Comparison of regioselective openings of epoxide 6 with imidazole

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>% Yield</th>
<th>Ratio 8:9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mg(ClO&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>3 hr</td>
<td>44&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.99&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Y(NO&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;·6H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>-</td>
<td>r.t.</td>
<td>24 h</td>
<td>92</td>
<td>41:59</td>
</tr>
<tr>
<td>3&lt;sup&gt;54&lt;/sup&gt;</td>
<td>-</td>
<td>Methanol</td>
<td>185°C</td>
<td>2 m</td>
<td>81</td>
<td>22:78</td>
</tr>
<tr>
<td>4&lt;sup&gt;54&lt;/sup&gt;</td>
<td>-</td>
<td>Acetonitrile</td>
<td>237°C</td>
<td>2 m</td>
<td>82</td>
<td>18:82</td>
</tr>
</tbody>
</table>

<sup>a</sup> Epoxide 6 500 mg (4.2 mmol), amine 7 (4.6 mmol), catalyst loading (2.1 mmol)

<sup>b</sup> Isolated after washing

<sup>c</sup> Ratio of peak areas from GC-MS chromatogram
Table 1.11 Comparison of regioselective openings of epoxide 6 with butylamine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>% Yield</th>
<th>Ratio 8:9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Mg(ClO₄)₂</td>
<td>Acetonitrile</td>
<td>70°C</td>
<td>4 h</td>
<td>70b</td>
<td>33:67c</td>
</tr>
<tr>
<td>249</td>
<td>Organothiourea</td>
<td>-</td>
<td>60°C</td>
<td>1.75 h</td>
<td>94</td>
<td>83:17</td>
</tr>
<tr>
<td>332</td>
<td>LiClO₄</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>1h</td>
<td>96</td>
<td>47:53</td>
</tr>
<tr>
<td>429</td>
<td>Modified montmorillonite clay</td>
<td>-</td>
<td>r.t.</td>
<td>5 h</td>
<td>24</td>
<td>0:100</td>
</tr>
</tbody>
</table>

*a Epoxide 6 500 mg (4.2 mmol), amine 7 (4.6 mmol), catalyst loading (2.1 mmol)*

*b Isolated after washing

*c Ratio of peak areas from GC-MS chromatogram*
of acetonitrile. The reactivity of aniline derivatives could be affected by electronics including \( \pi-\pi \) stacking interactions that may stabilize a transition state in favor of aminoalcohol 9j. Finally, similar to imidazole, aminolysis with butylamine also achieves the highest reported selectivity when using magnesium perchlorate as catalyst (Table 1.1). Whether or not this unique reactivity will extend to other asymmetric epoxides is a topic that warrants further study. Also, the underlying mechanism behind this selectivity must be understood if it is to be improved upon. One experiment that must be run is to find the kinetics of the various components in the reaction. Small metal cations, such as lithium and magnesium, are known to form complex clusters in solution and so if this is contributing to the reactivity it may be hinted at by the kinetics. All results are based on the use of racemic styrene oxide. It would be interesting to study if enantiopurity is eroded when using either \((R)\)-styrene oxide or \((S)\)-styrene oxide.

1.2.7.4 Regioselectivity in the synthesis of aminoalcohols via a bromohydrin

One final observation in this work is related to the use of boron tribromide as a Lewis acid. Early results suggested that it is an excellent catalyst for favoring the formation of regioisomer 9 (Table 1.12). This could be a function of the nature of the boron catalyst as boron trifluoride also favors the formation of aminoalcohol 9. However, another possible mechanism may be at play, especially to explain the cases where there is no reaction to form regioisomer 8. Boron tribromide possesses highly reactive boron-halogen bonds and is known, among other reactions, to cleave ethers (one of the few reagents capable of reacting with such a stable group). Excellent boron reagents have been created for the synthesis of halohydrin 26 from styrene oxide. The halohydrin then can function as an excellent substrate for either an \( \text{S}^1 \) or \( \text{S}^2 \) reaction (Scheme 1.2). This mechanism is supported by detection of intermediate 26 by GC-MS and \(^1\text{H}-\text{NMR}\).
Table 1.12 Evaluation of boron compounds on the regioselectivity during opening of epoxide 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Loading</th>
<th>Solvent</th>
<th>Temperature</th>
<th>% Yield</th>
<th>Ratio 8:9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BBr&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10%</td>
<td>DCM</td>
<td>r.t.</td>
<td>18%</td>
<td>1:99</td>
</tr>
<tr>
<td>2</td>
<td>BBr&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10%</td>
<td>DCM</td>
<td>r.t.</td>
<td>31%</td>
<td>23:77</td>
</tr>
<tr>
<td>3</td>
<td>BBr&lt;sub&gt;3&lt;/sub&gt;</td>
<td>50%</td>
<td>DCM</td>
<td>r.t.</td>
<td>27%</td>
<td>22:78</td>
</tr>
<tr>
<td>4</td>
<td>BBr&lt;sub&gt;3&lt;/sub&gt;</td>
<td>50%</td>
<td>DCM</td>
<td>r.t.</td>
<td>14%</td>
<td>1:99</td>
</tr>
<tr>
<td>5</td>
<td>BBr&lt;sub&gt;3&lt;/sub&gt;</td>
<td>50%</td>
<td>DCM</td>
<td>r.t.</td>
<td>6%</td>
<td>1:99</td>
</tr>
<tr>
<td>6</td>
<td>BBr&lt;sub&gt;3&lt;/sub&gt;</td>
<td>200%</td>
<td>DCM</td>
<td>r.t.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>BBr&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10%</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>33%</td>
<td>16:84</td>
</tr>
<tr>
<td>8</td>
<td>BBr&lt;sub&gt;3&lt;/sub&gt;</td>
<td>50%</td>
<td>DCM</td>
<td>-30</td>
<td>10%</td>
<td>1:99</td>
</tr>
<tr>
<td>9</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt; dihydrate</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>9%</td>
<td>1:99</td>
</tr>
<tr>
<td>10</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt; dihydrate</td>
<td>50%</td>
<td>DCE</td>
<td>r.t.</td>
<td>5%</td>
<td>1:99</td>
</tr>
<tr>
<td>11</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt; etherate</td>
<td>50%</td>
<td>DCM</td>
<td>r.t.</td>
<td>8%</td>
<td>30:70</td>
</tr>
<tr>
<td>12</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt; etherate</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>4%</td>
<td>40:60</td>
</tr>
<tr>
<td>13</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt; THF</td>
<td>50%</td>
<td>DCE</td>
<td>r.t.</td>
<td>9%</td>
<td>1:99</td>
</tr>
<tr>
<td>14</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt; THF</td>
<td>50%</td>
<td>Acetonitrile</td>
<td>r.t.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>B(OH)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>50%</td>
<td>DCE</td>
<td>r.t.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>B(OH)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>50%</td>
<td>DCE</td>
<td>reflux</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>B(OPh)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>50%</td>
<td>DCE</td>
<td>r.t.</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Epoxide 6 500 mg (4.2 mmol), amine 7 (4.6 mmol)

Scheme 1.27 Formation of aminoalcohol 9c through a purported bromohydrin intermediate
While this methodology may prove to be an excellent way to gain high yields of aminoalcohol 9 and its analogues, we abandoned this path for several reasons. First, boron tribromide is incredibly reactive and even at cold temperatures the reaction is difficult to control. This problem may be avoided by using the Roy-Brown bromoboron reagents. The other disadvantage is likely more intractable: boron-based Lewis acids are also excellent catalysts of the Meinwald rearrangement (Scheme 1.28). Particularly with boron trifluoride, the Meinwald rearrangement is likely the faster reaction under the conditions studied. Lastly the yield were 33%, while this path may offer even better selectivity than magnesium perchlorate, it was magnesium that was pursued in depth due to its reliability and ease of use.

![](image)

Scheme 1.28 The Meinwald rearrangement of epoxides

1.3 Conclusion

In total, 72 compounds were produced in this work of which 56 were previously unreported in the literature. Magnesium perchlorate in acetonitrile gave the best results for phenanthroline-based epoxides, as well as others. Especially when the aminoalcohol product is not easily dehydrated, magnesium perchlorate offers a wide scope for choice of amine and epoxide for the aminolysis. The catalyst gave reliably good and scaleable yields often regardless of steric or electronic effects in the amine. Particularly useful was the unique reactivity observed for the aminolyses of styrene oxide in acetonitrile with magnesium perchlorate. Magnesium perchlorate offered the highest selectivity of any reported reaction for the isolation of product that results from
opening on the more hindered side of the epoxide. These reactions offer excellent yields of isolated aminoalcohols as substrates for the formation of substituted oxazoles and related heterocycles by oxidation and cyclization.

1.4 References


(58) Kohler, L. In *Preparation of 1,10-phenanthroline derivatives with B-Ring functionalization and their application / by Lars Kohler; Schoffers, E., Western Michigan University. Department of Chemistry, Eds.; 2011.*


CHAPTER 2: SYNTHESIS OF 1,10-PHENANTHROLINE AND PHENANTHRENE OXAZOLES FROM THEIR CORRESPONDING AMINOALCOHOLS

2.1 Introduction

Moody and coworkers reported that iminoquinones could be formed from aniline and 5,6-dihydro-1,10-phenanthroline-5,6-epoxid (Scheme 2.1).\(^1\) Lars Kohler, in his dissertation, discovered that when phenanthroline aminoalcohols were benzylamine adducts, the oxidation would go further to form an oxazole (Scheme 2.2).\(^2\) This was an unexpected transformation because the reaction requires the removal of six electrons, six protons, and a cyclization to convert the starting material to the subsequent product. This is not commonly seen in oxidation reactions especially with a mild oxidant like manganese dioxide. This reagent often provides a wide reaction scope because of its broad functional group tolerance. At the time of Kohler’s dissertation, only a small library was built based on analogues of benzoxazole that showed interesting photophysical properties; the scope of this reaction was never fully explored. This work expands these findings to

![Scheme 2.1 Preparation of an iminoquinone from an aminoalcohols](image-url)
probe if aminolysis followed by oxidation is a good path for the preparation of oxazoles and related heterocyclic compounds as was postulated previously (Scheme 2.3).

2.1.1 Importance of the oxazole functional group in materials

![Scheme 2.2 Kohler synthesis of an oxazole from an aminoalcohol](image)

Scheme 2.2 Kohler synthesis of an oxazole from an aminoalcohol

![Scheme 2.3 Dissertation hypothesis that heterocyclic compounds can be formed from epoxides](image)

Scheme 2.3 Dissertation hypothesis that heterocyclic compounds can be formed from epoxides

The oxazole functional group has gained increasing importance in recent years because it displays several interesting properties. Due to its photophysical properties it is incorporated in materials such as dyes, organic light emitting diodes, photovoltaics, supramolecular structures, and polymers. Further as the heterocyclic moiety contains a nitrogen lone pair available for metal binding, oxazole compounds are used as ligands for catalysts. For example Andersson’s work employed biaryl phosphite-oxazole ligands for asymmetric hydrogenation reactions (Figure 2.1). Due to their aromaticity, oxazoles find purpose as pi extensions of...
photosensitizer ligands and have been used to link photosensitizers to catalytic metals such as the cobaloxime unit. These complexes were developed as photosynthesis mimics where light activates a photoredox complex based on ruthenium and the electrons are passed to a redox catalyst to accomplish a reduction reaction. In the case of Fihri’s catalyst, the unit was cobaloxime to convert protons to hydrogen (Figure 2.2). Karlsson, using a similar strategy, instead chose to pass electrons to titanium dioxide nanoparticles (Figure 2.3).
Figure 2.2 Fihri’s complex for hydrogen production

Figure 2.3 Karlsson’s complex for hydrogen production
2.1.2 Methods for synthesizing benzoxazole-like compounds

Attention has been given to developing improved methods for the synthesis of functionalized oxazoles. As benzoxazoles are related to these phenanthroline oxazoles, their reported syntheses are particularly relevant to this study. They are often isolated after oxidative cyclization of an aminophenol Schiff’s base by mild oxidants. Bougrin et al. synthesized benzoxazoles from aldehydes and aminophenol using manganese dioxide on silica to oxidize the cyclized product of the 2-(alkylidnamino)phenol intermediate (Scheme 2.4). Many other reports of this oxidative cyclization have appeared using various oxidants including: lead tetraacetate, nickel peroxide, silver oxide, manganese triacetate, hypervalent iodine, oxygen, DDQ, PCC, and hydrogen-transfer catalysis.

Scheme 2.4 Bourgin synthesis of substituted 2-phenylbenzoxazole

2.1.3 The Japp oxazole synthesis and other methods for the synthesis of phenanthroline oxazoles

The synthesis of oxazolo[4,5-f][1,10]phenanthrolines and phenanthro[9,10-d]oxazoles are of particular interest because many of the compounds display interesting photophysical properties for material design. Since phenanthroline-5,6-dione and phenanthrene-9,10-dione are common starting materials for functionalization at those positions, the Japp synthesis is frequently used to
produce the oxazole moiety.\textsuperscript{4, 8, 10-17, 32-35} For this family of compounds the Japp synthesis is low yielding in oxazole formation whereas the imidazole is the major product of the reaction (Scheme 2.5).\textsuperscript{35} Other methods have been attempted but they suffer from low yields of the oxazole.\textsuperscript{36-40} A more efficient synthesis of these compounds is needed.

![Scheme 2.5 Japp synthesis of oxazoles](image)

\textbf{2.2 Results and Discussion}

\textbf{2.2.1 Synthesis of phenanthroline oxazoles}

Oxidation of the phenanthroline aminoalcohols from the previous chapter gave the respective oxazole product for each compound even for relatively weak nucleophiles like aliphatic amines 1a-1e (Scheme 2.6). Our method allowed for the preparation of a wide variety of oxazoles, including aliphatic, vinylic, benzylic, and phenyl substituted oxazoles. Different electronic effects are tolerated ranging from the strong electron donating methoxy groups to the strong electron withdrawing trifluoromethyl and nitro groups. This functional group tolerance is something rather unprecedented in traditional condensation methods. Our yields were often quantitative and compounds were easily purified by recrystallization. The most challenging reaction was the cyclization of derivative 1a which ran for 6 days at room temperature without full conversion.
Scheme 2.6 Oxidation of aminoalcohols 1a-w
Heating the reaction to 60°C afforded product 2a in 2 days. The oxidation of aminoalcohols 1t and 1v yielded an unidentified vividly colored side product (red for 2-nitrophenyl, yellow for 4-nitrophenyl) which, in the case of the 4-nitrophenyl oxidation, represents 40% of the theoretical yield. One other problematic compound was the benzylic substituted oxazole 2h, which readily underwent oxidation when exposed to light and air at room temperature. However, storage of this particular compound in the freezer prevented oxidation problems. Even for the few sensitive conversions, the reaction provided high yields (58-89%) making this a versatile method for the formation of phenanthroline oxazoles.

It is important to note that no commercial source of manganese dioxide worked. The only manganese dioxide that afforded the product was the Attenburrow preparation of activated manganese dioxide. There is a moderate degree of variability in the oxidizing power of the manganese dioxide produced by the reaction. One hypothesis is that washing greatly affects reagent quality. The amount of rinsing was tested by taking aliquots of the manganese dioxide over the course of rinsing after the Attenburrow preparation. It was found that the excess potassium permanganate must be thoroughly washed out to produce manganese dioxide suitable for our method. The value for pH mattered far less with values from 7.5-10.5 performing equally well in the reaction. Due to the variability in the quality of manganese dioxide we decided to standardize the oxidizing power of each batch of manganese dioxide. This is done by determining the number of equivalents that must be used to convert aminoalcohol 1i to oxazole 2i. Ideally a batch will be sufficiently strong enough to fully oxidize the material with 5-10 equivalents.
2.2.2 Synthesis of phenanthrene oxazoles

The oxidation chemistry for 1,10-phenanthroline derivatives extends quite well to the corresponding phenanthrene aminoalcohols (Scheme 2.7). Oxidation of their aminoalcohols gave similar results with several derivatives obtained in quantitative yield after recrystallization. Once again, a wide substrate scope is available with alkyl, vinyl, and phenyl groups with a range of electronics able to form the oxazole.

Scheme 2.7 Oxidation of aminoalcohols 3a-e
2.2.3 Efforts at probing the mechanism of the oxidation

Seeing such success previous groups have had in synthesizing oxazoles from 2-(alkylidenamino)phenols (Scheme 2.4) we propose a mechanism for our reaction that involves a similar species, as outlined in Scheme 2.8. Several attempts were made to view intermediates by NMR spectroscopy. Unfortunately, manganese dioxide cannot be present in an NMR sample making it necessary to filter off the oxidant. It was not possible to identify an intermediate of the reaction. It may be possible that intermediates of the oxidation adhere tightly to the manganese dioxide particles making it impossible to detect them when the oxidant is filtered out. Another reason may be that reactions of the intermediates are sufficiently fast that the intermediates are never in sufficient quantity to be detected. Another attempt to identify intermediates was made using a substoichiometric amount of oxidant. The only compounds observed were aminoalcohol starting material and oxazole product. Further, no intermediates have ever been identified in either

Scheme 2.8 Proposed mechanism for the formation of oxazole
GC-MS or ESI-MS of these reactions. The only evidence to support the proposed mechanism comes from pH and electronic effects on the reaction.

Expecting a deprotonation step as part of the mechanism, Kohler briefly investigated the role of the pH of the manganese dioxide oxidant. Acidic manganese dioxide was prepared by acid washing the Attenburrow manganese dioxide with a dilute nitric acid solution. The pH’s listed in Table 2.1 are that of the filtrate after rinsing the solids. While basic manganese dioxide afforded products in high yields, the acid washed manganese dioxide showed no conversion for the five aminoalcohols tested. It is clear from the reaction times in Scheme 2.6 that electron donating groups, like the methoxy group, slow down the reaction and electron withdrawing groups, like the trifluoromethyl group, speed up the reaction. The rate enhancement from electron withdrawing groups is consistent with the negatively charged intermediate in Scheme 2.8 as it stabilizes the enolate ion allowing the enol to be more easily deprotonated.

Table 2.1 Effects of acidity on the oxidation of aminoalcohols with MnO₂

<table>
<thead>
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<th>R=</th>
<th>MnO₂ (pH=8-9) % Yield</th>
<th>MnO₂ (pH=4-5)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2i</td>
<td>Ph</td>
<td>99</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>2q</td>
<td>2-MeOPh</td>
<td>99</td>
<td>a</td>
</tr>
<tr>
<td>3</td>
<td>2k</td>
<td>4-MeOPh</td>
<td>99</td>
<td>a</td>
</tr>
<tr>
<td>4</td>
<td>2r</td>
<td>2,4-(MeO)₂Ph</td>
<td>99</td>
<td>a</td>
</tr>
<tr>
<td>5</td>
<td>2w</td>
<td>-CO₂tBu</td>
<td>70</td>
<td>a</td>
</tr>
</tbody>
</table>

a: No conversion after 48 hours as evidenced by TLC and yield after work-up.
2.2.4. Evaluation of the effectiveness of a one-pot reaction

The single largest loss to the overall yield from this two-step process occurs during the purification of the aminoalcohol. The compounds tend to oil-out during recrystallization, which often will contain the starting amine as an impurity, necessitating the use of column chromatography. If the reaction could be run as a one-pot method, it should afford an increase in the overall yield, as it would skip the costly and time consuming isolation of the aminoalcohol intermediate. Also, as the Lewis acid would likely adhere to the manganese dioxide the work up procedure would simply involve filtration followed by recrystallization of the oxazole. This reaction has been attempted using benzyl amine as the nucleophile with a 96% yield (Scheme 2.9). While there is little yield difference between this and the two-step process (overall 91% yield) the work up of the one pot procedure is far less time consuming because much of the magnesium perchlorate is removed in filtration allowing for simple recrystallization of the product. Also, we expect that the results for other reactions will be more dramatic as many other compounds have far larger losses of yield for the isolated aminoalcohol intermediate.

Scheme 2.9 One-pot synthesis of a phenanthroline oxazole
2.3 Conclusion

In conclusion, we have developed a two-step procedure for the synthesis of oxazoles from epoxide starting materials using manganese dioxide as the oxidant. Previous syntheses of related phenanthroline and phenanthrene compounds suffered from low yields. Our new method offers higher yields than the other reported syntheses often allowing for >85% yield over two steps. Yields for the oxidation to the oxazole ranged from 23-99%. In total, 28 compounds were prepared of which 23 were previously unreported, and all new compounds were fully characterized. We showed that the method is amenable to a one-pot synthesis strategy for oxazole 2i and could be extended to other substrates with increased yields and decreased through-put times. The following chapter attempts to extend this method to a diverse suite of epoxides where the final product is not a benzo oxazole analogue.

2.4 References


(2) Kohler, L. In Preparation of 1,10-phenanthroline derivatives with B-Ring functionalization and their application / by Lars Kohler; Schoffers, E., Western Michigan University. Department of Chemistry, Eds.; 2011; .


3.1 Introduction

The previous chapter explored the hypothesis that epoxide opening followed by oxidation is a viable method for the synthesis of oxazole derivatives. The method works very well when substrates like the phenanthroline and phenanthrene aminoalcohols are used. These templates are excellent because oxazole formation leads to a larger delocalized $\pi$-system. This chapter will continue to explore the original hypothesis using substrates that do not have as strong of a driving force to form the oxazole. This chapter will also determine whether or not the aminoalcohol intermediate can be diversified into other heterocycles such as oxazolines and bromooxazoles.

3.1.1 Bioactivity of oxazole and oxazoline containing compounds

It was previously established that oxazole compounds are useful for their photophysical properties. In addition, this functional group is found in many bioactive compounds, both natural and synthetic. The bulk of the naturally occurring oxazoles have been isolated from marine organisms such as sponges and tunicates.$^{1-5}$ Oxazoles are biosynthesized from amino acids such as alanine and serine. The oxazole ring and its close relative the oxazoline ring are privileged structures in natural cyclopeptides (Figure 3.1). Telomestatin is an exciting, recently-discovered oxazole-containing cyclopeptide.$^6$ It has probably the most complex polyoxazole ring in existence, containing seven oxazoles in a chain, which is closed by an additional thiazoline ring. Telomestatin
is the most potent inhibitor of telomerase discovered to date. For this reason, it may become an excellent treatment for various cancers that have telomerase activity. Ulicyclamide is an example of an oxazoline containing cyclopeptide.\(^7\) Ulicyclamide demonstrates that this class of cyclopeptides can incorporate a diverse array of side-chains derived from various amino acids. Many of these cyclopeptides are now being explored by pharmaceutical companies as treatments for various diseases.

![Telomestatin, an oxazole-containing cyclopeptide](image1)

![Ulicyclamide, an oxazoline-containing cyclopeptide](image2)

**Figure 3.1 Oxazole and oxazoline containing natural products**

Oxazole and oxazoline compounds are also found in synthetic drugs. In particular the oxazole functional group is often explored in the development of a pharmaceutical as it is an isostere for the carboxylic acid functional group. It is excellent for giving a compound the electronic and solubility properties that are typical for a carboxylic acid without having an acidic proton. Aleglitazar is an oxazole-containing drug developed by Roche for the treatment of type II diabetes (Figure 3.2).\(^8\) One reason the oxazole was preferred over the oxazoline in this compound is that it does not introduce any new stereocenters. For a similar reason the oxazole group was included in the NSAID oxaprozin (Figure 3.2).\(^9\) The latter was developed as a COX inhibitor to
displace long-term use of aspirin and acetaminophen for those who suffer from chronic inflammation. It was made available in 1993 and has remained a popular NSAID since.

Oxazolines on the other hand are far less explored as they bear stereocenters if they are substituted at the fourth or fifth position. Oxazolines also can tautomerize under physiological conditions eroding the enantiopurity at these positions. Thus, there are few oxazoline drugs on the market. Aminorex is a rare example of an oxazoline-containing medication originally developed as a therapy for weight-loss (Figure 3.3). It, however, had too many side effects to be administered to relatively healthy adults and was taken off of the market. It is now listed as a controlled substance by most governments because it is closely related to a recreational drug. 4-Methylaminorex, also known as “Ice” or “U4Euh” is a highly addictive recreational drug that has

Figure 3.2 Oxazole-containing drugs

Figure 3.3 Oxazoline-containing drugs
similar effects to methamphetamine (Figure 3.3). Its addiction profile is close to that of cocaine or methamphetamine and is almost as easy to produce as methamphetamine making it a rather dangerous substance. This drug is an interesting example of a bioactive oxazoline compound as all four stereoisomers are active and produce similar physiological effects. This means that epimerization in the body does not deactivate the compound.

3.1.2 Other uses for oxazoline compounds

While oxazolines may not be ideal for drug development, they have found uses in many other materials. One important issue in pharmaceutical development is drug delivery. Here oxazolines have found great use in forming poly(2-oxazolines) which have very interesting properties for encapsulation and delivery of an active pharmaceutical ingredient. Much research has gone into this area since the discovery of the living anionic ring-opening polymerization of oxazolines. Particularly the morphology of the polyoxazoline is sensitive to rather subtle changes in pH or ionic strength of a solution. Tuning these properties so that the drug is released at the target organ or tissue can make for an ideal drug delivery platform.

Oxazolines also find common use in asymmetric synthesis methodology. They are easily prepared from amino acids, making them an excellent source of stereochemical information in a reaction. For this reason, many asymmetric syntheses use oxazolines as either chiral auxiliaries or as C\textsubscript{2} symmetric ligands for metals. Many oxazolines have been developed as C\textsubscript{2} ligands with the most common being the bisoxazoline or BOX ligands (Figure 3.4). These ligands are typically made by condensation of two amino acids with a dialdehyde. The BOX ligand in Figure 3.4 can be synthesized from phenylalanine and glyoxal. These ligands can then pass the
stereochemical information to a reaction substrate by an induction mechanism. These condensation methods do not translate well to all oxazoline syntheses and so other methods have been explored for their preparation.

![Figure 3.4 BOX ligand](image)

### 3.1.3 Synthesis of oxazoline compounds

Many methods have been developed for the preparation of oxazolines (Scheme 3.1).\(^{18,19}\) The majority rely heavily on the use of functional groups from the carboxylic acid family. Oxazolines can be formed via the cyclization of allyl amides\(^{20-22}\) or propargyl amides.\(^{23,24}\) These functional groups feature prominently in other methods too, including cyclization of amidoalcohols,\(^{25}\) addition and cyclization between alkenes and either acids\(^{26}\) or nitriles,\(^{27}\) and the condensation between aminoalcohols and acids,\(^{28}\) nitriles,\(^{29,30}\) or aldehydes.\(^{31,32}\) Other recent methods reported in the literature include a four-component Ugi condensation\(^ {33}\) and a decarboxylative rearrangement reaction.\(^ {34}\) The chief method for forming oxazolines is the condensation between an aminoalcohol and aldehyde followed by oxidative cyclization. The method is quite similar to our proposed process except that the C-N bond is formed by
condensation rather than epoxide opening. Using epoxide opening gives a much higher atom efficiency as no molecule of water must be eliminated in the course of the process.

3.1.4 Synthesis of oxazole compounds

Oxazoles, even though they are aromatic, are far harder to produce than the corresponding oxazolines. In the past, the functional group was produced by the cyclodehydration of β-ketoamides.\textsuperscript{35-38} These reactions often use strong acids or phosphorus oxychloride (POCl\textsubscript{3}) to

Scheme 3.1 Methods for the synthesis of oxazolines

3.1.4 Synthesis of oxazole compounds

Oxazoles, even though they are aromatic, are far harder to produce than the corresponding oxazolines. In the past, the functional group was produced by the cyclodehydration of β-ketoamides.\textsuperscript{35-38} These reactions often use strong acids or phosphorus oxychloride (POCl\textsubscript{3}) to
catalyze the dehydration. The scope is quite limited in these reactions as it cannot tolerate acid sensitive or easily oxidized functional groups. Often in the total synthesis of oxazole-containing natural products, the ring is found in the starting material or installed early in the reaction. This is the case in the first Nicolau synthesis of diazonamide A, which begins with one of the two oxazole rings already formed (Scheme 3.2). The second ring is then formed with POCl₃ necessitating the use of protecting groups on most heteroatoms. Wipf applied a modification of this cyclodehydration method, which uses a β-amidoalcohol instead of the β-ketoamide. The ketone is then produced in situ by oxidation with DMP. The utility of the Wipf modification was demonstrated in his synthesis of muscoride A (Scheme 3.3). However, this reaction had the

Scheme 3.2 Nicolau synthesis of diazonamide A
oxazole rings also in place early in the synthesis. No literature method currently allows for late stage functionalization of a compound with an oxazole.

![Scheme 3.3 Wipf synthesis of muscoride A](image)

For these reasons, chemists developed other methods for the synthesis of oxazoles using milder reagents (Scheme 3.4). In recent years oxazoles have been synthesized by aza-Wittig reactions, intermolecular reactions with α-diazocarbonyl compounds, additions to alkynes, addition to α-haloketones, iodine-promoted cascade reactions, cycloisomerization of propargylamides, cyclodehydration of amino acids, oxidative cyclization of enamides and other groups, as well as other strategies. Many of these methods, however, still do not apply well to a late stage functionalization. Our method should solve this problem by combining the chemoselectivity of the aminolysis reaction and mild oxidizing reagents to achieve good functional group tolerance.
3.2 Results and Discussion

3.2.1 Screening of oxidants

Preliminary results identified that hydrolysis of intermediates may pose a problem in generalizing our method. This isn’t surprising as manganese dioxide must have some moisture in order to function. Other oxidants found in the literature to form oxazoles from oxazolines were screened against the phenanthroline-derived aminoalcohol 1 (Table 3.1). Of these results, the most interesting is that lead tetraacetate may stop oxidation at the iminoquinone intermediate. This result was not followed further because it is difficult to remove the lead from the product. With some
development, it could prove to be a method for further diversification of aminoalcohol intermediates. Next, we pursued a brominating agent such as NBS, which stood out as an ideal candidate to affect the transformation from aminoalcohol 1 to oxazole 2. Preliminary reactions with aminoalcohol 3 had evidence for the production of oxazoline 4 as well as oxazole 5. An oxazoline was not seen in the oxidation of phenanthroline aminoalcohols described in Chapter 2.

It was decided that a bromine-based oxidation method would be investigated in addition to the manganese dioxide method. This new method was optimized for the oxidation of the benzylamine adduct to styrene oxide (3) (Scheme 3.5, Table 3.2) This proved to be the most interesting substrate for optimization as five reaction products could be identified by GC-MS. We found that low temperatures and low loadings of the brominating agent favor formation of the oxazoline 4. The yield improved by adding a base. High temperatures and high loadings of the brominating agent favored formation of the bromooxazole 6. NBS and DBDMH were both used to form these products but NBS seemed to favor oxazoline 4 and DBDMH bromooxazole 6. At no point could oxazole 5 be identified as a major product of the reaction.

Scheme 3.5 Oxidation products for the reaction of aminoalcohol 3 with NBS
Table 3.1 Evaluation of alternative oxidants

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<th>Co-oxidant</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
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<th>Product</th>
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<td>-</td>
<td>-</td>
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<td>r.t.</td>
<td>24 h</td>
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<td>Oxazole</td>
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<td>24 h</td>
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<td>Aminoalcohol</td>
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Table 3.2 Optimization for the synthesis of oxazoline 4 from aminoalcohol 3

See Scheme 3.5

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<th>Equiv.</th>
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<th>Co-ox</th>
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Table 3.2 con’t. Optimization for the synthesis of oxazoline 4 from aminoalcohol 3

See Scheme 3.5

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3.2.2 Oxidation of dimethylphenanthroline aminoalcohols

Oxidation of the dimethylphenanthroline aminoalcohols with manganese dioxide gave similar results to the substrates in the previous chapter (Scheme 3.6). The same breadth of functional groups was tolerated, allowing for oxazole formation using aliphatic, allylic and benzylic aminoalcohols. The products of the reaction were less crystalline than the phenanthroline analogues but they were still isolated by recrystallization. Based on TLC analysis, the oxazoline was never a dominant product of the reaction, whereas the oxazole appeared to dominate from the beginning. This suggests that the reaction to form the oxazole is faster than the reactions that form the oxazoline. No oxazoline was isolated after column chromatography which was likely due more
to the small scale of the reactions than degradation. It was encouraging that crude NMR spectra never showed a benzylic bromination of the phenanthroline methyl groups. As benzylic and allylic brominations are competing reactions, it is exciting that it was not observed for this substrate.

3.2.3 Oxidation of stilbene aminoalcohols

Oxidation of stilbene aminoalcohols with manganese dioxide gave results similar to the phenanthrolines with one key exception (Scheme 3.7). At room temperature the butyl amine derivative did not form the oxazole in a reasonable amount of time. Instead, the iminoquinone and iminoenol products were isolated (Scheme 3.8). It is possible that the oxazole could form if the

\[ \text{MnO}_2 \text{DCM, r.t.} \]

\[ 11 \rightarrow 12 \]

\[ R \]

\[ \text{CH}_2\text{CH}_2\text{CH}_3 \]

\[ 12a \]

\[ 0\% \]

\[ \text{CH}_2\text{CH}_3 \]

\[ 12b \]

\[ 0\% \]

\[ \text{OCH}_3 \]

\[ 12d \]

\[ 95\% \]

\[ \text{O}_2\text{N} \]

\[ 12e \]

\[ 40\% \]

\[ \text{O} \]

\[ 12f \]

\[ 75\% \]

Scheme 3.7 Oxidation of aminoalcohols 11a-f with manganese dioxide
reaction was run at a higher temperature. The other aminoalcohols formed the oxazole product, which was easily isolated as a crystalline solid.

Using NBS as the oxidant in the presence of K$_2$CO$_3$ as a base allowed for the formation of the oxazoline (Scheme 3.9). The difference in reactivity between dimethylphenanthroline aminoalcohols and stilbene aminoalcohols afforded the oxazoline as the dominant product. This difference is most likely due to the conformational locking of phenanthroline versus the free rotation of the stilbene-derived aminoalcohol. Most loss of yield was due to bromination side products. It was these side products that made it difficult to isolate the oxazoline via recrystallization necessitating a column. Column chromatography proved to be an efficient approach for the isolation of products 15a-f.

Scheme 3.8 Oxidation of aminoalcohol 11a with manganese dioxide
3.2.4 Oxidation of styrene aminoalcohols

Oxidation of the styrene aminoalcohols demonstrated that the ability to diversify the aminoalcohol intermediate is often lost when there is no aromatic ring in the 4- or 5-position of the oxazole. Oxidation with manganese dioxide produced the oxazoles as seen in the previous reactions for phenyl and 4-methoxyphenyl substitution at the 2-position on the ring 17 and 19c-d (Schemes 3.10-11). This is encouraging given that the styrene-derived aminoalcohols 16 and 18 have one less benzylic position activating the compound, compared with previous substrate 11. The two regioisomers 17 and 19 were similar in yield for this functionality. Unfortunately the method did not extend to alkyl and vinyl substituted substrates.
The alkyl and vinyl substitutions also proved problematic in the synthesis of oxazolines and bromooxazoles. For substrates 16 and 18c-d, oxazoline formation happens readily using NBS at room temperature (Schemes 3.12-13). The ability to diversify a phenyl-substituted aminoalcohol into several heterocyclic substrates is demonstrated throughout this section. It is particularly noticeable in the reaction between aminoalcohols 16 or 18 and DBDMH which produced bromooxazoles (Schemes 3.14-15). The yields are quite good for these compounds. This final set of compounds is an interesting template. Bromooxazoles are able to partner in many different C-C coupling reactions, which could serve as a further point of diversification.
Scheme 3.10 Oxidation of aminoalcohols 16a-f with manganese dioxide

Scheme 3.11 Oxidation of aminoalcohols 18a-f with manganese dioxide
Scheme 3.12 Oxidation of aminoalcohols 16a-f with NBS

Scheme 3.13 Oxidation of aminoalcohols 18a-f with NBS
Scheme 3.14 Oxidation of aminoalcohols 16a-f with DBDMH

Scheme 3.15 Oxidation of aminoalcohols 18a-f with DBDMH
3.2.5 Oxidation of cyclohexene aminoalcohols

Unfortunately, the method outlined above could not be extended to the preparation of cyclohexane oxazoles. Neither manganese dioxide nor a halogenating agent (NBS, DBDMH, DCDMH) were able to produce oxazoline or oxazoles. There is some evidence from GC-MS that when using manganese dioxide, the aminoalcohol will over-oxidize to produce a benzoazoxole. It was, however, never a major product of the reaction. Products of oxidation with manganese dioxide often seemed to be related to hydrolysis and oxidation. Products of oxidation with NBS were typically di- and tribrominations of what is likely the cyclohexane ring. Using DBDMH or DCDMH as an oxidant did not fix this issue.

3.2.6 Attempts at extending to one-pot methodology

Attempts were made to extend the oxidation reactions to stilbene and styrene aminoalcohols to a one-pot method like that which was described in the previous chapter for the phenanthroline-derived aminoalcohols. These attempts, however, showed no promising results for the stilbene or styrene templates. This is likely because aminoalcohols 11, 16 and 18 are already less reactive than the phenanthroline analogues. This gives far greater room for side reactions to dominate which was supported by analysis of the reactions. Oxidation with manganese dioxide typically yielded no reaction or hydrolysis products. For NBS, the magnesium perchlorate appeared to catalyze the bromination of benzene rings leading to many products for the reaction. Perhaps if a non-metal catalyzed aminolysis were used, a one-pot method could be developed.

3.3 Conclusion

In conclusion, the wide scope of substrates achieved using this method demonstrates the utility of preparing heterocyclic compounds from epoxides via an aminoalcohol intermediate. The
aminoalcohol is a highly diversifiable group that, using conditions in this work, forms oxazoles, oxazolines, and bromooxazoles. This method could not be extended to cyclohexane-based substrates nor was it amenable to a one-pot strategy. It did, however, prove to work for substrates that have benzylic groups and benzylic bromination was avoided. In total 24 compounds were prepared of which seven compounds were previously unreported in the literature and two more were fully characterized. The aminoalcohols and oxazoles formed in these reactions may ultimately prove useful in other fields, such as in chemical sensors. The last chapter explores the use of some of these compounds as fluorescent sensors for nerve agent analogues.

3.4 References

(1) Copp, B. R. 


(42) Huang, Nian-Yu Nie, Yi-Bo Ding, Ming-Wu Synlett **2009**, 2009, 611-614.


(88) Kohler, L. In Preparation of 1,10-phenanthroline derivatives with B-Ring functionalization and their application / by Lars Kohler; Schoffers, E., Western Michigan University. Department of Chemistry, Eds.; 2011; .


4.1 Introduction

4.1.1 Nerve agents

The term “chemical warfare” often calls WWI to mind as many soldiers suffered from the devastating effects of chemicals such as mustard gas and phosgene. Chemical weapons are still a threat today with the Sarin attack in Syria being a recent reminder. It is important for national security to have portable detection methods for sensing nerve agents, such as the G-series compounds (Figure 4.1). Nerve agents are part of a class of compounds named organophosphates which also includes certain pesticides. Nerve agents inhibit an enzyme in the body known as acetylcholinesterase which is vital for nervous system function. Small doses of nerve agent vapors can quickly lead to death.

![Figure 4.1 G-series nerve agents]

Sarin (GB)  Soman (GD)  Tabun (GA)
4.1.2 Methods for detecting suspected nerve agents in the field

Both military personnel and emergency first responders are frequently tasked with deciding if an unknown liquid or gas could be a life threatening nerve agent. In a national survey of Emergency First Responders the prevailing methods of detection for unknown chemicals are colorimetric (measurement by color change).\(^2\) The current state of the art for detecting nerve agents is based on technology incorporated in M8 and M9 paper strips used by the U.S. military and first responders. The strips function by having paper with embedded dye molecules (referred to as the sensor or chemosensor) that react with a nerve agent producing a color change. The M8 and M9 detection methods are notorious for giving false positives for substances such as acids and bases, antifreeze, hairspray, insect repellent amongst other chemicals commonly found in households or an urban environment.\(^3\) False positives lead to problems such as unnecessary evacuations and costly identification of non-hazardous substances. Further these paper-based methods are limited to detecting liquids and so cannot detect nerve agent vapors. It is critical that new detection methods for nerve agents be developed that have high specificities for nerve agents both as liquids and vapors while maintaining the ease of use of paper strips. A good candidate sensor must be able to detect nerve agents by a color change without false positives. It also must have a long shelf life, be able to function in wet environments, and should be amenable to solution based sensing for quantitation of nerve agent concentrations.
4.1.3 Colorimetric chemosensors for nerve agents

Sensors for nerve agents and related organophosphorus compounds have been subject to extensive review.\textsuperscript{1,4-7} Since these reviews, several other reports have been published describing colorimetric sensors for nerve agents\textsuperscript{8-16} with the most exciting being produced by Ana Costero’s laboratory.\textsuperscript{17-20} The best established mechanism in the literature for selective sensing of G-type nerve agents comes from reports by Zhang and Swager\textsuperscript{21} as well as Dale & Rebek.\textsuperscript{22} In these sensors, a molecule with an alcohol group (O-H bond) and a nitrogen functional group can selectively sense diethyl chlorophosphate (DCP, a nerve agent analogue) without false positives (Scheme 4.1).\textsuperscript{21} Unfortunately, these sensors need dry conditions and are therefore unsuitable for practical use in the field. Derivatives of 1,10-phenanthroline have great potential as functional sensor molecules. Dyes made from 1,10-phenanthroline often perform well in aqueous (water) environments.\textsuperscript{23} Our hypothesis is that by using 1,10-phenanthroline as the color changing domain, sensors will have improved functionality in wet conditions and could be applied for use in nerve agent detection paper. We believe our compounds will be able to function according to the Zhang and Swager mechanism, thus allowing for good chemoselectivity for nerve agent analogues (Scheme 4.2).

\[
\begin{align*}
\text{Scheme 4.1 Zhang and Swager mechanism for the detection of DCP}
\end{align*}
\]
4.2 Results and Discussion

Aminoalcohol derivatives capable of undergoing the mechanism described in Scheme 4.2 were prepared according to methods previously described in this work (Scheme 4.3). Initial results suggested that they may be able to function as turn-on sensors, though something interesting may also be happening. When DCP was added in a fluorescence titration the graphs lacked something called an isobestic point (Figure 4.2). This point is critical in a titration because it shows that there are only two species of dye in the reaction (the starting dye and that which has reacted with the nerve agent). Since the graphs lack this isobestic point it means that there is some unidentified third species present in solution. Our hypothesis is that this third species arises due to an interaction between the diimino moiety of the 1,10-phenanthroline based sensor and DCP. Hoping to remedy this problem, phenanthrene analogues of compounds 1, 3, and 5 were also prepared (Scheme 4.3). Interestingly the phenanthrene derivatives are not directly comparable to the phenanthroline derivatives. For example, phenanthroline derivative 5 acted as a turn-on sensor (Figure 4.2e) while phenanthrene derivative 6 displayed no change upon addition of DCP (Figure 4.3f).

Scheme 4.2 Phenanthroline aminoalcohols for the detection of DCP
These results, however, should be called into question. Previous results could not be reproduced shown in Figures 4.2 and 4.3. Analysis of the DCP used showed that at some point during the project it degraded into the acid 8 and pyrophosphate 10. It is possible that the results achieved are actually due to the reaction between the sensor and the pyrophosphate rather than DCP.

Scheme 4.3 Synthesis of aminoalcohols 1-6

These results, however, should be called into question. Previous results could not be reproduced shown in Figures 4.2 and 4.3. Analysis of the DCP used showed that at some point during the project it degraded into the acid 8 and pyrophosphate 10. It is possible that the results achieved are actually due to the reaction between the sensor and the pyrophosphate rather than DCP.
Figure 4.2 Fluorescence titrations of compound 1, 3, 5
Figure 4.3 Fluorescence titrations of compound 2, 4, 6
4.3 Future Aims for these Sensors

It is possible to take advantage of sensing the pyrophosphate for other applications. Figure 4.4 shows the three main forms of inorganic phosphorus (not bound to carbon) in a cell, with pyrophosphate $13^*$ particularly relevant to this project. Pyrophosphate (PP$_i$) is a common compound in cells, in several types of bacteria it has been measured at concentrations between 0.1–2 mM across several studies (as a perspective the cellular concentration of glucose in fat cells is often near 2 mM).$^7$

$$\text{EtO}^-\text{POCl}_2^- + \text{H}_2\text{O} \rightarrow \text{EtO}^-\text{PO}^-\text{OH} + \text{EtO}^-\text{PO}^-\text{O}^- + \text{EtO}^-\text{PO}^-\text{O}^-\text{Et}$$

Scheme 4.4 Degradation products of DCP

$7^*$

PP$_i$ is most commonly formed when free nucleotides are incorporated into DNA. Not only is PP$_i$ a marker of DNA formation, it also has been recognized as a biomarker of several health problems including calcification of soft tissues.$^8$ The ability to detect the intracellular and extracellular distribution of pyrophosphate could greatly improve research into the causes behind calcification and it’s related diseases. The only reported fluorescent sensor selective for PP$_i$
functions by causing the PP\textsubscript{i} to aggregate.\textsuperscript{9} Due to this it cannot effectively measure the distribution of dissolved cellular PP\textsubscript{i}. Also no further report has appeared where this sensor has been used in fluorescence cellular imaging. This represents a gap in the literature that needs to be filled in order to fully understand the role of PP\textsubscript{i} in the cell. As phosphorus is present in many different structures in a cell, this sensor has the potential to aid researchers investigating a host of diseases and disorders involving mineral misregulation.

Fluorescent sensors are very useful when detecting compounds in living cells. This is due to the light being emitted from one molecule that is often nearly 1 million times smaller than a cell. When these sensors are put into cells they give such great spatial resolution that you can “see” what part of the cell has the particular compound being detected. For example, in Figure 4.5 the sensor shows that in the cell the greatest density of hydrogen peroxide is found in close proximity to the mitochondria.

![Fluorescence imaging of hydrogen peroxide in cells](image)

Figure 4.5 Fluorescence imaging of hydrogen peroxide in cells

Sensors for small anions in cells have recently been subject to an extensive review.\textsuperscript{10} Neither before nor after this review are there reports of sensors that satisfy the criteria of being able to sense dissolved PP\textsubscript{i} without using metal ions. Many of the sensors reported in the literature are indeed selective for phosphorus species, however they are either based on metal complexes or
pull PP$_i$ out of solution as part of their sensing mechanism. One such example is the sensor developed by Gogoi and Das, which is related to our work. While their sensor selectively detects for PP$_i$, it pulls it out of solution into sensor-PP$_i$ aggregates that are then fluorescent.$^3$ It is possible that compounds 1-6 may be able to be repurposed for the detection of pyrophosphate in cells.

4.4 Conclusion

In conclusion, candidate sensor compounds were developed using the epoxide opening method previously described in this work. Initial results with phenanthroline-derived aminoalcohols suggested that the diimino moiety may be inferring with detection due to its own interaction with DCP. Phenanthrene-derived aminoalcohols were prepared for other interesting candidate sensors, however they were not directly comparable to their phenanthroline analogues. The initial results proved to have problems of reproducibility, which may be due to the degradation of DCP into a pyrophosphate. It is possible that this project may be modified for sensors for intracellular imaging of inorganic phosphate. In total, twelve compounds were produced in this body of work with six that were previously unreported in the literature.

4.5 References


EXPERIMENTAL

E.1 Reagents and Solvents

All reagents and solvents were obtained in 98%+ purity from Sigma-Aldrich and used without further purification. Bleach was purchased from local grocery stores, generally either Chlorox or Meijer brand bleach was used.

E.2 Instrumentation

Melting points were determined in open capillaries using a Thomas-Hoover Unimelt instrument. NMR spectra were recorded using a 400 MHz Jeol Eclipse nuclear magnetic resonance instrument. IR spectra were recorded with either a Mattson Satellite FTIR Spectrometer or a Bruker Equinox 55. Elemental analyses were carried out by Numega Resonance Labs, Inc. in San Diego, CA. EI-HRMS data was determined using a Waters Micromass GCT instrument. ESI-HRMS data was collected on a Waters Synapt G1 instrument with electrospray ionization in the positive mode with these parameters of: capillary 4 kV, sample cone 42 V, extraction cone 4.0 V, source temperature 120°C, desolvation gas temperature 175°C, desolvation gas (nitrogen) flow 500 L/hr, cone gas flow 23 L/hr. Samples were prepared as 1 µM solution in Fluka LC-MS Chromasolv® methanol and injected at a rate of 10 µL/min.
E.3 Preparation of Epoxides

Preparation of 5,6-dihydro-1,10-phenanthroline-5,6-epoxide [I.2]

The title compound was prepared by dissolving 2.00 g of 1,10-phenanthroline monohydrate and 1.72 g of tetrabutylammonium hydrogen sulfate in 20 mL of chloroform. To this was added 100 mL of commercial bleach adjusted to pH of 8.6 using conc. sulfuric acid. This was stirred for 30 minutes. After stirring, the organic layer was separated and the aqueous layer extracted with chloroform (1 x 50 mL and 1 x 30 mL). The organic layers were combined and washed with water (2 x 100 mL), sat. sodium bicarbonate (2 x 100 mL), and brine (2x 100 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered, concentrated and recrystallized from chloroform/hexane. Pure epoxide crystals were collected in 66.8% (1.32 g) yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.92 (2H, dd, J = 4.72 Hz, J = 1.84 Hz), 8.02 (2H, dd, J = 7.72, J = 1.48), 7.41 (2H, J = 4.76, J = 3.84), 4.61 (2H, s).

Preparation of 9,10-dihydrophenanthrene-9,10-epoxide [I.11]

The title compound was prepared by dissolving 1.00 g of phenanthrene (5.6 mmol) and 0.47 g of tetrabutylammonium hydrogen sulfate (1.4 mmol) in 120 mL of dichloromethane. To this was added 275 mL of commercial bleach adjusted to pH of 8.6 using conc. sulfuric acid. This was stirred for 15 minutes. After stirring, 180 mL of dichloromethane was added, the bleach decanted, and the organic layer was washed with cold water (5 x 300 mL) and brine (1 x 300 mL). The organic layer was then dried over anhydrous potassium carbonate, filtered, concentrated and recrystallized from dichloromethane/pentanes. Pure epoxide crystals were collected in 84% (0.91 g) yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.11
(2H, d, J = 8.1 Hz), 7.66 (2H, dd, J = 7.4 Hz, 1.5 Hz), 7.48 (2H, td, J = 7.3 Hz, 1.4 Hz), 7.38 (2H, td, J = 7.3 Hz, 1.1 Hz), 4.57 (2H, s); $^{13}$C NMR (100 MHz, D$_2$O): δ 131.6, 131.1, 129.4, 128.1, 123.8, 123.8, 56.8.

Preparation of 5,6-dihydro-2,9-dimethyl-1,10-phenanthroline-5,6-epoxide [I.13]

The title compound was prepared by dissolving 1.00 g of 2,9-dimethyl-1,10-phenanthroline (5.6 mmol) and 0.47 g of tetrabutylammonium hydrogen sulfate (1.4 mmol) in 120 mL of dichloromethane. To this was added 275 mL of commercial bleach adjusted to pH of 8.6 using conc. sulfuric acid. This was stirred for 15 minutes. After stirring, 180 mL of dichloromethane was added, the bleach decanted, and the organic layer was washed with cold water (5 x 300 mL) and brine (1 x 300 mL). The organic layer was then dried over anhydrous potassium carbonate, filtered, concentrated and recrystallized from dichloromethane/pentanes. Pure epoxide crystals were collected in 46% (0.49 g) yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.88 (2H, d, J = 8.1 Hz), 7.26 (2H, d, J = 7.1 Hz), 4.59 (2H, s), 2.77 (6H, s); Previously synthesized in 49% yield by Kohler et al. using a similar procedure.
E.4 Preparation of Amino Alcohols

**Method A**

1,10-Phenanthroline-5,6-epoxide (1.5g, 7.6 mmol) was dissolved in 20ml of acetonitrile and 6 ml of chloroform. Basic alumina, Brockman activity Grade 1 (60g, 588 mmol, 40 equivalents wt/wt) and appropriate amine were mixed in 30 ml of acetonitrile in a 250 ml round bottom flask. This was allowed to stir for 15 minutes and then the phenanthroline solution was added dropwise over the course of 15 minutes while the reaction was heated up to 60°C. The addition flask was replaced with a condenser and heated at reflux for 24-72 hours, until the reaction was determined to be complete by TLC. Upon completion, the reaction was allowed to cool to room temperature and 100 ml of methanol added to stir with the alumina for four hours to desorb the products. The reaction mixture was filtered through diatomaceous earth to remove alumina and concentrated *in vacuo*.

**Method B**

1,10-Phenanthroline-5,6-epoxide (1.5g, 7.6 mmol) was dissolved in 20ml of acetonitrile and 6 ml of chloroform. Basic alumina, Brockman activity Grade 1 (60g, 588 mmol), appropriate amine and ethyldiisopropylamine (3.0g, 22.8 mmol) were mixed in 30 ml of acetonitrile in a 250 ml round bottom flask. This was allowed to stir for 15 minutes and then the phenanthroline solution was added dropwise over the course of 15 minutes while the reaction was heated up to 60°C. The addition flask was replaced with a condenser and heated at reflux for 24-72 hours, until the reaction was determined to be complete by TLC. Upon completion, the reaction was allowed to cool to room temperature and 100 ml of methanol added to stir with the alumina for four hours to desorb
the products. The reaction mixture was filtered through celite to remove alumina and concentrated *in vacuo*.

**Method C**

1,10-Phenanthroline (1.5g, 7.6 mmol), magnesium perchlorate (2.13g, 9.6 mmol) and the appropriate amine (11.5 mmol) were dissolved in 25 ml of acetonitrile. The mixture was refluxed for 24 to 72 hours until the reaction was determined to be complete by TLC. The reaction was quenched with 50ml of water and 100ml of chloroform added. The two phases were separated and the aqueous layer was extracted with chloroform (1 x 100 ml and 1 x 50 ml). The combined organic layer was washed with deionized water (2 x 250 ml) and brine (2 x 250 ml), dried with sodium sulfate, filtered and concentrated.

**Method D**

The epoxide (0.50 g, 1 equivalent), calcium perchlorate hydrate (0.5 equivalents), and the appropriate amine (1.1 equivalents) were dissolved in 10 ml of acetonitrile. The mixture was heated at 60°C for 8 hours until the reaction was determined to be complete by TLC. The reaction was quenched with 10ml of water and 100ml of chloroform added. The organic layer was washed with deionized water (2 x 100 ml) and brine (1 x 100 ml), dried with sodium sulfate, filtered and concentrated.

**Method E**

The epoxide (0.50 g, 1 equivalent), magnesium perchlorate (0.5 equivalents), and the appropriate amine (1.1 equivalents) were dissolved in 10 ml of acetonitrile. The mixture was
heated at 60°C for 8 hours until the reaction was determined to be complete by TLC. The reaction often produced a thick gel upon addition of the third reagent and remained a gel over the course of the reaction. The reaction was quenched with 10ml of water and 100ml of chloroform added. The organic layer was washed with deionized water (2 x 100 ml) and brine (1 x 100 ml), dried with sodium sulfate, filtered and concentrated.

*Preparation of 5,6-dihydro-6-amino-1,10-phenanthrolin-5-ol [I.14]*

The title compound was prepared by the method of Sanfilippo & Nicolosi. ² 1,10-phenanthrolin-5,6-epoxide (200 mg, 1.02 mmol) was refluxed in ammonium hydroxide (30% aqueous, 12 ml) for 12 minutes. The solution was concentrated *in vacuo* to afford the product in 99% (217 mg) yield. ¹H NMR (400 MHz, D₂O): δ 8.58 (1H, app dd, J = 11.2, 4.8 Hz), 7.95 (1H, app dd, J = 15.7, 7.7 Hz), 7.54-7.48 (2H, m), 4.72 (1H, d, J = 7.0 Hz), 4.12 (1H, d, J = 7.0 Hz).

*Preparation of trans-5,6-dihydro-6-(methylamino)-1,10-phenanthrolin-5-ol [I.15a]*

This compound was synthesized according to Method A using a 40% methyl amine/water solution (7.5 ml, 91.7 mmol of amine) and carried out at room temperature instead of reflux. The reaction was quenched after 96 hrs and concentrated to yield a brown viscous oil that had a strong odor of methylamine. The crude mixture was redissolved in the minimum amount of methanol and then precipitated out with the addition of acetonitrile to yield the product as a white solid 0.95 g (55%); m.p. 158-161°C; Rf 0.34 (Al₂O₃, 3% methanol/chloroform); ¹H NMR (400 MHz, D₂O): δ 8.66 (2H, app dd, J = 8.0, 4.8 Hz), 7.93 (2H, dd, J = 13.2, 7.7 Hz), 7.50 (2H, m),

112
5.0 (1H, d, J = 2.9 Hz), 3.94 (1H, d, J - 2.9 Hz), 2.55 (1H, s), 2.26 (3H, s); \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.62 (2H, m), 7.90 (2H, dd, J = 13.5, 7.9 Hz), 7.46 (2H, m), 4.96 (1H, d, J = 3.3 Hz), 3.90 (1H, d, J = 3.3 Hz), 2.52 (1H, s); \(^1^3^C\) NMR (100 MHz, D\(_2\)O): \(\delta\) 150.4, 149.7, 149.3, 149.1, 139.8, 139.1, 132.3, 131.8, 68.9, 61.7, 32.8; FT-IR (thin film, neat) \(\nu/cm^{-1}\): 3190, 3048, 2848, 1707, 1688, 1562, 1434, 1373, 1345, 1322, 1218, 1170, 1110, 1076, 1016, 870, 794, 743, 699; HRMS (ESI) calcd for C\(_{18}\)H\(_{13}\)N\(_3\)ONa [M+Na\(^+\)]: 250.0957, found: 250.0949.

**Preparation of trans-5,6-dihydro-6-(ethylamino)-1,10-phenanthrolin-5-ol [1.15b]**

This compound was synthesized according to Method A using 40 ml of 2.0M ethylamine in tetrahydrofuran (80 mmol) instead of acetonitrile. The reaction carried out at room temperature, quenched after 72 hrs, and concentrated to yield the product as a brown viscous oil 1.83g (99%); Rf 0.22 (SiO\(_2\), 5% methanol/chloroform); \(^1^H\) NMR (400 MHz, D\(_2\)O): \(\delta\) 8.64 (2H, app dd, J = 10.2, 5.1 Hz), 7.91 (2H, dd, J = 14.6, 7.9 Hz), 7.49-7.47 (2H, m), 4.99 (1H, app s), 4.06 (1H, app s) 2.63-2.59 (2H, m), 0.96 (3H, t, J = 1.48 Hz); \(^1^3^C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 150.5, 149.4, 149.2, 148.9, 135.5, 135.4, 135.2, 133.6, 124.2, 124.0, 69.1, 61.3, 41.3, 15.3; FT-IR (thin film from dichloromethane) \(\nu/cm^{-1}\): 3227, 3056, 2965, 2864, 1653, 1518, 1559, 1418, 1271, 1212, 1185, 1124, 1071, 800, 746; HRMS (ESI) calcd for C\(_{18}\)H\(_{15}\)N\(_3\)ONa [M+Na\(^+\)]: 264.1113, found: 264.1111.
Preparation of trans-5,6-dihydro-6-(butylamino)-1,10-phenanthrolin-5-ol [1.15c]

This compound was synthesized according to Method A using butyl amine 1.96g (26.8 mmol). The reaction was quenched at 24 hrs concentrated to yield a brown viscous oil. Further purification was conducted by redissolving the product in 250 ml of chloroform and washed with deionized water (2 x 250 ml) and brine (2 x 250 ml), dried with sodium sulfate, filtered and concentrated to give a brown viscous oil 1.46g (71%); Rf 0.16 (SiO₂, 5% methanol/chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.69-8.67 (2H, m), 7.96 (1H, app d, J = 7.7 Hz), 7.75 (1H, app d, J = 7.7 Hz), 7.31-7.28 (2H, m), 4.75 (1H, d, J = 9.9 Hz), 3.92 (1H, d, J = 9.2 Hz), 2.90-2.83 (1H, m), 2.71-2.63 (1H, m) 1.55-1.44 (2H, app sextet, J = 7.0 Hz), 1.36 (2H, sextet, J = 7.3 Hz), 0.88 (3H, t, J = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 150.8, 149.6, 149.5, 149.2, 135.2, 134.5, 134.4, 134.1, 124.2, 124.0, 69.7, 61.8, 46.9, 32.9, 20.4, 14.1; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 3244, 3061, 2957, 2930, 2870, 1661, 1582, 1564, 1464, 1428, 1126, 1071, 801, 746; HRMS (ESI) calcd for C₁₆H₁₉N₃ONa [M+Na]⁺: 292.1426, found: 292.1423.

Preparation of trans-5,6-dihydro-6-(hexylamino)-1,10-phenanthrolin-5-ol [1.15d]

This compound was synthesized according to Method A using hexyl amine 2.32g (22.9 mmol). The reaction mixture was quenched after 12 hrs and concentrated to afford a brown viscous oil. Further purification was conducted by redissolving the product in 250 ml of chloroform and washed with deionized water (2 x 250 ml) and brine (2 x 250 ml), dried with sodium sulfate, filtered and concentrated to give a
brown viscous oil 2.11g (93%); Rf 0.09 (SiO\textsubscript{2}, 5% methanol/chloroform); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 8.67 (2H, app t, J = 2.2 Hz), 7.95 (1H, app d, J = 7.3 Hz), 7.75 (1H, app d, J = 7.3 Hz), 7.31-7.29 (2H, m), 4.75 (1H, d, J = 9.9 Hz), 3.89 (1H, d, J = 10.2 Hz), 2.90-2.83 (1H, m), 2.69-2.63 (1H, m), 1.58-1.45 (2H, m), 1.38-1.24 (6H, m), 0.86 (3H, t, J = 6.6 Hz); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 150.5, 149.5, 149.0, 148.7, 135.9, 135.0, 134.6, 134.3, 124.1, 124.0, 69.3, 61.6, 46.9, 31.7, 30.6, 26.9, 22.6, 14.0; FT-IR (thin film from dichloromethane) \(\nu/cm^{-1}\) 3277, 3064, 2954, 2926, 2855, 1653, 1581, 1564, 1465, 1418, 1137, 1071, 799, 747; HRMS (ESI) calcd for C\textsubscript{18}H\textsubscript{23}N\textsubscript{3}ONa [M+Na\textsuperscript{+}]: 320.1739, found: 320.1708.

**Preparation of trans-5,6-dihydro-6-(allylamino)-1,10-phenanthroline-5-ol [1.15e]**

This compound was synthesized according to Method A and scaled appropriately for 1,10-phenanthroline (1g, 5.1 mmol) and allyl amine (1.72g, 30.6 mmol). The reaction was quenched after 18 hrs and concentrated to afford a brown viscous oil with a strong allyl amine odor. The product was purified by column chromatography (SiO\textsubscript{2}; gradient elution 3%-15% methanol / chloroform). When put under low pressure the product foamed giving a brown oily foam 0.80g (62%); Rf 0.45 (Al\textsubscript{2}O\textsubscript{3}, 3% methanol / chloroform); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 8.65 (2H, app dt, J = 4.8, 2.2 Hz), 7.94 (1H, app d, J = 7.4 Hz), 7.76 (1H, app d, J = 7.0 Hz), 7.28 (2H, dd, J = 7.7, 4.8 Hz), 5.92-5.86 (1H, m), 5.55 (1H, bd), 5.19 (1H, dd, J = 15.8, 1.5 Hz), 5.10 (1H, dd, J = 10.2, 1.4 Hz), 4.80 (1H, d, J = 9.5 Hz), 3.95 (1H, d, J = 9.5 Hz), 3.49-3.28 (2H, ABq of d, J = 60.4, 13.9, 5.8 Hz), 1.95 (1H, s), 1.84 (1H, bs); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 150.9, 149.9, 149.7, 149.5, 136.3, 134.7, 134.6, 134.6, 133.7, 124.3, 124.0, 116.8, 70.1, 61.0, 49.8; FT-IR (thin film from CDCl\textsubscript{3}) \(\nu/cm^{-1}\) 3248, 3067, 2919, 2850, 1664, 1642, 1582,
1564, 1126, 1076, 1040, 800, 644; HRMS (ESI) calcd for C_{15}H_{15}N_{3}ONa [M+Na]^+: 276.1113, found: 276.1103.

**Preparation of trans-5,6-dihydro-6-(2-picolyamino)-1,10-phenanthroin-5-ol [1.15f]**

1,10-Phenanthroline-5,6-epoxide (500 mg) was reacted with 2-picolyamine (788 uL) using a slurry of basic alumina (75 mol equivalents) in a minimum amount of chloroform. The reaction was run at 50 °C for 45 hrs, then quenched with 40 ml of methanol for with vigorous stirring for 48 hrs, filtered through Celite and concentrated. The product was washed with deionized water (3 x 100 mL) and brine (2 x 100 mL), dried with sodium sulfate, concentrated and isolated as a brown oil 600mg (72%); m.p. 62.1-64.9; Rf 0.48 (Al_{2}O_{3}, 3% methanol / chloroform); ^1H NMR (400 MHz, CDCl_{3}): δ 8.64 (2H, app t, J = 4.8 Hz), 8.52 (1H, app d, J = 3.3 Hz), 8.06 (1H, d, J = 7.7 Hz), 8.01 (1H, d, J = 7.7 Hz), 7.60 (1H, t, J = 7.3 Hz), 7.29-7.17 (4H, m), 4.90 (1H, d, J = 11.0 Hz), 4.16-4.13 (3H, m); ^13C NMR (100 MHz, CDCl_{3}): δ 160.0, 151.5, 149.8, 149.5, 148.9, 137.5, 136.7, 135.4, 134.4, 133.8, 133.7, 124.2, 124.0, 122.8, 122.7, 122.0, 121.3, 68.9, 62.7, 60.1; FT-IR (thin film from DCM) ν/cm\(^{-1}\) 3248, 3056, 2860, 1929, 1665, 1590, 1565, 1472, 1418, 1268, 1146, 1126, 1070, 1047, 995, 801, 747, 623; HRMS (ESI) calcd for C_{18}H_{16}N_{4}ONa [M+Na]^+: 327.1222, found: 327.1215.
**Preparation of trans-5,6-dihydro-6-(cyclohexanemethylamino)-1,10-phenanthrolin-5-ol [1.15g]**

This compound was synthesized according to Method C using cyclohexanemethylamine 1.39g (12.2 mmol) and the reaction was quenched after 24 hrs. The crude mixture was purified by column chromatography (SiO₂; 3% methanol / chloroform). Upon concentration, the product foamed leaving an airy pale orange solid 1.83g (72%); m.p. 80-82°C; Rf 0.19 (Al₂O₃, 3% methanol/chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.65 (2H, app d, J = 2.2 Hz), 7.96 (1H, app d, J = 7.7 Hz), 7.76 (1H, app d, J = 7.7 Hz), 7.30-7.25 (2H, m), 4.76 (1H, d, J = 10.6 Hz), 3.87 (1H, d, J = 10.3 Hz), 2.73-2.70 (1H, m), 2.51-2.48 (1H, m), 1.76-1.63 (6H, m), 1.45-1.43 (1H, m), 1.23-1.17 (2H, m), 0.94-0.89 (2H, m); ¹³C NMR (100 MHz, CDCl₃): δ 151.0, 149.7, 149.6, 149.4, 134.9, 134.0, 124.2, 124.0, 69.9, 54.1, 39.0, 31.5, 26.7, 26.1; FT-IR (thin film, neat) ν/cm⁻¹ 3266, 3066, 2919, 2849, 1684, 1647, 1576, 1559, 1419, 1260, 1181, 1135, 1071, 1036, 798, 746; HRMS (ESI) calcd for C₁₉H₂₃N₃ONa [M+Na]⁺: 332.1739, found: 332.1714.

**Preparation of trans-5,6-dihydro-6-(phenethylamino)-1,10-phenanthrolin-5-ol [1.15h]**

This compound was synthesized according to Method C using phenethylamine 1.39g (11.5 mmol). The reaction was quenched after 24 hrs. The product was isolated after column chromatography (SiO₂; 3% methanol / chloroform). Upon concentration, the product foamed leaving an airy orange solid 1.69g (70%); m.p. 95-96°C; Rf 0.37 (Al₂O₃, 3% methanol/chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.60 (2H, s), 7.91 (1H, d, J = 7.7 Hz), 7.53 (1H, d, J = 7.3 Hz), 7.20 (7H, m), 4.78 (1H, d, J = 9.5 Hz), 4.05 (1H, bs), 3.93 (1H, d, J = 9.9 Hz).
Hz), 3.16 (1H, m), 2.99 (1H, m), 2.85 (2H, m); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 150.9, 149.8, 149.6, 139.5, 134.6, 134.3, 128.8, 128.7, 126.6, 124.3, 124.0, 69.7, 61.8, 48.5, 36.8; FT-IR (thin film from dichloromethane) v/cm$^{-1}$: 3273, 3060, 3026, 2923, 2854, 1581, 1563, 1495, 1453, 1418, 1265, 1182, 1125, 1081, 876, 800, 746, 699; HRMS (ESI) calcd for C$_{20}$H$_{20}$N$_3$O [M+H]$^+$: 318.1606, found: 318.1573.

**Preparation of trans-5,6-dihydro-6-benzylamino-1,10-phenanthrolin-5-ol [1.15i]**

This compound was synthesized according to Method C using benzyl amine (1.25 ml, 11.5 mmol) and quenched after 48 hours. The product was isolated by column chromatography (SiO$_2$; gradient elution 3-5% methanol / chloroform) and afforded the product as a brown viscous oil, 2.13 g (92%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.72-8.76 (2H, m), 7.93 (1H, app d, J = 7.7 Hz), 3.34 (1H, br s), 7.81 (1H, app d, J = 7.7 Hz), 7.24-7.40 (7H, m), 4.85 (1H, d, J = 9.2 18.5Hz), 4.07 (1H, d, J = 13.6 Hz), 4.04 (1H, d, J = 10.2 Hz), 3.92 (1H, d, J = 13.2 Hz). This compound was previously synthesized by Schoffers et al.$^3$ Schoffers, E.; Tran, S. D.; Mace, K. *Heterocycles* 2003, 60, 769-772.
Preparation of trans-5,6-dihydro-6-(3-methoxybenzylamino)-1,10-phenanthrolin-5-ol [1.15j]

This compound was synthesized according to Method C (with reagents scaled appropriately for 200mg of epoxide) using 3-methoxybenzylamine 210mg (1.5 mmol) and quenched after 44 hrs. The product was purified by column chromatography (SiO$_2$; gradient elution 3-5% methanol / chloroform). Concentration of sample afforded the product as a yellow waxy solid 262mg (77%); Rf 0.31 (Al$_2$O$_3$, 3% methanol / chloroform); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (2H, app d, J= 4.4 Hz), 7.89 (1H, d, J = 7.7 Hz), 7.79 (1H, d, J = 7.7 Hz), 7.24-7.17 (3H, m), 6.86 (1H, s), 6.84 (1H, s), 6.74 (1H, app d, J = 8.1 Hz), 4.89 (1H, d, J = 9.2 Hz), 4.01 (1H, d, J = 9.2 Hz), 3.83 (2H, ABq, J = 56.8, 13.6 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.9, 150.9, 149.8, 149.7, 149.5, 141.4, 134.9, 134.8, 134.7, 133.5, 129.7, 124.3, 124.0, 120.4, 113.8, 113.7, 70.1, 60.2, 55.3, 51.0; FT-IR (thin film from CDCl$_3$) v/cm$^{-1}$ 3276, 3061, 2938, 2835, 1600, 1584, 1563, 1488, 1469, 1418, 1364, 1263, 1186, 1153, 1126, 1069, 1045, 876, 799, 783, 694, 671, 642, 621; HRMS (ESI) calcd for C$_{20}$H$_{20}$N$_3$O$_2$ [M+H]$^+$: 334.1555, found: 334.1529.

Preparation of trans-5,6-dihydro-6-(4-methoxybenzylamino)-1,10-phenanthrolin-5-ol [1.15k]

This compound was synthesized according to Method C using 4-methoxybenzyl amine (1.5 ml, 11.5 mmol) and quenched after 24 hours. The product was purified by column chromatography (SiO$_2$; 3% methanol / chloroform). Concentration of sample afforded the product as a brown viscous oil, 2.21 g (87%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.75-8.72 (2H, m), 7.93 (1H, app d, J = 7.7 Hz), 7.80 (1H, app d, J = 7.6), 7.35-7.31 (2H, m), 7.29-
7.24 (2H, m), 6.90-6.85 (2H, m), 4.80 (1H, d, J = 9.5), 3.99 (1H, d, J = 9.5), 3.99 (1H, d, J = 12.4), 3.83 (1H, d, J = 12.8), 3.79 (3H, s), 3.38 (1H, br s). This compound was previously synthesized by Schoffers et al. Schoffers, E.; Tran, S. D.; Mace, K. *Heterocycles* **2003**, *60*, 769-772.

**Preparation of trans-5,6-dihydro-6-(3-chlorobenzylamino)-1,10-phenanthrolin-5-ol [1.15I]**

This compound was synthesized according to Method C using 3-chlorobenzylamine 1.63g (11.5 mmol) and quenched after 40 hrs. The product was purified by column chromatography (SiO$_2$; 3% methanol / chloroform). Upon concentration, the product foamed leaving an airy, brown solid 1.96g (76%); m.p. 173-176°C; Rf 0.18 (Al$_2$O$_3$, 1% methanol/chloroform); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.63 (2H, app dd, J = 16.5, 4 Hz), 7.89 (1H, app d, J = 7.7 Hz), 7.81 (1H, app d, J = 7.0 Hz), 7.37 (1H, app s), 7.34-7.22 (6H, m), 4.97 (1H, app d, J = 8.1 Hz), 4.10 (1H, app d, J = 8.0 Hz), 4.03 (1H, d, ABq, J = 13.6 Hz), 3.90 (1H, d, ABq, J = 13.4 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 150.7, 149.9, 149.6, 149.5, 141.6, 135.1, 135.1, 134.5, 133.0, 129.9, 128.2, 127.6, 126.3, 124.4, 124.1, 70.0, 61.2, 50.5; FT-IR (thin film from dichloromethane) ν/cm$^{-1}$ 3261, 3060, 2862, 1653, 1597, 1563, 1474, 1418, 1364, 1264, 1204, 1125, 1074, 869, 798, 781, 745, 681; HRMS (ESI) calcd for C$_{19}$H$_{17}$N$_3$O [M+H]$^+$: 338.1060, found: 338.1046.
Preparation of trans-5,6-dihydro-6-(3-fluorobenzylamino)-1,10-phenanthrolin-5-ol [1.15m]

This compound was synthesized according to Method C using 3-fluorobenzylamine 1.44g (11.5 mmol) and quenched after 40 hrs. The product was purified by column chromatography (SiO₂; 3% methanol / chloroform). Upon concentration, the product foamed leaving an airy, pale orange solid 1.47g (61%); m.p. 164-168°C; Rf 0.16 (Al₂O₃, 1% methanol/chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.51 (2H, app dd, J = 4.8, 1.2 Hz), 7.89 (1H, app d, J = 6.7 Hz), 7.79 (1H, app d, J = 7.7 Hz), 7.24-7.16 (3H, m), 7.02-6.95 (2H, m), 6.93-6.84 (1H, m), 4.92 (1H, d, J = 9.5 Hz), 3.99 (1H, d, J = 9.5 Hz), 3.88 (1H, d, ABq, J = 9.5 Hz), 3.75 (1H, d, ABq, J = 9.5 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 164.3, 161.8, 150.8, 149.8, 149.6, 149.5, 142.7, 142.6, 134.9, 133.6, 124.4, 124.1, 123.5, 114.9, 114.7, 114.1, 70.1, 61.2, 50.4; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 3266, 3062, 2856, 1615, 1585, 1564, 1418, 1251, 1128, 1071, 941, 873, 800, 746, 684; HRMS (ESI) calcd for C₁₉F₁₆N₃ONa [M+Na]⁺: 344.1175, found: 344.1155.

Preparation of trans-5,6-dihydro-6-(4-fluorobenzylamino)-1,10-phenanthrolin-5-ol [1.15n]

This compound was synthesized according to Method C using 4-fluorobenzylamine 1.44g (11.5 mmol) and quenched after 24 hrs. The product was purified by column chromatography (SiO₂; 3% methanol / chloroform). Upon concentration, the product foamed leaving an airy, pale orange solid 1.92g (78%); m.p. 95-96°C; Rf 0.31 (Al₂O₃, 3% methanol/chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.62 (2H, dd, J = 4.8, 1.5 Hz), 7.91 (1H, app d, J = 6.7 Hz), 7.89 (1H, app d, J = 7.7 Hz), 7.29-7.25 (4H, m), 6.98 (2H, app t, J = 8.8 Hz),
4.86 (1H, d, J = 9.2 Hz), 3.99 (1H, d, J = 9.1 Hz), 3.94 (1H, ABq, J = 13.2 Hz), 3.80 (1H, d, ABq, J = 13.2 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 163.4, 161.0, 150.1, 149.7, 149.7, 135.4, 134.8, 134.7, 134.4, 133.3, 129.8, 129.7, 124.4, 124.0, 115.7, 115.4, 70.3, 61.2, 50.6; FT-IR (thin film from dichloromethane) v/cm$^{-1}$ 3269, 3063, 2853, 1601, 1581, 1563, 1508, 1418, 1219, 1125, 1069, 822, 800, 746; HRMS (ESI) calcd for C$_{19}$F$_{16}$N$_{3}$O$_{2}$Na $[\text{M+Na}]^+$: 344.1175, found: 344.1150.

Preparation of trans-5,6-dihydro-6-(3-trifluoromethylbenzylamino)-1,10-phenanthroline-5-ol [1.15o]

This compound was synthesized according to Method C (reagents scale for 1.00g of epoxide) using 3-trifluoromethylbenzylamine 1.34g (7.7 mmol) and quenched after 24 hrs. The product was purified by recrystallization from chloroform / acetonitrile to afford beige flakes 1.06g (56%); m.p. 192.8-194.3°C; Rf 0.29 (Al$_2$O$_3$, 3% methanol/chloroform); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.85 (1H, d, J = 5.1 Hz), 8.78 (1H, d, J = 5.1 Hz), 8.51 (1H, d, J = 7.7 Hz), 8.27 (1H, d, J = 8.1 Hz), 7.94 (1H, app t, J = 7.7 Hz), 7.78 (1H, app t, J = 5.1 Hz), 7.63-7.40 (4H, m), 5.50 (1H, d, J = 3.7 Hz), 5.02 (1H, d, J = 3.3 Hz), 4.44-4.19 (2H, ABq, J = 89.4, 12.8 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 162.7, 162.4, 161.7, 150.6, 145.8, 144.9, 143.5, 143.2, 142.7, 133.6, 133.1, 130.8, 130.1, 130.0, 128.5, 128.0, 126.7, 125.5, 117.6, 114.8, 65.0, 58.3, 49.6; FT-IR (thin film from dichloromethane) v/cm$^{-1}$ 3259, 3060, 2835, 1563, 1416, 1328, 1161, 1121, 1072, 798, 746, 702; HRMS (ESI) calcd for C$_{20}$F$_{3}$H$_{17}$N$_{3}$O $[\text{M+H}]^+$: 372.1323, found: 372.1292.
Preparation of trans-5,6-dihydro-6-(1-naphthylmethylamino)-1,10-phenanthroline-5-ol \([1.15p]\)

This compound was synthesized according to Method C (reagents scaled appropriately for 500mg of epoxide) using 1-naphthylmethylamine 0.64mL (3.8 mmol) and quenched after 24 hrs. The product was purified by column chromatography (SiO\(_2\); 3% methanol / chloroform). Upon concentration, the product foamed leaving a brown, oily foam 895mg (99%); m.p. 205-212\(^{\circ}\)C; Rf 0.33 (Al\(_2\)O\(_3\), 3% methanol/chloroform); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.70 (2H, m), 8.08 (1H, app d, \(J = 9.2\) Hz), 7.88-7.77 (4H, m), 7.55-7.47 (3H, m), 7.41 (1H, app t, \(J = 7.1\) Hz), 7.29-7.26 (2H, m), 4.84 (1H, d, \(J = 9.5\) Hz), 4.52-4.34 (2H, ABq, \(J = 56.8, 13.2\) Hz), 4.10 (1H, d, \(J = 9.5\) Hz), 3.46 (1H, bs), 2.13 (1H, bs); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta\) 151.3, 150.7, 149.6, 149.2, 137.1, 136.8, 136.4, 136.1, 136.0, 134.7, 133.9, 128.9, 127.8, 126.4, 126.3, 126.2, 126.0, 124.5, 124.4, 124.3, 69.8, 61.5, 48.3; FT-IR (thin film from dichloromethane) \(\nu/\text{cm}^{-1}\) 3264, 3266, 3058, 2854, 1518, 1509, 1419, 1264, 1140, 1071, 792, 779, 746; HRMS (ESI) calcd for C\(_{23}\)H\(_{20}\)N\(_3\)O [M+H]\(^+\): 354.1606, found: 354.1632.

Preparation of trans-5,6-dihydro-6-(2-methoxybenzylamino)-1,10-phenanthroline-5-ol \([1.15q]\)

1,10-Phenanthroline-5,6-epoxide (500 mg, 2.55 mmol) and ytterbium triflate (790 mg, 1.28 mmol) were dissolved in acetonitrile (1 ml). 2-methoxybenzylamine (499 \(\mu\)l, 3.83 mmol) was added and the reaction mixture was refluxed for 2 hours. The reaction was quenched with NaOH solution (10%, 15 ml) and chloroform (100 ml) was added. The organic phase was separated and the aqueous phase extracted with chloroform (2 x 50 ml).
The combined organic layer was washed with brine (100 ml), dried with Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated. The product was purified via column chromatography (SiO\textsubscript{2}; (1) EtOAc / Hexane 4:1, (2) chloroform / 3% methanol). Concentration of the sample afforded the product as a brown viscous oil: 849 mg (100%); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 8.74-8.72 (2H, m), 7.98 (1H, app d, \(J = 7.7\) Hz), 7.93 (1H, app d, \(J = 7.7\) Hz), 7.36-7.27 (4H, m), 6.97 (1H, app t, \(J = 7.5\) Hz), 6.92 (1H, app d, \(J = 8.8\) Hz), 4.82(1H, d, \(J = 10.6\) Hz), 4.12 (1H, d, \(J = 12.4\) Hz), 4.01 (1H, d, \(J = 10.6\) Hz), 3.87 (3H, s), 3.85 (1H, d, \(J = 12.4\) Hz), 1.96 (2H, br s); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 157.6, 151.1, 149.8, 149.7, 149.5, 134.8, 134.2, 134.0, 133.8, 130.2, 129.0, 127.8, 124.2, 124.0, 120.9, 110.6, 70.0, 61.8, 55.4, 47.4; FT-IR (KBr, pellet) \(\nu/cm\textsuperscript{-1}\) 3278, 3063, 3003, 2937, 2835,1601, 1582, 1563, 1492, 1464, 1418, 1288, 1242, 1122, 1069, 1049, 1028, 800, 747; HRMS (EI, \(m/z\)) calcd for C\textsubscript{20}H\textsubscript{19}N\textsubscript{3}O\textsubscript{2} (M\textsuperscript{+}) 333.1477, found 333.1483.

**Preparation of trans-5,6-dihydro-6-(2,4-dimethoxybenzylamino)-1,10-phenanthroline-5-ol [1.15r]**

1,10-Phenanthroline-5,6-epoxide (500 mg, 2.55 mmol) and ytterbium triflate (790 mg, 1.28 mmol) were dissolved in acetonitrile (1 ml). 2,4-dimethoxybenzylamine (574 \(\mu\)l, 3.83 mmol) was added and the reaction mixture was refluxed for 2 hours. The reaction was quenched with NaOH solution (10\%, 15 ml) and chloroform (100 ml) was added. The organic phase was separated and the aqueous phase extracted with chloroform (2 x 50 ml). The combined organic layer was washed with brine (100 ml), dried with Na2SO4, filtered and concentrated. The product was purified via column chromatography (SiO\textsubscript{2}; (1) EtOAc / Hexane 4:1, (2) chloroform / 3% methanol). Concentration of the sample afforded the
product as a yellow solid: 926 mg (100%); $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 8.70-8.67 (2H, m), 7.95 (1H, app d, J = 7.7 Hz), 7.90 (1H, app d, J = 7.7 Hz), 7.29 (2H, dd, J = 7.7, 4.8 Hz), 7.15 (1H, d, J = 8.1 Hz), 6.46 (1H, d, J = 2.6 Hz), 6.42 (1H, dd, J = 8.1, 2.6 Hz), 4.80 (1H, d, J = 10.6 Hz), 4.01 (1H, d, J = 12.5 Hz), 3.97 (1H, d, J = 10.6 Hz), 3.78 (3H, s), 3.81 (3H, s), 3.76 (1H, d, J = 12.8 Hz), 2.88 (2H, br s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 160.6, 158.6, 151.1, 149.7, 149.5, 134.8, 134.1, 134.0, 133.9, 130.7, 124.2, 124.0, 120.3, 104.1, 98.9, 70.0, 61.6, 55.5, 55.4, 47.0; FT-IR (KBr, pellet) $\nu$/cm$^{-1}$ 3262, 3235, 3062, 3003, 2988, 2957, 2933, 2881, 2847, 2835, 1613, 1591, 1565, 1508, 1463, 1438, 1420, 1287, 1256, 1208, 1184, 1155, 1111, 1070, 1035, 825, 811, 747; HRMS (EI, m/z) calcd for C$_{21}$H$_{21}$N$_3$O$_3$ (M$^+$) 363.1583, found 363.1582.

Preparation of trans-5,6-dihydro-6-(2,4,6-trimethoxybenzylamino)-1,10-phenanthrolin-5-ol [1.15s]

1,10-Phenanthroline (250mg, 1.25 mmol), ytterbium triflate (2.13g, 9.6 mmol) and the hydrochloric acid salt of 2,4,6-trimethoxybenzylamine 440mg (1.88 mmol) were dissolved in 20 ml of acetonitrile. The mixture was refluxed for 10 hours until the reaction was determined to be complete by TLC. The reaction was quenched with 15ml of 10% NaOH solution and 50ml of chloroform added. The two phases were separated and the aqueous layer was extracted with chloroform (2 x 50 ml). The combined organic layer was washed with brine (2 x 40 ml), dried with mixed sodium sulfate/magnesium sulfate, filtered and concentrated. The product was purified by column chromatography (SiO$_2$; 3% methanol / chloroform). Concentration of sample afforded the product as a yellow oil 170mg (35%); $R_f$ 0.32 (Al$_2$O$_3$, 3% methanol/chloroform); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.70-8.67 (2H, m), 7.95 (1H, app d, J = 7.7 Hz), 7.90 (1H, app d, J = 7.7 Hz), 7.29 (2H, dd, J = 7.7, 4.8 Hz), 7.15 (1H, d, J = 8.1 Hz), 6.46 (1H, d, J = 2.6 Hz), 6.42 (1H, dd, J = 8.1, 2.6 Hz), 4.80 (1H, d, J = 10.6 Hz), 4.01 (1H, d, J = 12.5 Hz), 3.97 (1H, d, J = 10.6 Hz), 3.78 (3H, s), 3.81 (3H, s), 3.76 (1H, d, J = 12.8 Hz), 2.88 (2H, br s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 160.6, 158.6, 151.1, 149.7, 149.5, 134.8, 134.1, 134.0, 133.9, 130.7, 124.2, 124.0, 120.3, 104.1, 98.9, 70.0, 61.6, 55.5, 55.4, 47.0; FT-IR (KBr, pellet) $\nu$/cm$^{-1}$ 3262, 3235, 3062, 3003, 2988, 2957, 2933, 2881, 2847, 2835, 1613, 1591, 1565, 1508, 1463, 1438, 1420, 1287, 1256, 1208, 1184, 1155, 1111, 1070, 1035, 825, 811, 747; HRMS (EI, m/z) calcd for C$_{21}$H$_{21}$N$_3$O$_3$ (M$^+$) 363.1583, found 363.1582.
CDCl₃: δ 8.72 (2H, d, J = 4.4 Hz), 7.99 (2H, t, J = 6.6 Hz), 7.32 (2H, dd, J = 7.7, 4.8 Hz), 6.14 (2H, s), 4.81 (1H, d, J = 11.0 Hz), 4.04-3.91 (2H, ABq, J = 40.0, 11.7 Hz), 3.96 (1H, d, J = 11.0 Hz), 3.82 (6H, s); ¹³C NMR (100 MHz, CDCl₃): δ 161.0, 159.3, 151.2, 149.7, 149.5, 134.8, 133.9, 133.6, 124.2, 124.0, 90.7, 69.7, 61.7, 55.9, 55.5, 39.1; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 3304, 3199, 3054, 3002, 2960, 2839, 1667, 1608, 1499, 1465, 1420, 1204, 1134, 1059, 909, 813, 788, 648.

Preparation of trans-5,6-dihydro-6-(2-nitrobenzylamino)-1,10-phenanthroline-5-ol [L.15t]

This compound was synthesized according to Method B using the hydrochloric acid salt of 2-nitrobenzylamine 4.33g (22.9 mmol) and quenched at 20 hrs. Concentration of the product gave a brown, glassy solid. The product was purified by column chromatography (SiO₂; 5% methanol / chloroform). Upon concentration, the product foamed leaving an airy, orange solid 1.71g (64%); m.p. 173-175°C; Rf 0.30 (SiO₂; 5% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.65 (2H, app d, J = 4.0 Hz), 7.95 (1H, d, J = 7.7 Hz), 7.91 (1H, d, J = 7.7 Hz), 7.84 (1H, app d, J = 7.7 Hz), 7.56 (2H, app q, J = 7.7 Hz), 7.42 (1H, app t, J = 8.1 Hz), 7.29 (2H, dd, J = 7.7, 4.8 Hz), 4.89 (1H, d, J = 9.5 Hz), 4.29 (1H, d, ABq, J = 13.9 Hz), 4.09 (1H, d, ABq, J = 14.3 Hz), 4.05 (1H, d, J = 9.5 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 150.9, 149.9, 149.7, 149.2, 135.1, 134.7, 134.5, 133.5, 133.3, 131.4, 128.5, 124.6, 124.4, 124.2, 76.8, 62.1, 48.7; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 3180, 3070, 2931, 2856, 1672, 1609, 1577, 1524, 1420, 1346, 1073, 857, 787, 730; HRMS (ESI) calcd for C₁₉H₁₇N₄O₃ [M+H]⁺: 349.1300, found: 349.1313.
Preparation of trans-5,6-dihydro-6-(3-nitrobenzylamino)-1,10-phenanthrolin-5-ol [1.15u]

This compound was synthesized according to Method B with all reagents adjusted to a 1g scale of 1,10-phenanthroline-5,6-epoxide (5.1 mmol) using the hydrochloric acid salt of 3-nitrobenzylamine 2.89g (15.3 mmol) and quenched after 20 hrs. Concentration of the product gave a brown, glassy solid. The product was purified by column chromatography (SiO₂; 3% methanol / chloroform). Upon concentration, the product foamed leaving an airy, brown solid 1.57g (88%); m.p. 72-74°C; Rₚ 0.33 (SiO₂; 3% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.53 (1H, app d, J = 4.8 Hz), 8.43 (1H, app d, J = 3.6 Hz), 8.20 (1H, app s), 8.01 (1H, app d, J = 8.0), 7.89 (1H, app d, J = 7.7 Hz), 7.83 (1H, app d, J = 7.7 Hz), 7.74 (1H, d, J = 7.7 Hz), 7.42 (1H, app t, J = 8.0 Hz), 7.31 (1H, dd, J = 7.7, 4.8 Hz), 7.23 (1H, dd, J = 7.7, 4.8 Hz), 5.01 (1H, d, J = 7.0 Hz), 4.15 (1H, d, J = 7.0 Hz), 4.04 (2H, app dd, J = 14.8, 11.9 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 150.6, 149.5, 149.2, 148.3, 142.4, 135.3, 135.1, 134.2, 133.8, 133.7, 129.9, 129.6, 129.4, 124.4, 124.3, 122.8, 122.7, 122.5, 122.3, 70.1, 61.2, 49.9, 45.1; FT-IR (thin film from CDCl₃) ν/cm⁻¹: 3270, 3060, 2859, 1687, 1580, 1563, 1510, 1418, 1211, 1125, 1070, 796, 777, 729, 645; HRMS (ESI) calcd for C₁₉H₁₇N₄O₃ [M+H]⁺: 349.1300, found: 349.1310.
Preparation of trans-5,6-dihydro-6-(4-nitrobenzylamino)-1,10-phenanthrolin-5-ol [1.15v]

This compound was synthesized according to Method B with all reagents adjusted to a 1g scale of 1,10-phenanthroline-5,6-epoxide (5.1 mmol) using the hydrochloric acid salt of 4-nitrobenzylamine 2.89g (15.3 mmol) and quenched after 20 hrs. Concentration of the reaction mixture gave a brown, glassy solid. The product was purified by column chromatography (SiO₂; 5% methanol / chloroform). Upon concentration, the product foamed leaving an airy, brown solid 1.53g (86%); m.p. 199-204°C; R_f 0.17 (SiO₂; 5% methanol / chloroform); ^1H NMR (400 MHz, CDCl₃): δ 8.62 (2H, app d, J = 4.4 Hz), 8.11 (2H, app d, J = 7.0 Hz), 7.93 (1H, app d, J = 7.7 Hz), 7.81 (1H, app d, J = 7.7 Hz), 7.49 (2H, d, J = 8.8 Hz), 7.29-7.27 (2H, m), 4.90 (1H, d, J = 8.4 Hz), 4.12-3.98 (2H, ABq, J = 53.4, 14.6 Hz), 4.03 (1H, d, J = 8.4 Hz); ^13C NMR (100 MHz, CDCl₃): δ 150.6, 149.6, 149.3, 147.8, 135.1, 135.0, 133.5, 128.5, 124.4, 124.2, 123.7, 70.2, 61.3, 50.1; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 3153, 3060, 2862, 1684, 1646, 1597, 1516, 1418, 1344, 1107, 1013, 856, 744; HRMS (ESI) calcd for C₁₉H₁₇N₄O₃ [M+H]^+: 349.1300, found: 349.1329.

Preparation of tert-butyl 2-(6-hydroxy-5,6-dihydro-1,10-phenanthrolin-5-ylamino)acetate [1.15w]

1,10-Phenanthroline-5,6-epoxide (500 mg, 2.55 mmol) and lithium perchlorate (542 mg, 5.10 mmol) were dissolved in acetonitrile (3 ml). Glycine tert-butyl ester hydrochloride (854 mg, 5.10 mmol) was dissolved in acetonitrile (7 ml), neutralized with triethylamine (710 μl, 5.10 mmol), added and the reaction mixture was refluxed for 1 day. The
reaction was quenched with sodium hydroxide solution (2%, 30 ml) and chloroform (200 ml) was added. The organic phase was separated and the aqueous phase extracted with chloroform (2 x 50 ml). The combined organic layer was washed with brine (50 ml), dried with sodium sulfate, filtered and concentrated. The product was purified via column chromatography (SiO₂; chloroform / 3% methanol). Concentration of the sample afforded the product as a brown oil: 750 mg (90%); ¹H-NMR (400 MHz, CDCl₃): δ 8.72-8.74 (2H, m), 8.09 (1H, app d, J = 7.7 Hz), 7.89 (1H, app d, J = 7.7 Hz), 7.31-7.37 (2H, m), 4.86 (1H, br s), 4.72 (1H, d, J = 11.0 Hz), 4.06 (1H, d, J = 11.0 Hz), 3.55 (2H, ABq, J = 18.3 Hz), 1.46 (9H, s); ¹³C NMR (100 MHz, CDCl₃): δ 173.9, 151.3, 149.6, 149.6, 149.5, 134.8, 134.4, 134.2, 133.0, 124.3, 124.0, 82.6, 69.6, 62.3, 48.3, 28.1; FT-IR (KBr, pellet) ν/cm⁻¹: 3278, 3067, 3005, 2979, 2933, 2873, 2820, 1739, 1585, 1565, 1418, 1393, 1368, 1239, 1152, 1070, 799, 747; HRMS (El, m/z) calcd for C₁₈H₂₁N₃O₃ (M⁺) 327.1583, found 327.1585.

Preparation of 6-(hexylamino)-1,10-phenanthroline [I.16]

This compound was synthesized according to Method B using 2.32g (22.9 mmol) and quenched after 12 hrs. The product was purified by column chromatography (SiO₂; chloroform / 3% methanol) to give an orange solid 0.25 g (12%); ¹H NMR (400 MHz, CDCl₃): δ 9.05 (1H, dd, J = 4.0, 1.2 Hz), 8.88 (1H, dd, J = 4.4, 1.6 Hz), 8.33 (1H, dd, J = 8.4, 1.6 Hz), 8.05 (1H, dd, J = 8.4, 1.6 Hz), 7.56 (1H, dd, J = 8.4, 4.4 Hz), 7.51 (1H, dd, J = 8.0, 4.8 Hz), 6.62 (1H, s), 3.33 (2H, t, J = 7.2 Hz), 1.82 (2H, p, J = 7.2 Hz), 1.51 (2H, p, J = 7.2 Hz), 1.41-1.33 (4H, m), 0.92 (3H, t, J = 7.2 Hz).
Preparation of 6-(butylamino)-5,6-dihydro-2,9-dimethyl-1,10-phenanthroline-5,6-ol [I.18a]

This compound was synthesized according to Method A at a 250 mg scale using butylamine (0.12 g, 1.7 mmol). The reaction was quenched after 24 hrs. The product was purified by via column chromatography (SiO2; chloroform / 3% methanol) to afford a brown viscous oil 0.13 g (42%); 1H NMR (400 MHz, CDCl3): δ 7.74 (1H, d, J = 7.6 Hz), 7.58 (1H, d, J = 7.6 Hz), 7.09 (2H, d, J = 8.4 Hz), 4.65 (1H, d, J = 8.8 Hz), 3.78 (1H, d, J = 8.8 Hz), 2.60 (6H, s), 2.75-2.69 (2H, m), 1.41 (2H, o, J = 7.2 Hz), 1.27 (2H, sextet, J = 7.2 Hz), 0.84 (3H, t, J = 7.6 Hz); 13C NMR (100 MHz, CDCl3): δ 173.2, 158.8, 158.4, 158.1, 150.1, 149.3, 149.1, 135.2, 135.2, 133.8, 131.7, 131.6, 130.8, 123.9, 123.6, 70.1, 61.7, 40.0, 32.7, 24.7, 24.5, 22.7, 20.4, 14.0.

Preparation of 6-(allylamino)-5,6-dihydro-2,9-dimethyl-1,10-phenanthroline-5,6-ol [I.18b]

This compound was synthesized according to Method A at a 250 mg scale using allylamine (0.10 g, 1.7 mmol). The reaction was quenched after 24 hrs. The product was purified by via column chromatography (SiO2; chloroform / 3% methanol) to afford a brown viscous oil 0.06 g (20%); 1H NMR (400 MHz, CDCl3): δ 7.80 (1H, d, J = 8.1 Hz), 7.62 (1H, d, J = 8.1 Hz), 7.18 (1H, d, J = 8.1 Hz), 7.17 (1H, d, J = 8.1 Hz), 5.90 (1H, ddt, J = 17.2, 10.3, 1.5 Hz), 5.20 (1H, dq, J = 17.2, 1.5 Hz), 5.12 (1H, dq, J = 10.3, 1.5 Hz), 4.70 (1H, d, J = 8.4 Hz), 3.87 (1H, d, J = 8.4 Hz), 3.39 (2H, ABq, J = 55.3, 14.3, 5.7 Hz), 2.69 (6H, s); 13C NMR (100 MHz, CDCl3): δ 159.3, 158.8, 136.3, 135.1, 135.0, 131.2, 130.5, 124.0, 123.6, 116.8, 77.6, 61.0, 50.1, 24.9, 24.8.
Preparation of 6-(benzylamino)-5,6-dihydro-2,9-dimethyl-1,10-phenanthroline-5,6-ol [I.18c]

This compound was synthesized according to Method A at a 250 mg scale using benzylamine (0.18 g, 1.7 mmol). The reaction was quenched after 24 hrs. The product was purified by via column chromatography (SiO$_2$; chloroform / 3% methanol) to afford a brown viscous oil 0.11 g (31%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.88 (1H, d, J = 8.1 Hz), 7.87 (1H, d, J = 7.7 Hz), 7.65 (1H, d, J = 8.4 Hz), 7.63 (1H, d, J = 8.4 Hz), 7.43 (1H, d, J = 8.4 Hz), 7.36-7.17 (4H, m), 4.75 (1H, d, J = 8.4 Hz), 3.93 (1H, d, J = 8.4 Hz), 3.94 (2H, ABq, J = 58.3, 13.2 Hz), 2.68 (3H, s), 2.66 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.3, 158.8, 150.3, 149.2, 139.7, 135.3, 135.2, 131.2, 130.4, 128.7, 128.2, 127.5, 124.0, 123.6, 70.5, 61.2, 51.4, 24.9, 24.8.

Preparation of 6-(4-methoxybenzylamino)-5,6-dihydro-2,9-dimethyl-1,10-phenanthroline-5,6-ol [I.18d]

This compound was synthesized according to Method A at a 250 mg scale using 4-methoxybenzylamine (0.23 g, 1.7 mmol). The reaction was quenched after 24 hrs. The product was purified by via column chromatography (SiO$_2$; chloroform / 3% methanol) and isolated as a brown viscous oil 0.06 g (15%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.76 (1H, d, J = 7.7 Hz), 7.62 (1H, d, J = 7.7 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.15 (1H, d, J = 7.7 Hz), 7.14 (1H, d, J = 7.7 Hz), 6.85 (2H, d, J = 8.4 Hz), 4.71 (1H, d, J = 8.4 Hz), 3.90 (1H, d, J = 8.1 Hz), 3.84 (2H, ABq, J = 56.0, 13.2 Hz), 3.78 (3H, s), 2.67 (3H, s), 2.66 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.2, 159.0, 158.8, 135.3, 135.2, 131.8, 131.3, 130.5, 129.4, 124.0, 123.6, 114.1, 70.5, 61.0, 55.4, 50.9, 24.9, 24.8.
Preparation of 6-(2-nitrobenzylamino)-5,6-dihydro-2,9-dimethyl-1,10-phenanthroline-5,6-ol [I.18e]

This compound was synthesized according to Method A at a 250 mg scale using 2-nitrobenzylamine (0.26 g, 1.7 mmol). The reaction was quenched after 24 hrs. The product was purified by via column chromatography (SiO₂; chloroform / 3% methanol) and isolated as a brown viscous oil 0.07 g (18%); ¹H NMR (400 MHz, CDCl₃): δ 7.93 (1H, d, J = 7.7 Hz), 7.80 (1H, d, J = 7.3 Hz), 7.68 (1H, d, J = 8.1 Hz), 7.56-7.52 (2H, m), 7.46-7.40 (1H, m), 7.16 (2H, d, J = 7.7 Hz), 4.78 (1H, d, J = 8.4 Hz), 4.16 (2H, ABq, J = 75.4, 13.9 Hz), 3.96 (1H, d, J = 8.4 Hz), 2.64 (6H, s); ¹³C NMR (100 MHz, CDCl₃): δ 159.2, 158.9, 150.1, 149.0, 134.1, 134.9, 133.1, 131.2, 131.0, 129.4, 128.9, 124.9, 124.3, 123.9, 123.1, 70.8, 62.0, 49.1, 25.8, 24.5.

Preparation of 6-((furan-2-ylmethyl)amino)-5,6-dihydro-2,9-dimethyl-1,10-phenanthroline-5,6-ol [I.18f]

This compound was synthesized according to Method A at a 250 mg scale using furfurylamine (0.16 g, 1.7 mmol). The reaction was quenched after 24 hrs. The product was purified by via column chromatography (SiO₂; chloroform / 3% methanol) and isolated as a brown viscous oil 0.16 g (45%); ¹H NMR (400 MHz, CDCl₃): δ 7.69 (1H, d, J = 7.7 Hz), 7.53 (1H, d, J = 7.7 Hz), 7.31-7.30 (1H, m), 7.05 (1H, d, J = 7.7 Hz), 7.04 (1H, d, J = 7.7 Hz), 6.26-6.25 (1H, m), 6.11 (1H, app d, J = 2.6), 4.67 (1H, d, J = 8.1 Hz), 3.87 (1H, d, J = 7.7 Hz), 3.75 (2H, ABq, J = 27.5, 14.7 Hz), 2.57 (6H, s); ¹³C NMR (100 MHz, CDCl₃):
\[ \delta 159.0, 158.6, 153.3, 150.0, 149.0, 142.1, 135.7, 131.3, 130.2, 124.0, 123.7, 110.4, 107.4, 70.4, \\
60.8, 43.8, 24.7, 24.5. \]

**Preparation of trans-9,10-dihydro-10-(butylamino)phenanthren-5-ol [1.19a]**

This compound was synthesized according to Method C scaled appropriately for phenanthrene oxide (0.5 g, 2.6 mmol) and butyl amine 1.0 mL (0.75 g, 10.3 mmol) and was quenched at 24 hrs. The product was purified via column chromatography (SiO2; chloroform / 3% methanol). Concentration of the product gave a brown viscous oil 0.35 g (46%); Rf 0.20 (Al₂O₃, 3% methanol/chloroform); \(^1^H\) NMR (400 MHz, CDCl₃): \( \delta \) 7.77 (1H, d, \( J = 7.7 \) Hz), 7.72 (1H, d, \( J = 7.3 \) Hz), 7.59 (1H, d, \( J = 7.3 \) Hz), 7.40-7.30 (4H, m), 7.06 (1H, d, \( J = 6.2 \) Hz), 4.68 (1H, d, \( J = 9.2 \) Hz), 4.59 (1H, bs), 3.90 (1H, d, \( J = 9.2 \)), 3.09 (1H, t, \( J = 3.3 \)), 2.93-2.90 (1H, m), 2.77-2.75 (1H, m), 1.56 (2H, m), 1.32 (2H, p, \( J = 7.3 \)), 0.87 (3H, t, \( J = 7.3 \)); \(^1^C\) NMR (100 MHz, CDCl₃): \( \delta \) 138.8, 133.5, 132.1, 128.6, 128.6, 128.5, 128.1, 127.4, 126.8, 126.6, 124.5, 123.9, 70.1, 62.2, 46.5, 31.5, 20.2, 13.9; FT-IR (thin film from dichloromethane) ν/cm\(^{-1}\) 3239, 3065, 2959, 2931, 2871, 1632, 1577, 1451, 1380, 1299, 1264, 1201, 1124, 1073, 753, 739, 619, 547.
Preparation of trans-9,10-dihydro-10-(allylamino)phenanthren-9-ol [1.19b]

This compound was synthesized according to Method C scaled appropriately for phenanthrene oxide (1g, 5.1 mmol) and allyl amine 0.76 mL (0.58 g, 10.2 mmol). Reaction was quenched at 24 hrs. The product was purified by column chromatography (SiO\textsubscript{2}; 5% methanol / chloroform). Upon concentration, the product gave a orange viscous oil 0.58 g (58%); Rf 0.40 (Al\textsubscript{2}O\textsubscript{3}, 3% methanol / chloroform); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textit{\delta} 7.76 (2H, app t, J = 8.1), 7.54 (1H, d, J = 7.3), 7.40-7.31 (5H, m), 5.9 (1H, ddt, J = 17.2, 10.2, 6.1), 5.20 (1H, dd, J = 17.24, 2.8), 5.11 (1H, dd, J = 10.24, 1.5), 4.65 (1H, d, J = 7.7), 3.83 (1H, d, J = 7.7), 3.45-3.34 (ABq d, 2H, J = 42.1, 9.5, 1.4); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \textit{\delta} 136.6, 136.1, 135.8, 133.2, 132.2, 128.8, 128.5, 128.1, 127.5, 127.4, 124.6, 124.0, 117.1, 71.3, 61.5, 50.3; FT-IR (thin film from CDCl\textsubscript{3}) \textit{v/cm}^{-1} 3344, 3068, 3034, 2915, 2849, 1662, 1600, 1483, 1451, 1392, 1295, 1201, 1121, 1036, 1004, 910, 754, 736, 646, 619.

Preparation of trans-9,10-dihydro-10-(benzylamino)phenanthren-9-ol [1.19c]

This compound was synthesized according to Method C scaled to 0.25 g phenanthrene oxide with benzyl amine (0.28 g, 1.6 mmol) and quenched after 24 hours. The product was purified by column chromatography (SiO\textsubscript{2}; 3% methanol / chloroform). Concentration of sample afforded the product as a brown viscous oil, 0.37 g (94%); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textit{\delta} 7.81 (2H, app t, J = 7.7), 7.53 (1H, d, J = 7.7), 7.45-7.34 (10H, m), 4.69 (1H, d, J = 7.7), 4.00-3.83 (2H, ABq, J = 55.7, 13.2), 3.85 (1H, d, J = 6.6); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \textit{\delta} 140.2, 136.8, 136.1, 133.3, 132.5, 128.9, 128.7, 128.4, 128.4, 128.4, 127.8, 127.4,
Preparation of trans-9,10-dihydro-10-(4-methoxybenzylamino)phenanthren-9-ol [1.19d]

This compound was synthesized according to Method C scaled to 0.50 g phenanthrene oxide with 4-methoxybenzyl amine (0.54 g, 3.9 mmol) and quenched after 24 hours. The product was purified by column chromatography (SiO$_2$; 3% methanol / chloroform). Concentration of sample afforded the product as a brown viscous oil, 0.46 g (72%); $R_f$ 0.31 (Al$_2$O$_3$, 3% methanol / chloroform); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.77 (2H, app t, $J = 8.8$), 7.55 (1H, d, $J = 7.3$), 7.39 (2H, app t, $J = 7.0$), 7.35-7.28 (5H, m), 6.85 (2H, d, $J = 8.8$), 4.65 (1H, d, $J = 7.7$), 3.98-3.81 (2H, ABq, $J = 53.9$, 12.8), 3.83 (1H, d, $J = 8.0$), 3.81 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.9, 136.8, 135.9, 133.3, 132.3, 131.8, 129.6, 128.6, 128.4, 128.4, 128.1, 127.4, 127.3, 124.6, 123.9, 114.0, 71.4, 61.6, 55.4, 51.0; FT-IR (thin film from dichloromethane) v/cm$^{-1}$ 3346, 3066, 3030, 2933, 2835, 1679, 1610, 1512, 1452, 1301, 1249, 1177, 1033, 909, 832, 755, 738, 518.
Preparation of trans-9,10-dihydro-10-(4-fluorobenzylamino)phenanthren-9-ol [1.19e]

This compound was synthesized according to Method C scaled to 1.00 g phenanthrene oxide with 4-fluorobenzyl amine (0.95 g, 7.5 mmol) and quenched after 24 hours. The product was purified by column chromatography (SiO₂; 3% methanol / chloroform). Concentration of sample afforded the product as a brown viscous oil, 0.86 g (61%); Rₚ 0.25 (Al₂O₃, 3% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 7.78 (2H, app t, J = 8.0), 7.52 (1H, d, J = 7.3), 7.42-7.29 (7H, m), 7.0 (2H, app t, J = 8.4), 4.68 (1H, d, J = 8.4), 3.97-3.79 (2H, ABq, J = 57.2, 13.2), 3.83 (1H, d, J = 6.6); ¹³C NMR (100 MHz, CDCl₃): δ 163.3, 160.9, 136.5, 135.8, 133.1, 132.4, 129.9, 129.8, 128.5, 128.1, 127.9, 124.6, 124.0, 124.0, 115.5, 115.3, 71.5, 61.6, 50.7; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 13349, 3067, 3034, 2848, 1693, 1602, 1509, 1483, 1453, 1294, 1221, 1156, 1090, 1014, 946, 908, 825, 754, 666, 619, 561.

Preparation of (1R,2S)-2-butylamino-1,2-diphenylethan-1-ol + en. [1.21a]

This compound was synthesized according to Method D using trans-stilbene oxide (2.6 mmol) and butylamine (0.20 g, 2.8 mmol). The product was purified by recrystallization from hexanes/chloroform to give a white solid 0.52 g (76%); m.p. 133-135°C; ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.21 (6H, m), 7.11-7.07 (4H, m), 4.82 (1H, d, J = 5.5 Hz), 3.88 (1H, d, J = 5.5 Hz), 2.53-2.42 (2H, m), 1.40 (2H, p, J = 6.7 Hz), 2.25 (2H, p, J = 7.3), 0.84 (3H, t, J = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 140.6, 139.6, 128.2, 128.2, 128.0, 127.6, 127.6, 126.8, 68.9, 47.2, 32.3, 20.4, 14.0.
**Preparation of (1R,2S)-2-allylamino-1,2-diphenylethan-1-ol + en. [I.21b]**

This compound was synthesized according to Method D using *trans*-stilbene oxide (2.6 mmol) and allylamine (0.16 g, 2.8 mmol). The product was purified by recrystallization from hexanes/chlorform to give a white solid 0.53 g (82%); m.p. 118-120°C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.29-7.20 (6H, m), 7.15-7.10 (4H, m), 5.84-5.74 (1H, m), 5.07-5.00 (2H, m), 4.82 (1H, d, J = 5.9 Hz), 3.94 (1H, d, J = 5.9 Hz), 3.18 (2H, ABqd, J = 46.9, 14.3, 5.1); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.6, 139.2, 136.5, 128.4, 128.3, 128.1, 127.8, 127.7, 126.9, 116.1, 76.7, 68.0, 49.7.

**Preparation of (1R,2S)-2-benzylamino-1,2-diphenylethan-1-ol + en. [I.21c]**

This compound was synthesized according to Method D using *trans*-stilbene oxide (2.6 mmol) and benzylamine (0.30 g, 2.8 mmol). The product was purified by recrystallization from hexanes/chlorform to give a white solid 0.53 g (68%); m.p. 151-153°C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.32-7.24 (9H, m), 7.18-7.15 (4H, m), 7.12-7.10 (2H, m), 4.82 (1H, d, J = 5.9 Hz), 3.93 (1H, d, J = 6.2 Hz), 3.61 (2H, ABq, J = 66.3, 13.2 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 140.5, 140.0, 139.3, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.1, 127.0, 76.8, 68.0, 51.2.
Preparation of (1R,2S)-2-(4-methoxybenzylamino)-1,2-diphenylethan-1-ol + en. [I.21d]

This compound was synthesized according to Method D using trans-stilbene oxide (2.6 mmol) and 4-methoxybenzylamine (0.38 g, 2.8 mmol). The product was purified by recrystallization from hexanes/chloroform to give a white solid 0.59 g (69%); m.p. 131-134°C; $^1$H NMR (400 MHz, CDCl₃): δ 7.30-7.21 (6H, m), 7.16-7.13 (2H, m), 7.10-7.06 (4H, m), 6.84-6.80 (2H, m), 4.81 (1H, d, J = 5.9), 3.91 (1H, d, J = 5.9), 3.79 (3H, s), 3.56 (2H, ABq, J = 65.5, 13.2); $^{13}$C NMR (100 MHz, CDCl₃): δ 187.7, 140.5, 139.3, 132.1, 129.3, 128.4, 128.3, 128.1, 127.7, 126.9, 113.9, 67.8, 55.4, 50.5.

Preparation of (1R,2S)-2-(2-nitrobenzylamino)-1,2-diphenylethan-1-ol + en. [I.21e]

This compound was synthesized according to Method D using trans-stilbene oxide (2.6 mmol) and 2-nitrobenzylamine (0.43 g, 2.8 mmol). The product was purified by recrystallization from hexanes/chloroform to give a white solid 0.79 g (89%); m.p. 139-141°C; $^1$H NMR (400 MHz, CDCl₃): δ 7.90 (1H, dd, J = 8.1, 1.1 Hz), 7.50 (1H, td, J = 7.7, 1.1 Hz), 7.38 (1H, td, J = 9.2, 1.5 Hz), 7.32-7.23 (7H, m), 7.20-7.18 (2H, m), 7.13-7.10 (2H, m), 4.76 (1H, d, J = 6.2 Hz), 3.86 (1H, d, J = 6.2 Hz), 3.81 (2H, ABq, J = 62.6, 14.2 Hz); $^{13}$C NMR (100 MHz, CDCl₃): δ 149.1, 140., 139.0, 135.2, 133.2, 131.7, 128.5, 128.3, 128.0, 127.9, 127.0, 126.9, 125.1, 124.8, 76.8, 68.4, 48.6.
Preparation of (1R,2S)-2-(furan-2-ylmethyl)amino-1,2-diphenylethan-1-ol + en. [I.21f]

This compound was synthesized according to Method D using trans-stilbene oxide (2.6 mmol) and furfurylamine (0.27 g, 2.8 mmol). The product was purified by recrystallization from hexanes/chloroform to give a white solid 0.60 g (80%); m.p. 143-145°C; \( ^1 \)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.31-7.24 (7H, m), 7.19-7.17 (2H, m), 7.12-7.11 (2H, m), 6.28-6.27 (1H, m), 6.01 (1H, app d, \( J = 2.9 \) Hz), 4.80 (1H, d, \( J = 5.9 \) Hz), 3.88 (1H, d, \( J = 5.9 \) Hz), 3.59 (2H, ABq, \( J = 65.9, 15.0 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 153.5, 142.0, 140.4, 138.9, 128.6, 128.4, 128.2, 127.9, 127.8, 127.0, 110.1, 107.2, 76.9, 67.5, 43.6.

Preparation of (1R,2R)-2-benzylamino-1,2-diphenylethan-1-ol + en. [I.23]

This compound was synthesized according to Method D using cis-stilbene oxide (2.6 mmol) and benzylamine (0.30 g, 2.8 mmol). The product was purified by column chromatography (SiO\(_2\); 3% methanol / chloroform) to give a white solid 0.41 g (68%); m.p. 76-81°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.32-7.22 (7H, m), 7.17-7.15 (4H, m), 7.07-7.04 (2H, m), 4.60 (1H, d, \( J = 8.4 \) Hz), 3.67 (1H, d, \( J = 8.4 \) Hz), 3.65 (2H, ABq, \( J = 58.6, 13.2 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 141.2, 139.8, 128.6, 128.5, 128.4, 128.0, 127.9, 127.6, 127.3, 127.0, 126.9, 69.7, 59.9, 51.4.
Preparation of trans-2-butylaminocyclohexanol [I.25a]

This compound was synthesized according to Method D using cyclohexene oxide (5.1 mmol) and butylamine (0.41 g, 5.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give an orange-brown oil 0.77 g (88%); ^1H NMR (400 MHz, CDCl₃): δ 3.12 (1H, td, J = 9.5, 4.8 Hz), 2.77 (1H, dt, J = 11.4, 7.0 Hz), 2.44 (1H, dt, J = 11.4, 7.7 Hz), 2.20-2.03 (4H, m), 1.71-1.70 (2H, m), 1.44 (2H, sextet, J = 6.2 Hz), 1.38 (2H, pentet, J = 7.0 Hz), 1.22-1.16 (3H, m), 0.91 (3H, t, J = 7.3 Hz); ^13C NMR (100 MHz, CDCl₃): δ 73.9, 63.7, 46.4, 33.4, 32.9, 30.7, 25.4, 24.5, 20.5, 14.9.

Preparation of trans-2-allylaminocyclohexanol [I.25b]

This compound was synthesized according to Method D using cyclohexene oxide (5.1 mmol) and allylamine (0.32 g, 5.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give an orange-brown oil 0.69 g (81%); ^1H NMR (400 MHz, CDCl₃): δ 5.92-5.78 (1H, m), 5.17 (1H, dq, J = 17.21, 1.5 Hz), 5.08 (1H, dq, J = 10.3, 1.5 Hz), 3.42-3.34 (1H, m), 3.18-3.11 (2H, m), 2.27-2.21 (1H, m), 2.03-1.92 (2H, m), 1.70-1.97 (2H, m), 1.29-1.17 (3H, m), 0.99-0.89 (2H, m); ^13C NMR (100 MHz, CDCl₃): δ 136.8, 116.6, 73.6, 62.9, 49.3, 33.6, 30.3, 25.1, 24.4.
Preparation of trans-2-benzylaminocyclohexanol [I.25c]

This compound was synthesized according to Method D using cyclohexene oxide (5.1 mmol) and benzylamine (0.60 g, 5.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give a light brown oil, 0.97 g (93%); \(^1\)H NMR (400 MHz, CDCl₃): δ 7.37-7.27 (5H, m), 3.91 (2H, ABq, J = 105.8, 12.8), 3.48-3.29 (1H, m), 2.44 (1H, td, J = 10.6, 4.0 Hz), 2.10-2.07 (1H, m), 2.01-1.94 (2H, m), 1.72-1.68 (2H, m), 1.28-1.13 (3H, m); \(^{13}\)C NMR (100 MHz, CDCl₃): δ 136.9, 128.9, 128.8, 128.0, 72.3, 62.8, 49.8, 33.6, 29.1, 24.8, 24.2.

Preparation of trans-2-(4-methoxybenzylamino)cyclohexanol [I.25d]

This compound was synthesized according to Method D using cyclohexene oxide (5.1 mmol) and 4-methoxybenzylamine (0.77 g, 5.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give an orange waxy solid 1.14 g (95%); m.p. 50-52°C; \(^1\)H NMR (400 MHz, CDCl₃): δ 7.25 (2H, d, J = 8.4 Hz), 6.85 (2H, d, J = 8.4 Hz), 3.77 (2H, ABq, J = 117.5, 12.5 Hz), 3.79 (3H, s), 2.34-2.29 (1H, m), 2.15-1.96 (3H, m), 1.73-1.70 (2H, m), 1.31-1.28 (3H, m), 1.07-0.98 (1H, m); \(^{13}\)C NMR (100 MHz, CDCl₃): δ 159.0, 131.4, 131.4, 129.6, 114.0, 62.9, 55.4, 49.9, 33.4, 30.1, 25.1, 24.4.
Preparation of trans-2-(2-nitrobenzylamino)cyclohexanol [I.25e]

This compound was synthesized according to Method D using cyclohexene oxide (5.1 mmol) and 2-nitrobenzylamine (0.85 g, 5.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give a brown oil 0.71 g (56%); ¹H NMR (400 MHz, CDCl₃): δ 7.98 (1H, d, J = 8.1 Hz), 7.61-7.96 (2H, m), 7.46 (1H, t, J = 7.7 Hz), 4.46-4.08 (3H, m), 3.40 (1H, m), 2.5 (1H, m), 2.13-2.01 (4H, m), 1.73 (2H, m), 1.27-1.21 (4H, m); ¹³C NMR (100 MHz, CDCl₃): δ 149.3, 135.6, 133.3, 131.4, 128.7, 124.0, 73.9, 63.8, 48.1, 33.3, 30.7, 25.1, 24.4.

Preparation of trans-2-([furan-2-yl)methylamino)cyclohexanol [I.25f]

This compound was synthesized according to Method D using cyclohexene oxide (5.1 mmol) and furfurylamine (0.54 g, 5.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give an orange-brown oil 0.81 g (81%); ¹H NMR (400 MHz, CDCl₃): δ 7.39-7.38 (1H, m), 6.37-6.32 (2H, m), 4.02 (2H, ABq, J = 63.3, 14.3 Hz), 3.44 (1H, td, J = 10.3, 4.0 Hz), 2.49 (1H, td, J = 10.9, 3.7 Hz), 2.04-1.95 (2H, m), 1.74-1.71 (2H, m), 1.23 (4H, app dt, J = 14.7, 10.6); ¹³C NMR (100 MHz, CDCl₃): δ 150.4, 142.8, 110.7, 109.3, 72.7, 62.8, 42.7, 33.8, 28.9, 24.7, 24.1.
Preparation of (S)-2-butylamino-1-phenylethan-1-ol + en. [I.8a]

This compound was synthesized according to Method D using racemic styrene oxide (4.2 mmol) and butylamine (0.30 g, 4.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give a pale yellow oil 0.43 g (53%); ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.38 (5H, m), 4.81-4.73 (1H, m), 2.87-2.66 (3H, m), 1.59-1.22 (4H, m), 0.96-0.90 (3H, m); ¹³C NMR (100 MHz, CDCl₃): δ 142.3, 128.8, 127.9, 126.1, 71.7, 63.6, 55.4, 28.8, 20.6, 14.1.

Preparation of (S)-2-allylamino-2-phenylethan-1-ol + en. [I.9b]

This compound was synthesized according to Method E using racemic styrene oxide (4.2 mmol) and allylamine (0.26 g, 4.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give a pale yellow oil 0.35 g (48%); ¹H NMR (400 MHz, CDCl₃): δ 7.42-7.30 (5H, m), 5.95-5.82 (1H, m), 5.21-5.15 (2H, m), 3.97 (1H, dd, J = 8.8, 4.0 Hz), 3.80-3.68 (2H, m), 3.24 (2H, ABqd, J = 51.0, 13.9, 5.5 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 137.8, 134.0, 129.1, 128.8, 128.5, 127.6, 125.9, 118.6, 65.8, 63.9, 49.4.
Preparation of \((S)-2\)-benzylamino-1-phenylethan-1-ol + en. [I.8c]

This compound was synthesized according to Method D using racemic styrene oxide (4.2 mmol) and benzylamine (0.49 g, 4.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give a pale yellow waxy solid 0.60 g (63%); \(^1\)H NMR (400 MHz, CDCl₃): δ 7.37-7.24 (10H, m), 4.73 (1H, dd, \(J = 8.8, 3.7\) Hz), 3.87 (2H, ABq, 26.1, 13.2 Hz), 2.97-2.72 (2H, m); \(^{13}\)C NMR (100 MHz, CDCl₃): δ 142.6, 129.9, 128.6, 128.2, 127.6, 127.3, 125.9, 71.9, 56.6, 53.6.

Preparation of \((S)-2\)-benzylamino-2-phenylethan-1-ol + en. [I.9c]

This compound was synthesized according to Method E using racemic styrene oxide (4.2 mmol) and benzylamine (0.49 g, 4.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give a pale yellow oil 0.55 g (58%); \(^1\)H NMR (400 MHz, CDCl₃): δ 7.38-7.31 (10H, m), 3.85-3.53 (5H, m); \(^{13}\)C NMR (100 MHz, CDCl₃): δ 140.4, 139.9, 128.8, 128.6, 128.4, 127.8, 127.5, 127.3, 66.8, 63.7, 51.2.

Preparation of \((S)-2\)-(4-methoxybenzylamino)-1-phenylethan-1-ol + en. [I.8d]

This compound was synthesized according to Method D using racemic styrene oxide (4.2 mmol) and 4-methoxybenzylamine (0.63 g, 4.6 mmol). The product was purified by column chromatography (SiO₂; 3% methanol / chloroform) to give a pale yellow oil 0.81 g (75%); \(^1\)H NMR (400 MHz, CDCl₃): δ 7.35-7.32 (5H, m), 7.21 (2H, d, \(J = 8.4\) Hz), 6.85
(2H, d, J = 8.4 Hz), 4.72 (1H, dd, J = 9.2, 3.7 Hz), 3.75 (1H, app d, J = 7.0 Hz), 2.91-2.70 (3H, m);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.9, 142.6, 131.8, 129.5, 128.5, 127.6, 125.9, 113.9, 71.8, 58.5, 55.4, 52.9.

Preparation of (S)-2-(2-nitrobenzylamino)-1-phenylethanol + en. [I.8e]

This compound was synthesized according to Method D using racemic styrene oxide (4.2 mmol) and 2-nitrobenzylamine (0.70 g, 4.6 mmol). The product was purified by column chromatography (SiO$_2$; 3% methanol / chloroform) to give a pale yellow oil 0.62 g (54%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.99 (1H, d, J = 8.1 Hz), 7.61-7.26 (9H, m), 4.82 (1H, dd, J = 9.2, 3.3 Hz), 4.13 (2H, ABq, 21.2, 10.6 Hz), 2.92-2.89 (2H, m); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 149.2, 141.8, 133.7, 133.2, 132.2, 129.0, 128.6, 127.8, 125.9, 125.3, 71.4, 56.2, 50.3.

Preparation of (S)-2-(furan-2-yl)-1-phenylethanol + en. [I.8f]

This compound was synthesized according to Method D using racemic styrene oxide (4.2 mmol) and 2-nitrobenzylamine (0.45 g, 4.6 mmol). The product was purified by column chromatography (SiO$_2$; 3% methanol / chloroform) to give a pale yellow oil 0.57 g (63%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.34-7.25 (5H, m), 6.31 (1H, app s.), 6.16 (1H, app d, 3.3 Hz), 4.70 (1H, app d, J = 12.5), 3.81 (2H, app s), 2.91-2.71 (2H, m); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 153.6, 142.5, 142.0, 128.5, 127.6, 125.9, 110.3, 107.2, 72.0, 56.3, 45.8.
Preparation of \( (S) \)-2-(furan-2-yl)-2-phenylethan-1-ol + en. [1.9f]

This compound was synthesized according to Method D using racemic styrene oxide (4.2 mmol) and 2-nitrobenzylamine (0.45 g, 4.6 mmol). The product was purified by column chromatography (SiO\(_2\); 3% methanol / chloroform) to give a pale yellow oil 0.55 g (60%); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.43-7.31 (5H, m), 6.28 (1H, app s), 6.11 (1H, app s), 3.85-3.55 (3H, m), 2.90-2.69 (2H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 153.2, 142.1, 139.7, 110.3, 102.5, 66.7, 63.6, 43.6.
E.5 Preparation of 1,10-Phenanthroline and Phenanthrene Oxazoles

Preparation of Attenburrow method activated manganese dioxide

An aqueous solution of manganese (II) sulfate (42.07 g in 75 mL H₂O) and an aqueous solution of sodium hydroxide (40%, 58.5 mL) were added simultaneously over the course of one hour to a hot (70°C) stirred solution of potassium permanganate (48 g in 300 mL H₂O). It continued to stir for one hour after the solutions had been fully added. The precipitated manganese dioxide was filtered and rinsed with water until the filtrate was clear. The brown precipitate was dried in an oven at 110°C for 4 hours, ground to a powder and continued to dry overnight for an 85% yield.

General procedure for manganese dioxide oxidation

The compound was prepared by dissolving 250 mg of the amino alcohol in 25 mL of CHCl₃ and 1250 mg of the MnO₂ (Attenburrow) was added. The mixture was allowed to stir overnight and then filtered through Celite® which was rinsed with CHCl₃. The filtrate was concentrated in vacuo to give the oxidised product.

Preparation of Oxazolo[5,4-f][1,10]phenanthroline [II.2a]

The compound was synthesized from 25mg of trans-5,6-dihydro-6-(methylamino)-1,10-phenanthrolin-5-ol (all reagents scale appropriately) and purified by recrystallization in chloroform/hexane to yield a beige solid in small needle like crystals 10mg (41%); m.p. 240.1-242.0°C; Rf 0.07 (Al₂O₃, 1% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 9.24 (2H, dt, J = 4.4, 1.8 Hz), 8.88 (1H, dd, J = 8.0, 1.8 Hz), 8.63 (1H, dd, J = 8.4, 1.8 Hz), 8.38 (1H, s), 7.79-7.76 (2H, m); ¹³C NMR (100 MHz, CDCl₃): δ152.7, 150.2, 149.8, 145.1, 145.1, 143.3, 132.9, 130.8, 128.9, 123.8, 123.5, 123.0,
118.1; FT-IR (thin film from CDCl$_3$) $\nu$/cm$^{-1}$ 3376, 3057, 1659, 1599, 1484, 1430, 1391, 1342, 1299, 1261, 1085, 800, 632; Anal. Calcd for C$_{13}$H$_7$N$_3$O·0.4H$_2$O: C, 68.36; H, 3.44; N, 18.40
Found: C, 68.46; H, 3.76; N, 18.11; HRMS (ESI) calcd for C$_{13}$H$_7$N$_3$ONa $[M+Na]^+$: 244.0487, found: 244.0501.

*Preparation of 2-methyloxazolo[5,4-f][1,10]phenanthroline [II.2b]*

The compound was synthesized from *trans*-5,6-dihydro-6-(ethylamino)-1,10-phenanthrolin-5-ol and purified by recrystallization in chloroform/hexane to yield a beige solid in small needle like crystals 88mg (23%); m.p. 237.5-239.2°C; R$_f$ 0.21 (SiO$_2$, 1% methanol / chloroform); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.20 (2H, m), 8.79 (1H, dd, J = 8.0, 1.8 Hz), 8.51 (1H, dd, J = 8.0, 1.8 Hz), 7.77-7.72 (2H, m), 2.80 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 164.5, 149.6, 149.1, 143.5, 133.8, 131.2, 128.7, 123.7, 123.6, 122.9, 118.1, 14.8; FT-IR (thin film from dichloromethane) $\nu$/cm$^{-1}$ 3392, 3063, 1637, 1609, 1580, 1554, 1508, 1435, 1388, 1345, 1289, 1224, 1158, 1112, 1061, 1020, 920, 803, 742, 652, 626; Anal. Calcd for C$_{14}$H$_9$N$_3$O: C, 71.48; H, 3.86; N, 17.86
Found: C, 71.08; H, 4.23; N, 18.06; HRMS (ESI) calcd for C$_{14}$H$_9$N$_3$ONa $[M+Na]^+$: 258.0644, found: 258.0640.
Preparation of 2-propyloxazolo[5,4-f][1,10]phenanthroline [II.2c]

The compound was synthesized from *trans*-5,6-dihydro-6-(butylamino)-1,10-phenanthroline-5-ol and purified by recrystallization in chloroform/hexane to yield a white solid as small needle like crystals 149 mg (59%); m.p. 155.8-156.9 °C; R_f 0.25 (SiO_2, 1% methanol / chloroform); \(^1\)H NMR (400 MHz, CDCl_3): \(\delta\) 9.23 (2H, app dd, J = 10.2, 4.4 Hz), 8.87 (1H, dd, J = 8.1, 1.5 Hz), 8.57 (1H, dd, J = 8.1, 1.8 Hz), 7.79-7.75 (2H, m), 3.08 (2H, t, J = 7.3 Hz), 2.01 (2H, sextet, J = 7.3 Hz), 1.11 (3H, t, J = 7.3 Hz); \(^{13}\)C NMR (100 MHz, CDCl_3): \(\delta\) 168.0, 149.5, 149.0, 143.8, 143.7, 143.4, 133.7, 131.4, 128.8, 123.7, 123.6, 123.1, 118.2, 30.8, 20.8, 13.9; FT-IR (thin film from dichloromethane) \(\nu/cm^{-1}\) 3350, 2965, 2935, 2875, 1636, 1573, 1507, 1438, 1391, 1345, 1062, 1024, 799, 737, 629; Anal. Calcd for C_{16}H_{13}N_{3}O·0.3H_{2}O: C, 71.52; H, 5.10; N, 15.64 Found: C, 71.73; H, 5.50; N, 15.76; HRMS (ESI) calcd for C_{16}H_{13}N_{3}O Na [M+Na]: 286.0957, found: 286.0978.

Preparation of 2-pentyloxazolo[5,4-f][1,10]phenanthroline [II.2d]

The compound was synthesized from *trans*-5,6-dihydro-6-(hexylamino)-1,10-phenanthroline-5-ol and purified by recrystallization in chloroform/hexane to yield a white solid as small needle like crystals 88 mg (23%); m.p. 144-145 °C; R_f 0.30 (SiO_2, 1% methanol/chloroform); \(^1\)H NMR (400 MHz, CDCl_3): \(\delta\) 9.24-9.22 (2H, m), 8.86 (1H, app d, J = 8.0 Hz), 8.57 (1H, app d, J = 8.1 Hz), 7.78-7.75 (2H, m), 5.10 (1H, bs), 3.08 (2H, t, J = 7.36 Hz), 1.97 (2H, quintet, J = 2.6 Hz), 1.51-1.38 (4H, m), 0.92 (3H, t, J = 7.0 Hz); \(^{13}\)C NMR (100 MHz, CDCl_3): \(\delta\) 168.2, 149.5, 149.0, 143.9, 143.7, 143.4, 133.7, 131.3, 128.8, 123.7, 123.6, 123.1,
Preparation of 2-ethenoxazolo[5,4-f][1,10]phenanthroline [II.2e]

The compound was synthesized from trans-5,6-dihydro-6-(allylamino)-1,10-phenanthrolin-5-ol and isolated as a white solid as long needle-like crystals 50mg (18%); m.p. 167.1-170.0°C; Rf 0.49 (Al2O3, 2% methanol / dichloromethane); 1H NMR (400 MHz, CDCl3): δ 9.20 (2H, m), 8.82 (1H, dd, J = 8.1, 1.8 Hz), 8.59 (1H, dd, J = 8.0, 1.8 Hz), 7.75-7.72 (2H, m), 6.88 (1H, dd, J = 17.6, 11.0 Hz), 6.58 (1H, dd, J = 17.6, 0.7 Hz), 5.92 (1H, dd, J = 11.0, 0.8 Hz); 13C NMR (100 MHz, CDCl3): δ 162.8, 149.9, 149.8, 145.0, 144.9, 143.1, 134.6, 130.7, 128.8, 125.0, 123.7, 123.5, 123.4, 122.9, 118.0; FT-IR (thin film from dichloromethane) v/cm⁻¹ 3377, 3055, 29220, 2856, 1504, 1439, 1391, 1064, 808, 767, 739; Anal. Calcd for C15H9N3O·0.6H2O: C, 69.81; H, 3.98; N, 16.28 Found: C, 69.96; H, 3.97; N, 16.42; HRMS (ESI) calcd for C15H9N3ONa [M+Na]+: 270.0644, found: 270.0638.
Preparation of 2-(pyridin-2-yl)oxazolo[5,4-f][1,10]phenanthroline [II.2f]

The compound was synthesized from trans-5,6-dihydro-6-(2-picolylamino)-1,10-phenanthroin-5-ol (reagents scaled for 168mg of aminoalcohol) and purified by recrystallization in dichloromethane/hexane to yield a grey solid as needle-like crystals 112mg (68%); m.p. 267-268°C; Rf 0.52 (Al2O3, 3% methanol / chloroform); 1H NMR (400 MHz, CDCl3): δ 9.22 (2H, d, J = 2.9 Hz), 8.98 (1H, d, J = 7.0 Hz), 8.87 (1H, d, J = 4.4 Hz), 8.77 (1H, d, J = 7.3 Hz), 8.42 (1H, d, J = 8.1 Hz), 7.94 (1H, t, J = 7.3 Hz), 7.75 (2H, dt, J = 7.7, 3.3 Hz), 7.48 (1H, app t, J = 7.0 Hz); 13C NMR (100 MHz, CDCl3): δ 162.2, 150.6, 150.2, 150.0, 145.9, 145.3, 145.2, 144.2, 137.4, 134.9, 131.0, 129.1, 125.7, 123.8, 123.5, 123.4, 123.1, 118.1; FT-IR (KBr, pellet) ν/cm⁻¹ 3384, 3056, 2972, 1653, 1586, 1559, 1507, 1445, 1393, 1063, 933, 802, 737, 703, 619. This compound was previously synthesized by Eseola et al. in a 9% yield using a Japp oxazole synthesis reacting phenanthroline-5,6-dione with 2-pyridinecarboxaldehyde and ammonium acetate in dichloromethane. (Eseola, A.O.; Li, W.; Sun, W.-H.; Zhang, M.; Xiao, L.; Woods, J.A.O. Dyes and Pigments 2011, 88, 262-273.)

Preparation of 2-cyclohexyloxazolo[5,4-f][1,10]phenanthroline [II.2g]

The compound was synthesized from trans-5,6-dihydro-6-(cyclohexanemethylamino)-1,10-phenanthroin-5-ol and isolated as a white solid in rosette like crystals 244mg (100%); m.p. 166.2-167.1°C; Rf 0.68 (SiO2, 3% methanol / chloroform); 1H NMR (400 MHz, CDCl3): δ 9.19-9.14 (2H, m), 8.82 (1H, app dd, J = 8.0, 1.4 Hz), 8.54 (1H, app dd, J = 8.0, 1.8 Hz), 7.73-7.68 (2H, m), 3.14-3.07 (1H, m), 2.24 (2H, app d, J = 12.5 Hz), 1.90 (2H, app dt, J = 12.8, 3.4 Hz), 1.84-
1.74 (3H, m), 1.51-1.34 (3H, m); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.1, 149.4, 149.2, 144.4, 144.3, 143.0, 133.6, 130.9, 128.6, 123.5, 123.3, 123.1, 118.2, 38.4, 30.9, 25.8, 25.7; FT-IR (thin film from dichloromethane) ν/cm$^{-1}$ 3357, 3037, 2930, 2853, 2668, 1640, 1610, 1567, 1504, 1436, 1390, 1343, 1296, 1156, 1123, 1060, 1021, 939, 892, 803, 740, 698, 633; Anal. Calcd for C$_{19}$H$_{17}$N$_3$O: C, 75.23; H, 5.65; N, 13.85 Found: C, 75.06; H, 6.00; N, 14.02; HRMS (ESI) calcd for C$_{19}$H$_{17}$N$_3$O [M+Na$^+$]: 326.1270, found: 326.1294.

**Preparation of 2-benzylazolo[5,4-f][1,10]phenanthroline [II.2h]**

The compound was synthesized from trans-5,6-dihydro-6-(phenethylamino)-1,10-phenanthroline-5-ol and purified by column chromatography (SiO$_2$, 1% methanol/chloroform) and isolated as a white powder 242mg (62%); m.p. 168.5-170.2°C; R$_f$ 0.58 (SiO$_2$, 3% methanol / chloroform); $^1$H NMR (400 MHz, CDCl$_3$): δ 9.21-9.18 (2H, m), 8.84 (1H, dd, J = 8.4, 1.8 Hz), 8.54 (1H, dd, J = 8.1, 1.5 Hz), 7.73 (1H, dd, J = 8.0, 4.4 Hz), 7.69 (1H, dd, J = 8.0, 4.4 Hz), 7.45 (2H, app d, J = 7.3 Hz), 7.38 (2H, t, J = 7.0 Hz), 7.32 (1H, d, J = 7.3 Hz), 4.45 (2H, s), 1.61 (2H, bs); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 165.6, 149.7, 149.5, 144.8, 144.7, 143.8, 134.8, 133.7, 130.7, 129.0, 128.7, 127.5, 123.6, 123.3, 117.9, 35.4; FT-IR (thin film from CDCl$_3$) ν/cm$^{-1}$ 3063, 3031, 1676, 1611, 1572, 1550, 1504, 1455, 1436, 1426, 1390, 1345, 1324, 1296, 1123, 1109, 1060, 1021, 937, 803, 698, 651, 628; HRMS (ESI) calcd for C$_{20}$H$_{13}$N$_3$ONa [M+Na$^+$]: 334.0957, found: 334.0980.
Preparation of 2-phenyloxazolo[5,4-f][1,10]phenanthroline [II.2i]

The compound was synthesized from trans-5,6-dihydro-6-(benzylamino)-1,10-phenanthroin-5-ol and isolated as a white powder: 49 mg (100%); \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.25-9.22 (2H, m), 8.95 (1H, app dd, \(J = 8.0\), 1.8 Hz), 8.69 (1H, app dd, \(J = 8.0\), 1.8 Hz), 8.39-8.35 (2H, m), 7.79-7.75 (2H, m), 7.56-7.62 (3H, m); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 163.8, 149.7, 145.0, 144.8, 143.4, 134.9, 131.6, 130.9, 129.2, 128.7, 127.4, 127.1, 123.6, 123.4, 123.0, 118.1; FT-IR (KBr, pellet) \(\nu/\text{cm}^{-1}\) 3423, 3056, 3029, 2964, 2934, 2876, 1640, 1586, 1560, 1502, 1488, 1452, 1436, 1392, 1345, 1319, 1288, 1172, 1064, 1023, 927, 800, 778, 741, 727, 706, 692; HRMS (EI, \(m/z\)) calcd for C\(_{19}\)H\(_{11}\)N\(_3\)O (M\(^+\)) 297.0902, found 297.0894.

Preparation of 2-(3-methoxyphenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2j]

The compound was synthesized from trans-5,6-dihydro-6-(3-methoxybenzylamino)-1,10-phenanthroin-5-ol (scaled to 220mg of aminoalcohol) and purified by recrystallization in chloroform/hexane to yield a white solid as small needle-like crystals 170mg (79%); m.p. 224-225°C; \(R_f\) 0.53 (Al\(_2\)O\(_3\), 3% methanol / chloroform); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.19 (2H, app p, \(J = 2.2\) Hz), 8.86 (1H, dd, \(J = 8.0\), 1.4 Hz), 8.59 (1H, dd, \(J = 8.0\), 1.4 Hz), 7.89 (1H, app d, \(J = 7.7\) Hz), 7.81 (1H, app s), 7.71 (2H, dt, \(J = 8.0\), 3.3 Hz), 7.45 (1H, t, \(J = 8.0\) Hz), 7.08 (1H, dd, \(J = 8.4\), 2.6 Hz), 3.94 (3H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 163.6, 160.1, 149.7, 145.0, 144.8, 143.3, 134.9, 130.8, 130.2, 128.6, 128.2, 123.6, 123.4, 123.0, 119.8, 118.0, 117.9, 112.0, 55.6; FT-IR (thin film from CDCl\(_3\)) \(\nu/\text{cm}^{-1}\) 3042, 3005, 2962, 2839, 1609, 1586, 1560, 1544, 1503, 1488, 1454, 1433, 1405, 1390, 1340, 1315, 1286, 1269, 1227, 1209, 1169, 1127, 1079, 1060, 1035,
966, 930, 883, 845, 801, 787, 740, 722, 696, 678; Anal. Calcd for C$_{20}$H$_{13}$N$_3$O$_2$·0.5H$_2$O: C, 71.42; H, 4.20; N, 12.49 Found: C, 71.10; H, 4.56; N, 12.50; HRMS (ESI) calcd for C$_{20}$H$_{13}$N$_3$O$_2$Na [M+Na$^+$]: 350.0906, found: 350.0868.

**Preparation of 2-(4-methoxyphenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2k]**

The compound was synthesized from trans-5,6-dihydro-6-(4-methoxybenzylamino)-1,10-phenanthrolin-5-ol and isolated as a white powder: 49 mg (100%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.10 (1H, app dd, J = 4.4, 1.8 Hz), 9.09 (1H, app dd, J = 4.4, 1.8 Hz), 8.70 (1H, app dd, J = 8.1, 1.8 Hz), 8.39 (1H, app dd, J = 8.2, 1.6 Hz), 8.06-8.10 (2H, m), 7.60 (1H, app dd, J = 7.9, 4.4 Hz), 7.58 (1H, app dd, J = 8.1, 4.4 Hz), 6.92-6.96 (2H, m), 3.84 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 163.7, 162.2, 149.4, 149.3, 144.7, 144.4, 142.8, 134.7, 130.6, 129.0, 128.3, 123.3, 122.8, 119.5, 117.8, 114.4, 55.5; FT-IR (KBr, pellet) $\nu$/cm$^{-1}$ 3419, 3059, 3017, 2972, 2929, 2840, 1611, 1588, 1498, 1459, 1437, 1391, 1322, 1308, 1262, 1176, 1113, 1081, 1064, 1024, 924, 835, 806, 742, 700, 623; HRMS (EI, m/z) calcd for C$_{20}$H$_{13}$N$_3$O$_2$ (M$^+$) 327.1008, found 327.1009.

**Preparation of 2-(3-chlorophenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2l]**

The compound was synthesized from trans-5,6-dihydro-6-(3-chlorobenzylamino)-1,10-phenanthrolin-5-ol and purified by recrystallization in chloroform/hexane to yield a white solid as small needle like crystals 314mg (80%); m.p. 233-236°C; R$_f$ 0.42 (Al$_2$O$_3$, 1% methanol / chloroform); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.19 (2H, dd, J = 4.0, 1.5 Hz), 8.82 (1H, dd, J = 8.1, 1.8
Hz), 8.57 (1H, dd, J = 8.0, 1.8 Hz), 8.27 (1H, app t, J = 1.1 Hz), 8.16 (1H, dt, J = 7.3, 1.5 Hz), 7.71 (2H, quintet, J = 4.0 Hz), 7.53-7.46 (2H, m), 1.80 (1H, bs); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 162.3, 149.9, 149.8, 144.9, 143.5, 135.3, 134.8, 131.5, 130.8, 128.7, 128.6, 127.3, 125.4, 123.7, 123.5, 122.9, 117.9; FT-IR (thin film from dichloromethane) ν/cm$^{-1}$ 3408, 3050, 2978, 1639, 1557, 1504, 1474, 1439, 1391, 1294, 1126, 1062, 932, 885, 802, 723, 715, 674; Anal. Calcd for C$_{19}$H$_{10}$ClN$_3$O·0.2H$_2$O: C, 68.05; H, 3.13; N, 12.53 Found: C, 68.33; H, 3.50; N, 12.73; HRMS (ESI) calcd for C$_{19}$ClH$_{10}$N$_3$ONa [M+Na$^+$]: 354.0410, found: 354.0410

**Preparation of 2-(3-fluorophenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2m]**

The compound was synthesized from *trans*-5,6-dihydro-6-(3-fluorobenzylamino)-1,10-phenanthroline-5-ol and purified by recrystallization in chloroform/hexane to yield a white powdery solid 237mg (60%); m.p. 236.2-238.1°C; R$_f$ 0.42 (Al$_2$O$_3$, 1% methanol / chloroform); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.20 (2H, dd, J = 4.0, 1.5 Hz), 8.86 (1H, dd, J = 8.4, 1.8 Hz), 8.60 (1H, dd, J = 8.4, 1.8 Hz), 8.10 (1H, app d, J = 7.7 Hz), 8.02-7.99 (1H, m), 7.73 (2H, quintet, J = 4.4 Hz), 7.56-7.51 (1H, m), 7.28-7.23 (1H, m), 1.76 (0.5H, bs); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 164.3, 162.4, 161.9, 149.9, 149.9, 145.0, 153.5, 134.8, 130.8, 129.0, 128.7, 123.7, 123.4, 123.0, 123.0, 118.7, 118.5, 118.0, 114.4, 114.2; FT-IR (thin film from dichloromethane) ν/cm$^{-1}$ 3358, 3054, 2977, 1596, 1566, 1484, 1453, 1391, 1272, 1194, 1048, 871, 801, 738, 675; Anal. Calcd for C$_{19}$H$_{10}$FN$_3$O·1.3H$_2$O: C, 67.37; H, 3.75; N, 12.41 Found: C, 67.23; H, 3.52; N, 12.52; HRMS (ESI) calcd for C$_{19}$FH$_{10}$N$_3$ONa [M+Na$^+$]: 338.0706, found: 338.0732.
Preparation of 2-(4-fluorophenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2n]

The compound was synthesized from trans-5,6-dihydro-6-(4-fluorobenzylamino)-1,10-phenanthroline-5-ol and purified by recrystallization in chloroform/hexane to yield a white solid as needle-like crystals 305 mg (78%); m.p. 278.2-279.6°C; Rf 0.42 (Al2O3, 1% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 9.27 (2H, dd, J = 11.0, 4.4 Hz), 8.97 (1H, dd, J = 8.1, 1.8 Hz), 8.69 (1H, dd, J = 8.0, 1.4 Hz), 8.37 (2H, app dd, J = 8.8, 5.1 Hz), 7.84-7.78 (2H, m), 7.30-7.26 (2H, m), 2.07 (2H, bs); ¹³C NMR (100 MHz, CDCl₃): δ 166.1, 162.9, 149.7, 149.6, 143.4, 134.8, 130.9, 129.6, 129.6, 128.6, 123.6, 123.4, 122.9, 118.0, 116.6, 116.3; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 3382, 3049, 2982, 1665, 1602, 1491, 1435, 1390, 1310, 1267, 1219, 1162, 1063, 1010, 840, 801, 764, 738, 693, 620, 544; Anal. Calcd for C₁₉H₁₀F₃N₃O·0.2H₂O: C, 71.56; H, 3.29; N, 13.18; Found: C, 71.96; H, 3.67; N, 13.29; HRMS (ESI) calcd for C₁₉F₁₁N₃O [M+H]+: 316.0886, found: 338.0857.

Preparation of 2-(3-trifluorophenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2o]

The compound was synthesized from trans-5,6-dihydro-6-(3-trifluoromethylbenzylamino)-1,10-phenanthroline-5-ol (reagents adjusted for a 200mg scale) and purified by recrystallization in chloroform/hexane to yield a white powdery solid in quantitative yield; m.p. 213-216°C; Rf 0.40 (Al₂O₃, 1% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 9.21 (2H, d, J = 3.6 Hz), 8.85 (1H, d, J = 7.7 Hz), 8.61 (1H, d, J = 8.0 Hz), 8.56 (1H, s), 8.48 (1H, d, J = 7.7 Hz), 7.81 (1H, app d, J = 7.7 Hz), 7.74-7.40 (3H, m); ¹³C NMR (100 MHz, CDCl₃): δ 162.2, 150.1, 149.9, 144.8, 143.8, 134.7, 132.1, 131.0, 130.4, 129.8, 128.9, 128.0, 127.9, 124.2, 123.8, 123.6, 122.9,
118.0; FT-IR (thin film from dichloromethane) ν/cm⁻¹: 3403, 3058, 2975, 1652, 1558, 1506, 1436, 1394, 1335, 1291, 1255, 1166, 1118, 1076, 1062, 905, 807, 138, 691. Anal. Calcd for C₂₀H₁₀F₃N₃O·1.4H₂O·0.75CHCl₃: C, 51.92; H, 2.84; N, 8.75 Found: C, 51.84; H, 2.77; N, 8.83; HRMS (ESI) calcd for C₂₀F₃H₁₀N₃O₄Na [M+Na⁺]: 388.0674, found: 388.0656.

Preparation of 2-naphthylazol[5,4-f][1,10]phenanthroline [II.2p]

The compound was synthesized from trans-5,6-dihydro-6-(naphthylmethylamino)-1,10-phenanthroline-5-ol (reagents scaled for 400 mg of aminoalcohol), filtered after 48 hours and purified by recrystalization in chloroform/hexane to yield a white powder 380mg (96%); m.p. 231-232°C; Rf 0.28 (Al₂O₃, 1% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 9.58 (1H, d, J = 8.4 Hz), 9.22 (2H, app s), 8.97 (1H, app d, J = 8.8 Hz), 8.64 (1H, app d, J = 8.1 Hz), 8.49 (1H, app d, J = 7.0 Hz), 8.03 (1H, d, J = 8.1 Hz), 7.94 (1H, d, J = 8.1 Hz), 7.74 (3H, app s), 9.64-9.59 (2H, m); ¹³C NMR (100 MHz, CDCl₃): δ 163.0, 149.5, 149.4, 144.7, 142.4, 134.6, 133.9, 132.3, 130.7, 130.2, 128.8, 128.7, 128.6, 128.3, 128.0, 126.5, 126.3, 125.4, 124.9, 123.4, 123.2, 122.8, 117.7; FT-IR (KBr pellet) ν/cm⁻¹: 3356, 3052, 1646, 1549, 1506, 1394, 1065, 800, 769, 738; Anal. Calcd for C₂₃H₁₃N₃O·0.5H₂O: C, 77.52; H, 3.96; N, 11.79 Found: C, 77.86; H, 4.33; N, 11.83; HRMS (ESI) calcd for C₂₃H₁₃N₃O₄Na [M+Na⁺]: 370.0957, found: 370.0974.
Preparation of 2-(2-methoxyphenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2q]

The compound was synthesized from trans-5,6-dihydro-6-(2-methoxybenzylamino)-1,10-phenanthrolin-5-ol and isolated as a white powder: 49 mg (100%); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 9.21-9.23\) (2H, m), 8.98 (1H, app dd, \(J = 8.0, 1.8\) Hz), 8.68 (1H, app dd, \(J = 8.1, 1.5\) Hz), 8.25 (1H, app dd, \(J = 7.7, 1.5\) Hz), 7.73-7.78 (2H, m), 7.52-7.57 (1H, m), 7.12-7.19 (2H, m), 4.07 (3H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 162.5, 158.3, 149.6, 149.5, 144.9, 144.8, 143.2, 134.7, 133.0, 131.2, 131.0, 128.8, 123.5, 123.3, 123.1, 121.0, 118.1, 116.2, 112.3, 56.3; FT-IR (KBr, pellet) \(\nu/cm^{-1}\) 3398, 3050, 2969, 2839, 1604, 1588, 1559, 1533, 1495, 1477, 1437, 1390, 1347, 1312, 1282, 1261, 1168, 1124, 1063, 1019, 968, 802, 739, 722, 700; HRMS (EI, \(m/z\)) calcd for C\(_{20}\)H\(_{13}\)N\(_3\)O\(_2\) (M\(^+\)) 327.1008, found 327.0999.

Preparation of 2-(2,4-dimethoxyphenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2r]

The compound was synthesized from trans-5,6-dihydro-6-(2,4-dimethoxybenzylamino)-1,10-phenanthrolin-5-ol and isolated as a yellow powder: 49 mg (100%); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 9.19-9.24\) (2H, m), 8.98 (1H, app dd, \(J = 8.2, 1.6\) Hz), 8.67 (1H, app dd, \(J = 8.3, 1.7\) Hz), 8.22 (1H, d, \(J = 8.8\) Hz), 7.72-7.79 (2H, m), 6.70 (1H, app dd, \(J = 8.8, 2.2\) Hz), 6.65 (1H, d, \(J = 2.2\) Hz), 4.06 (3H, s), 3.93 (3H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 163.7, 162.7, 159.8, 149.4, 149.4, 144.9, 144.6, 142.8, 134.8, 132.4, 131.0, 128.7, 123.4, 123.3, 123.1, 118.1, 109.2, 105.7, 99.3, 56.3, 55.7; FT-IR (KBr, pellet) \(\nu/cm^{-1}\) 3421, 3048, 3013, 2966, 2938, 2837, 1615, 1584, 1501, 1486, 1466, 1435, 1390, 1330, 1297, 1282, 1269, 1213, 1171, 1128, 1081, 1064, 814, 741; HRMS (EI, \(m/z\)) calcd for C\(_{21}\)H\(_{15}\)N\(_3\)O\(_3\) (M\(^+\)) 357.1113, found 357.1110.
Preparation of 2-(2,4,6-trimethoxyphenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2s]

The compound was synthesized from trans-5,6-dihydro-6-(2,4,6-trimethoxybenzylamino)-1,10-phenanthroin-5-ol (reagents scaled for 150mg of aminoalcohol) and purified by recrystallization in chloroform/hexane to yield a white-green solid as fine powder; 34mg (23%); m.p. 294-296° C; R_f 0.65 (Al_2O_3, 3% methanol / chloroform); ^1H NMR (400 MHz, CDCl_3): δ 9.21 (2H, app dd, J = 4.4, 1.5 Hz), 8.97 (1H, dd, J = 8.4, 1.5 Hz), 8.64 (1H, dd, J = 8.1, 1.8 Hz), 7.74 (2H, m), 6.24 (2H, s), 3.91 (3H, s), 3.81 (6H, s); ^13C NMR (100 MHz, CDCl_3): δ 164.0, 161.1, 149.6, 149.4, 131.0, 129.0, 123.5, 123.2, 90.7, 56.1, 55.7; FT-IR (thin film from CDCl_3) v/cm\(^{-1}\): 3060, 3006, 2955, 2940, 2841, 1673, 1618, 1587, 1485, 1469, 1435, 1416, 1391, 1341, 1228, 1206, 1158, 1132, 1061, 1025, 909, 809, 645; Analysis cald for C_{22}H_{17}N_{3}O_{4}·0.75H_2O: C, 65.91%; H, 4.65%; N, 10.48% Found: C, 66.05%; H, 4.72%; N, 10.56%; HRMS (ESI) cald for C_{22}H_{17}N_{3}O_{4}Na [M+Na]^+: 410.1117, found: 410.1119.

Preparation of 2-(2-nitrophenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2t]

The compound was synthesized from trans-5,6-dihydro-6-(2-nitrobenzylamino)-1,10-phenanthroin-5-ol and purified by recrystallization in chloroform/hexane to yield a yellow solid as small square crystals 214mg (99%); m.p. 289.1-290.4° C; R_f 0.61 (SiO_2, 1% methanol / chloroform); ^1H NMR (400 MHz, CDCl_3): δ 9.19 (2H, app dd, J = 4.4, 1.8 Hz), 8.85 (1H, dd, J = 8.0, 1.8 Hz), 8.55 (1H, dd, J = 8.0, 1.8 Hz), 8.23 (1H, dd, J = 7.3, 1.4 Hz), 7.93 (1H, dd, J = 8.0, 1.1 Hz), 7.80-7.70 (4H, m); ^13C NMR (100 MHz, CDCl_3): δ 159.2, 150.3, 150.0, 149.1, 145.2, 145.1, 144.2, 132.6, 132.1, 131.4, 130.9, 129.0, 124.4, 123.8, 123.6, 122.8, 117.8; FT-IR (thin film
from CDCl₃ v/cm⁻¹  3068, 1725, 1692, 1619, 1538, 1450, 1370, 1174, 1110, 1062, 1015, 897, 853, 805, 758, 635, 439; Anal. Calcd for C₁₉H₁₀N₄O₃·0.15H₂O: C, 66.14; H, 3.01; N, 16.24; Found: C, 66.35; H, 3.37; N, 16.44; HRMS (ESI) calcd for C₁₉H₁₀N₄O₃Na [M+Na⁺]: 365.0651, found: 365.0620.

Preparation of 2-(3-nitrophenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2u]

The compound was synthesized from trans-5,6-dihydro-6-(3-nitrobenzylamino)-1,10-phenanthrolin-5-ol and purified by recrystallization in chloroform/hexane to yield a pink solid as small needle-like crystals 220mg (89%); m.p. 299.5-300.8°C; Rf 0.61 (SiO₂, 1% methanol / chloroform);¹H NMR (400 MHz, CDCl₃): δ 9.21 (2H, app t, J = 2.2 Hz), 8.86 (1H, app d, J = 8.0 Hz), 8.55 (1H, app d, J = 8.0 Hz), 8.23 (1H, app d, J = 7.4 Hz), 7.92 (1H, app d, J = 8.0 Hz), 7.79-7.69 (4H, m), 2.03 (0.5 H, m);¹³C NMR (100 MHz, CDCl₃): δ 159.2, 150.3, 150.0, 149.0, 145.1, 145.0, 144.2, 134.6, 132.6, 132.1, 131.4, 131.0, 129.0, 124.4, 123.8, 123.6, 122.8, 121.0, 117.8; FT-IR (thin film from CDCl₃) v/cm⁻¹  3060, 1528, 1503, 1415, 1391, 1348, 1259, 1168, 1100, 1060, 1020, 935, 872, 805, 706; Anal. Calcd for C₁₉H₁₀N₄O₃·0.3H₂O: C, 65.63; H, 3.07; N, 16.11; Found: C, 65.62; H, 3.17; N, 16.20; HRMS (ESI) calcd for C₁₉H₁₀N₄O₃Na [M+Na⁺]: 365.0651, found: 365.0641.
Preparation of 2-(4-nitrophenyl)oxazolo[5,4-f][1,10]phenanthroline [II.2v]

The compound was synthesized from trans-5,6-dihydro-6-(4-nitrobenzylamino)-1,10-phenanthrolin-5-ol and purified by recrystallization in chloroform/hexane to yield a yellow solid as small square crystals 150mg (58%); m.p. >305°C; Rf 0.50 (Al2O3, 3% methanol / dichloromethane); 1H NMR (400 MHz, CDCl3): δ 9.25 (2H, app s), 8.92 (1H, d, J = 8.0 Hz), 8.69 (1H, d, J = 8.0 Hz), 8.55 (2H, app d, J = 7.7 Hz), 8.45 (2H, app d, J = 7.7 Hz), 8.28 (1H, app d, J = 8.0 Hz), 7.99 (1H, app d, J = 8.0 Hz), 7.81-7.78 (2H, m); 13C NMR (100 MHz, CDCl3): δ 161.4, 150.4, 150.2, 149.4, 145.4, 145.2, 144.3, 135.2, 132.5, 130.9, 128.9, 128.6, 128.1, 124.5, 124.0, 123.9, 123.7, 122.9, 117.9; FT-IR (KBr pellet) ν/cm⁻¹ 3376, 3104, 1666, 1603, 1519, 1441, 1394, 1344, 1105, 1067, 859, 805, 708; Anal. Calcd for C19H10N4O3·0.15CHCl3: C, 63.85; H, 2.84; N, 15.55 Found: C, 63.90; H, 2.75; N, 15.81; HRMS (ESI) calcd for C19H10N4O3Na [M+Na]+: 365.0651, found: 365.0641.

Preparation of tert-butyl oxazolo[5,4-f][1,10]phenanthroline-2-carboxylate [II.2w]

The compound was synthesized from tert-butyl 2-(6-hydroxy-5,6-dihydro-1,10-phenanthrolin-5-ylamino)acetate (reagents scaled for 50mg of aminoalcohol) and purified by recrystallization in dichloromethane/hexane to yield an orange solid as needle-like crystals: 35 mg (70%); 1H NMR (400 MHz, CDCl3): δ 9.28 (1H, app dd, J = 4.4, 1.8 Hz), 9.25 (1H, app dd, J = 4.6, 1.6 Hz), 8.96 (1H, app dd, J = 8.1, 1.8 Hz), 8.74 (1H, app dd, J = 8.2, 1.6 Hz), 7.78 (2H, app dd, J = 8.1, 4.4 Hz), 1.74 (9H, s); 13C NMR (100 MHz, CDCl3): δ 155.0, 154.3, 151.0, 150.3, 146.1, 145.3, 144.7, 134.1, 131.2, 129.6, 124.0, 123.7, 122.9, 117.8, 85.6, 28.2; FT-IR (KBr, pellet) ν/cm⁻¹ 3395,
Preparation of 2-propylphenanthro[9,10-d]oxazole [II.4a]

The compound was synthesized from trans-9,10-dihydro-10-(butylamino)phenanthren-9-ol and purified by recrystallization in chloroform/hexane to yield a white waxy solid 20 mg (50%); m.p. R_f 0.93 (Al_2O_3, 1% methanol / chloroform); ^1H NMR (400 MHz, CDCl_3): δ 8.72 (2H, app t, J = 8.0), 8.51 (1H, dd, J = 8.4, 1.5), 8.22 (1H, d, J = 7.7), 7.73-7.62 (4H, m), 3.07 (2H, t, J = 7.3), 2.01 (2H, sextet, J = 7.7), 1.11 (3H, t, J = 7.3); ^13C NMR (100 MHz, CDCl_3): δ 166.2, 144.8, 134.4, 129.0, 128.8, 127.4, 126.2, 126.2, 125.9, 123.8, 122.8, 121.2, 120.7, 30.9, 21.0, 13.9; FT-IR (thin film from dichloromethane) ν/cm^-1 3300, 3063, 2963, 2872, 1693, 1580, 1452, 1344, 1234, 1053, 1034, 754, 725.


Preparation of 2-vinylphenanthro[9,10-d]oxazole [II.4b]

The compound was synthesized from trans-9,10-dihydro-10-(allylamino)phenanthren-9-ol and purified by recrystallization in chloroform/hexane to yield a white prism crystals 130 mg (65%); m.p. 93-96°C R_f 0.69 (Al_2O_3, 1% methanol / chloroform); ^1H NMR (400 MHz, CDCl_3): δ 8.70 (2H, t, J = 7.7), 8.51 (1H, d, J = 7.7), 8.25 (1H, d, J = 6.9), 7.72-7.67 (4H, m), 6.88 (1H, dd, J = 17.6, 11.4), 6.53 (1H, d, J = 17.6), 5.85 (1H, d, J = 11.0); ^13C NMR (100 MHz, CDCl_3): δ 161.4,
144.7, 129.6, 129.0, 127.6, 127.4, 126.7, 126.3, 126.1, 123.9, 123.8, 123.7, 123.5, 122.9, 121.1, 121.0; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 3418, 3062, 3029, 2923, 1618, 1526, 1452, 1430, 1347, 1234, 1054, 1034, 966, 936, 750, 722, 672. Previously synthesized by Katritzky. Katritzky, A.R. *J. Org. Chem.* **2003**, *68*, 9093-9099.

*Preparation of 2-phenylphenanthro[9,10-d]oxazole [II.4c]*

The compound was synthesized from trans-9,10-dihydro-10-(benzylamino)phenanthren-9-ol and purified by recrystallization in chloroform/hexane to yield a white prism crystals 205 mg (99%); m.p. 135-139°C Rf 0.74 (Al₂O₃, 1% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.70 (2H, t, J = 7.7), 8.61 (1H, d, J = 7.7), 8.36 (2H, d, J = 8.1), 8.30 (1H, d, J = 7.7), 7.76-7.65 (4H, m), 7.57-7.53 (3H, m); ¹³C NMR (100 MHz, CDCl₃): δ 162.2, 144.9, 135.6, 131.0, 129.4, 129.0, 127.7, 127.5, 127.3, 126.3, 126.2, 123.9, 123.5, 123.0, 121.1, 120.9; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 3064, 1548, 1479, 1450, 1346, 1315, 1235, 1164, 1124, 1058, 1034, 965, 928, 775, 709, 693. Previously synthesized by Pfundt. Pfundt, G. *Tetrahedron Lett.* **1965**, *28*, 2411-2415.
Preparation of 2-(4-methoxyphenyl)phenanthro[9,10-d]oxazole [II.4d]

The compound was synthesized from trans-9,10-dihydro-10-(4-methoxybenzylamino)phenanthren-9-ol and purified by recrystallization in chloroform/hexane to yield a white needle-like crystals 245 mg (99%); m.p. 206-210°C Rf 0.56 (Al₂O₃, 1% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.72 (2H, t, J = 7.7), 8.60 (1H, d, J = 7.7), 8.30 (3H, app d, J = 9.2), 7.77-7.62 (4H, m), 7.05 (2H, d, J = 9.2), 3.90 (3H, s); ¹³C NMR (100 MHz, CDCl₃): δ 162.4, 161.9, 144.6, 135.6, 129.4, 129.1, 129.0, 128.9, 127.4, 127.3, 126.3, 126.2, 126.1, 123.8, 123.0, 121.2, 120.8, 120.3, 114.4, 113.9, 55.5; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 3066, 2945, 2838, 1609, 1540, 1459, 1424, 1316, 1304, 1250, 1172, 1032, 835, 754, 736, 721, 690. Previously synthesized by Schonberg. Schonberg, A. J. Chem. Soc. 1950, 374-379

Preparation of 2-(4-fluorophenyl)phenanthro[9,10-d]oxazole [II.4e]

The compound was synthesized from trans-9,10-dihydro-10-(4-fluorobenzylamino)phenanthren-9-ol and purified by recrystallization in chloroform/hexane to yield a white needle-like crystals 244 mg (99%); m.p. >280°C Rf 0.57 (Al₂O₃, 1% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.73 (2H, t, J = 8.8), 8.60 (1H, d, J = 8.1), 8.38-8.30 (3H, m), 7.76-7.68 (4H, m), 7.27-7.22 (2H, m); ¹³C NMR (100 MHz, CDCl₃): δ 165.7, 163.2, 161.4, 150.2, 145.0, 135.5, 129.5, 129.0, 127.6, 127.4, 126.5, 126.3, 126.2, 123.9, 123.5, 123.0, 121.1, 120.9, 116.4, 116.2; FT-IR (thin film from dichloromethane) ν/cm⁻¹ 3056, 1604, 1494, 1450, 1217, 1154, 1060, 841, 754, 732, 699. Previously synthesized by Doroshenko et al.
Preparation of 6,9-dimethyl-2-propyloxazolo[4,5-f][1,10]phenanthroline [III.10a]

The compound was synthesized from 6-(butylamino)-5,6-dihydro-2,9-dimethyl-1,10-phenanthroline-5,6-ol and purified by recrystallization in chloroform/hexane to yield a white waxy solid 15 mg (59%); Rf 0.93 (Al₂O₃, 1% methanol / chloroform); ¹H NMR (400 MHz, CDCl₃): δ 8.72 (2H, app t, J = 8.0), 8.51 (1H, dd, J = 8.4, 1.5), 8.22 (1H, d, J = 7.7), 7.73-7.62 (4H, m), 3.07 (2H, t, J = 7.7), 2.01 (2H, sextet, J = 7.7), 1.11 (3H, t, J = 7.3); ¹³C NMR (100 MHz, CDCl₃): δ 166.2, 144.8, 134.4, 129.0, 128.8, 127.4, 126.2, 126.2, 125.9, 123.8, 122.8, 121.2, 120.7, 30.9, 21.0, 13.9.

Preparation of 6,9-dimethyl-2-vinlyoxazolo[4,5-f][1,10]phenanthroline [III.10b]

The compound was synthesized from 6-(allylamo)-5,6-dihydro-2,9-dimethyl-1,10-phenanthroline-5,6-ol and purified by recrystallization in chloroform/hexane to yield a white solid 9 mg (43%); ¹H NMR (400 MHz, CDCl₃): δ 8.73 (1H, d, J = 8.4 Hz), 8.51 (1H, d, J = 8.1 Hz), 7.61 (2H, app dd, J = 8.1, 6.6 Hz), 6.87 (2H, dd, J = 17.6, 11.0 Hz), 6.56 (1H, d, J = 17.6 Hz), 5.89 (1H, d, J = 11.4 Hz), 2.97 (3H, s), 2.96 (3H, s).
Preparation of 6,9-dimethyl-2-phenyloxazolo[4,5-f][1,10]phenanthroline [III.10c]

The compound was synthesized from 6-(phenylamino)-5,6-dihydro-2,9-dimethyl-1,10-phenanthrolin-5,6-ol and purified by recrystallization in chloroform/hexane to yield a white solid 26 mg (85%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.83 (1H, d, J = 8.4 Hz), 8.56 (1H, d, J = 8.1 Hz), 8.36-8.34 (2H, m), 7.64 (1H, d, J = 8.4 Hz), 7.62 (1H, d, J = 8.1 Hz), 7.58-7.56 (3H, m), 2.97 (3H, s), 2.96 (3H, s).

Preparation of 6,9-dimethyl-2-(4-methoxyphenyl)oxazolo[4,5-f][1,10]phenanthroline [III.10d]

The compound was synthesized from 6-(4-methoxyphenylamino)-5,6-dihydro-2,9-dimethyl-1,10-phenanthrolin-5,6-ol and purified by recrystallization in chloroform/hexane to yield a white solid 7 mg (31%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.82 (1H, d, J = 8.4 Hz), 8.56 (1H, d, J = 8.1 Hz), 8.29 (2H, d, J = 8.8 Hz), 7.64-7.61 (2H, m), 7.08 (2H, d, J = 8.8 Hz), 3.92 (3H, s), 2.98 (3H, s), 2.97 (3H, s).

Preparation of 6,9-dimethyl-2-(furan-2-yl)oxazolo[4,5-f][1,10]phenanthroline [III.10f]

The compound was synthesized from 6-(furan-2-ylmethylamino)-5,6-dihydro-2,9-dimethyl-1,10-phenanthrolin-5,6-ol and purified by recrystallization in chloroform/hexane to yield a white solid 16 mg (81%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.83 (1H, d, J = 8.1 Hz),
8.54 (1H, d, J = 8.4 Hz), 7.71 (1H, d, J = 1.8 Hz), 7.62 (2H, app t, J = 8.1 Hz), 7.33 (1H, d, J = 3.7 Hz), 6.66 (1H, dd, J = 3.0, 1.8 Hz), 2.97 (3H, s), 2.96 (3H, s).

Preparation of 2,4,5-triphenyloxazole [III.12c]

The compound was synthesized from (1R,2S)-2-phenylamino-1,2-diphenylethan-1-ol and purified by recrystallization in chloroform/hexane to yield a white solid 48 mg (96%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.17-8.15 (2H, m), 7.74-7.72 (2H, m), 7.69-7.67 (2H, m), 7.51-7.47 (3H, m), 7.41-7.31 (6H, m); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 160.2, 145.6, 136.9, 132.7, 130.5, 129.4, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 127.6, 127.5, 126.6, 126.5.

Preparation of 2-(4-methoxyphenyl)-4,5-diphenyloxazole [III.12d]

The compound was synthesized from (1R,2S)-2-(4-methoxybenzyl)amino-1,2-diphenylethan-1-ol and purified by recrystallization in chloroform/hexane to yield a white solid 47 mg (95%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.09 (2H, d, J = 9.2 Hz), 7.73-7.71 (2H, m), 7.67-7.65 (2H, m), 7.40-7.34 (6H, m), 6.99 (2H, d, J = 9.2 Hz), 3.92 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 161.5, 160.3, 145.1, 136.7, 132.8, 129.2, 128.8, 128.7, 128.5, 128.2, 126.5, 55.5.
Preparation of 2-(furan-2-yl)-4,5-diphenyloxazole [III.12f]

The compound was synthesized from (1R,2S)-2-(furan-2-ylmethyl)amino-1,2-diphenylethan-1-ol and purified by recrystallization in chloroform/hexane to yield a white solid 34 mg (75%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.88 (1H, d, J = 8.4 Hz), 7.71 (2H, d, J = 8.1 Hz), 7.65 (2H, d, J = 8.1 Hz), 7.59-7.34 (6H, m), 7.11 (1H, d, J = 2.9 Hz), 6.57-6.55 (1H, m); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.7, 153.1, 147.1, 145.2, 144.6, 142.9, 136.5, 133.7, 132.2, 129.5, 129.1, 128.8, 128.7, 128.5, 128.2, 126.7, 121.0, 113.2, 120.2, 111.8.

Preparation of (Z)-2-(((E)-butylidene)amino)-1,2-diphenylethen-1-ol [III.13]

The compound was synthesized from (1R,2S)-2-butylamino-1,2-diphenylethan-1-ol and purified by recrystallization in chloroform/hexane to yield a white solid 87 mg (34%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.91 (2H, d, J = 8.4 Hz), 7.69 (2H, d, J = 7.0), 7.52-7.46 (3H, m), 7.41-7.33 (3H, m), 3.44 (2H, t, 7.0 Hz), 1.66 (2H, pentet, J = 7.3 Hz), 0.87 (3H, t, J = 7.0 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 199.3, 166.3, 135.4, 135.0, 134.8, 134.7, 133.1, 130.8, 130.0, 129.3, 129.1, 128.7, 127.3, 53.8, 33.2, 20.6, 14.0.
Preparation of 2-(butylimino)-1,2-diphenylethan-1-one [III.14]

The compound was synthesized from (1R,2S)-2-butylamino-1,2-diphenylethan-1-ol and purified by recrystallization in chloroform/hexane to yield a white solid 105 mg (49%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.99-7.92 (3H, m), 7.68-7.63 (1H, m), 7.52-7.33 (6H, m), 2.52-2.37 (2H, m), 1.70 (2H, sextet, $J = 7.3$ Hz), 0.97 (3H, t, $J = 7.3$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.7, 194.1, 173.3, 135.0, 133.5, 130.0, 129.2, 129.4, 129.1, 128.9, 128.7, 35.9, 18.5, 13.7.

Preparation of 2,4,5-triphenyl-4,5-dihydrooxazole [III.15c]

The compound was synthesized from (1R,2S)-2-phenylamino-1,2-diphenylethan-1-ol and purified by recrystallization in chloroform/hexane to yield a white solid 40 mg (83%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.17 (2H, d, $J = 8.4$ Hz), 7.59-7.39 (4H, m), 7.09-7.01 (6H, m), 6.98-6.90 (3H, m), 6.03 (1H, d, $J = 10.3$ Hz), 5.75 (1H, d, $J = 9.9$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.1, 137.8, 136.7, 131.9, 128.7, 128.6, 127.9, 127.8, 127.7, 127.5, 127.1, 126.4, 85.4, 74.5.

Preparation of 2-(4-methoxyphenyl)-4,5-diphenyl-4,5-dihydrooxazole [III.15d]

The compound was synthesized from (1R,2S)-2-(4-methoxybenzyl)amino-1,2-diphenylethan-1-ol and purified by recrystallization in chloroform/hexane to yield a white solid 111 mg (92%); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.13 (2H, d, $J = 8.4$ Hz), 7.09-6.91 (12H, m), 5.99 (1H, d, $J = 9.9$ Hz), 5.71 (1H, d, $J = 9.9$ Hz); 3.92 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$):
δ 162.6, 138.0, 136.8, 130.5, 128.3, 128.0, 127.8, 127.6, 127.5, 127.1, 126.5, 119.9, 114.0, 85.3, 74.4, 55.6.
Appendix

$^1$H NMR, $^{13}$C NMR, and IR Spectra
I.14

HO NH₂

+ en.
I.15o  +  en.
\begin{align*}
\text{O}_2\text{N} & \quad \text{HO} \\
\text{NH} & \quad \text{NH} \\
\text{H}_3\text{C} & \quad \text{en.} \\
\text{I.18d} & \quad \text{CH}_3
\end{align*}
X: parts per Million : 1H

X: parts per Million : 13C

I.19e

HO
NH

HO
NH

I.19e

F

F

+ en.
X : parts per Million : 1H

X : parts per Million : 13C

246
X : parts per Million : 1H

II.2o

X : parts per Million : 13C

II.2o
I.4b

N. parts per Million: 1H

X: parts per Million: 13C

305
The image contains two sets of data, each with a different x-axis scale. The top set is labeled with parts per Million (ppm) for H nuclei, ranging from 0 to 9.0 ppm. The bottom set is labeled with parts per Million (ppm) for 13C nuclei, ranging from 0 to 200.0 ppm.