New Chemistry of Donor-Acceptor Cycloalkanes and Studies Towards the Synthesis of Streptorubin B

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Graduate Program in Chemistry

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Abstract and Keywords

Abstract

This dissertation presents two separate chapters within the broad area of synthetic organic chemistry. The first chapter describes the annelation chemistry of donor-acceptor (DA) cyclopropanes and cyclobutanes for the synthesis of heterocycles. The Yb(OTf)₃-catalyzed [4+2] cycloaddition between DA cyclobutanes and nitrosoarenes facilitated the synthesis of tetrahydro-1,2-oxazines in good to excellent yields as single diastereomers. Additionally, an unexpected deoxygenation occurred with electron-rich nitrosoarenes under MgI₂-catalysis that afforded pyrrolidine products. The GaCl₃-catalyzed [4+2] cycloaddition of DA cyclobutanes and cis-diazenes provided hexahydropyridazine derivatives in good to excellent yields as single diastereomers. Furthermore, a procedure to make spiroketals from the [4+2] cycloaddition of spirocyclic DA cyclobutanes and aldehydes is also disclosed. Lastly, a cascade reaction of DA cyclopropanes with nitrosoarenes is discussed. The reaction results in formation of tetrahydro-1,2-oxazine instead of normal cycloadduct isoxazolidine via a tandem ring opening, elimination, and cycloaddition sequence. A detailed discussion of the results along with associated mechanisms is presented.

The second chapter describes multiple strategies applied towards the synthesis of the prodigiosin alkaloid streptorubin B. The key aspect of the strategies is utilization of our group developed [3+2] cycloaddition between DA cyclopropanes and nitriles. An overview of this methodology and its application towards the synthesis of natural products is presented.
Keywords

donor-acceptor cyclopropane, donor-acceptor cyclobutane, annelation, annulation, cycloaddition, Lewis acid, catalysis, nitrosoarene, cis–diazene, tetrahydro-1,2-oxazine, pyrroldidine, hexahydropyridazine, spiroketal, pyrroles, streptorubin B, cascade reaction, methodology, total synthesis, thiabenzene 1-oxide.
Co-Authorship Statement

Chapter 1 involves collaborative work with Andrew C. Stevens (Ph.D. 2013), Tyler B. Schon (B.Sc. 2011), and Tristan Chidley (M.Sc. 2015). In section 1.2.1.1, Dr. Stevens and Mr. Schon were responsible for reaction discovery, optimization, and some substrate scope examples. Mr. Chidley was responsible for a major portion of the experimental of the results presented in sections 1.2.1.2 and 1.2.2.
For my lost self
Acknowledgments

There are many great people and experiences that helped me to become who I am today. First and foremost, I am indebted to my mother Suguna Vemula, who has been my inspiration, strength, and best friend. There was a time, due to extreme poverty, that I decided to give up on studies, and it was my uneducated mother who insisted I pursue higher studies. Now, I am scared to imagine how my life would have been without education.

I am grateful to my supervisor, Prof. Brian Pagenkopf for all that he has taught me over the last five years. I can most certainly say, the intellectual freedom he gave me to explore my own ideas, to write manuscripts, and present research at conferences has helped me grow as an independent researcher. He always respected and supported my (amateur) chemistry ideas, tolerated my weird work hours, and provided guidance whenever necessary, and for that I am thankful.

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<td>18-C-6</td>
<td>1,4,7,10,13,16-hexaoxacyclooctadecane</td>
</tr>
<tr>
<td>A</td>
<td>electron-acceptor</td>
</tr>
<tr>
<td>Å</td>
<td>Angstrom</td>
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<tr>
<td>AACD</td>
<td>alkoxy-activated cyclobutane-1,1-dicarboxylate</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>Chloramine-T</td>
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D  electron-donor

d  doublet

DA  donor-acceptor

dd  doublet of doublets

dba  dibenzylideneacetone

ddd  doublet of doublet of doublets

dddd  doublet of doublet of doublet of doublets

DBU  1,8-diaza-bicyclo[5.4.0]undec-7-ene

DCE  1,2-dichloroethane

DCM  dichloromethane

d\text{e}  diastereomeric excess

DEF  N,N-diethylformamide

DIBAL-H  diisobutylaluminum hydride

DMAP  4-(dimethylamino)pyridine

DME  1,2-dimethoxyethane

DMF  N,N-dimethylformamide

DMP  Dess-Martin periodinane (1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1\text{H})-one)

DMS  dimethyl sulfide

DMSO  dimethyl sulfoxide

dq  doublet of quartets

\text{dr}  diastereomeric ratio

dt  doublet of triplets

\text{ee}  enantiomeric excess
E⁺  electrophile
Et    ethyl
eq    equation
equiv equivalent
g     gram (s)
Grubbs II (1,3-*bis*(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphos-
        phine)ruthenium
h     hour (s)
HMBC heteronuclear multiple-bond correlation spectroscopy
HRMS high-resolution mass spectrometry
Hz    hertz
imid imidazole
iPr   isopropyl
J     coupling constant
KAPA potassium 3-aminopropylamide
Kcal  kilogram calorie (s)
KHMD3 potassium *bis*(trimethylsilyl)amide
m     multiplet
MAD   methylaluminum *bis*(2,6-di-tert-butyl-4-methylphenoxide)
mbar  millibar
Me    methyl
mg    milligram (s)
MHz   megahertz
min  minute (s)
mL   milliliter (s)
mol  mole (s)
MRs  medium-sized rings
MS   molecular sieves
Ms   methanesulfonyl
ms   millisecond (s)
m/z  mass to charge ratio
nBu  n-butyl
Nu^- nucleophile
NMR  nuclear magnetic resonance
NTf_2 N,N-bis(trifluoromethylsulfonyl)imide
nOe  nuclear Overhauser effect
ORTEP Oak Ridge Thermal Ellipsoid Plot
OTf  trifluoromethanesulfonate
Ph   phenyl
PMP  para-methoxyphenyl
ppm  parts per million
PTAD 4-phenyl-1,2,4-triazoline-3,5-dione
Py   pyridine
PCC  pyridinium chlorochromate
q    quartet
qd   quartet of doublets
quin quintet
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<td>RM</td>
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</table>
Preface

It is every synthetic organic chemist’s vision to make a complex product from trivial starting materials in a manner that absolutely controls regio- and stereoselectivity. Intermolecular cycloaddition chemistry offers a tool which assists in turning this vision into a reality. One manner of facilitating cycloaddition chemistry is through exploitation of ring strain in carbocycles. In this regard cyclopropanes, typically bearing vicinally substituted electron donating and electron accepting groups, suitably named as donor-acceptor (DA) cyclopropanes, are extensively studied. While this area continues to mature, reports on extending similar synthetic transformations to the homologous cyclobutanes are comparatively limited. Recently, the Pagenkopf group has begun exploring application of DA cyclobutanes in cycloaddition chemistry. While exploring this reaction space in collaboration with co-workers, new modes of reactivity were discovered.

The first chapter of this thesis will discuss several novel reactions of DA cyclobutanes and cyclopropanes. We have disclosed the first example of a [4+2] cycloaddition between DA cyclobutanes and nitrosoarenes. The reaction proceeds well with electron neutral and deficient nitrosoarenes, but electron-rich nitrosoarenes required a stronger Lewis acid, MgI₂. Interestingly, with electron-rich nitrosoarenes, a deoxygenation process was observed resulting in the formation of pyrrolidines from tetrahydro-1,2-oxazines in MgI₂ conditions. We have also developed the first example of a [4+2] cycloaddition between DA cyclobutanes and cis-diazenes. The reaction proceeds smoothly with alkoxy activated cyclobutanes as well as aryl activated cyclobutanes to form hexahydropyridazines in good to excellent yields. Furthermore, a procedure to make spiroketals from [4+2] cycloaddition of spirocyclic DA cyclobutanes with aldehydes was also developed. In
addition, we have discovered a cascade reaction of DA cyclopropanes with nitrosoarenes to form tetrahydro-1,2-oxazines. The cascade reaction proceeds through a ring opening of DA cyclopropane, followed by fragmentation to a nitrone intermediate and cycloaddition with second equivalent of DA cyclopropane to generate the tetrahydro-1,2-oxazines as single diastereomers in good to excellent yields.

The second chapter discusses the different strategies applied towards the synthesis of the biologically active prodigiosin alkaloid streptorubin B, using our group's [3+2] cycloaddition of DA cyclopropanes and nitriles.

It is my sincere hope that the reader, through the results discussed throughout the thesis, can arrive at a better understanding of the chemistry of DA cyclopropanes and cyclobutanes.

-Naresh Vemula
Chapter 1. New Chemistry of Donor-Acceptor Cycloalkanes

This chapter discusses new reactions of DA cyclopropanes and cyclobutanes. In collaboration with fellow graduate student Andrew C. Stevens (Ph.D. 2013) and undergrad Tyler B. Schon (B.Sc. 2011), we have developed the first example of a [4+2] cycloaddition of DA cyclobutanes and nitrosoarenes. In an attempt to extend this methodology to DA cyclopropanes, we discovered a novel cascade reaction that ultimately generated tetrahydro1,2-oxazines. In collaboration with fellow graduate student Tristan Chidley, we studied the mechanism through crossover experiments. The first example of a [4+2] cycloaddition of DA cyclobutanes and cis-diazenes was also developed, in collaboration with Tristan Chidley. Additionally, a procedure to make spiroketals from spirocyclic DA cyclobutanes was also developed.
1.1 Introduction

1.1.1 General Introduction to Cyclopropanes and Cyclobutanes

Cyclopropanes and cyclobutanes are highly strained carbocycles.\(^1\) The strain in any cyclic compound is a composite of three types of individual strain: transannular strain due to Van der Waals interactions between atoms across the ring, torsional strain (also called as Pitzer strain) due to eclipsing conformations between adjacent atoms, and angle strain (also called as Baeyer strain) due to distorted bond angles from the ideal for a given hybridization.\(^2\) While transannular strain is predominant in medium-sized rings (see, section 2.4), cyclopropanes, and cyclobutanes experience severe Baeyer and Pitzer strains. Although, these two strained carbocycles have similar ring strain (27.5 kcal/mol for cyclopropane and 26.3 kcal/mol for cyclobutane), there are notable differences in their structures.\(^3\) While cyclopropane has 60° C-C-C bond angles, similar to a planar equatorial triangle, cyclobutanes adopt a puckered conformation to reduce the Pitzer strain, but at the expense of Baeyer strain, and thus the C-C-C bond angle is <90° (Figure 1-1). Also the strain energy in cyclobutane is distributed over four carbons (6.6 kcal/mol/C–C bond) compared to three carbons in case of cyclopropane (9.2 kcal/mol/C-C bond).

![Figure 1-1. Pictorial representation of puckering conformation of cyclobutane.](image)

1.1.2 Donor-Acceptor Cyclopropanes

The reactivity of the cyclopropanes can be predictable by the substitution pattern around the ring (Figure 1-2). Electron-donating groups (D, such as amino or alkoxy) activate the
cyclopropane and increase its ability to react with electrophiles (eq 1, Figure 1-2). Likewise, electron-acceptor groups (A, such as carbonyl or nitro) increase the electrophilicity of the cyclopropane ring allowing homo-Michael type additions (eq 2, Figure 1-2). Interestingly, when both electron donating and electron-accepting groups are vicinally substituted, the strained C-C bond becomes polarized through a push-pull mechanism resulting in a 1,3-zwitterionic intermediate. This can be trapped by appropriate dipolarophiles, such as aldehydes or nitrones, to access annulated compounds (eq 3, Figure 1-2). These three types of substitution patterns on cyclopropanes, classifies them into three categories, namely, donor cyclopropanes, acceptor cyclopropanes, and donor-acceptor (DA) cyclopropanes.

Substituent-activated chemistry of cyclopropanes was pioneered by the groups of Wenkert (on donor cyclopropanes),6 Danishefsky (on acceptor cyclopropanes),7 and Reissig (on DA cyclopropanes).9a-b The first formal cycloaddition of DA cyclopropanes was reported by Reissig (Scheme 1-1).8 In this seminal report, Reissig reported the
annulation of DA cyclopropane 1-1 with benzophenone (1-2), mediated by TiCl₄, which resulted in tetrahydrofuran 1-3 in almost quantitative yield.

![Chemical structure](image)

**Scheme 1-1.** First cycloaddition of DA cyclopropane 1-1 with benzophenone (1-2).

Since this seminal report, a plethora of discoveries have been published in this area.⁹ Two of the finest reactions in this field relevant to this thesis are, the [3+2] cycloaddition of DA cyclopropanes with nitriles¹⁰ (which is reviewed in section 2.3) and the [3+3] cycloaddition of DA cyclopropanes with nitrones.¹¹

1.1.2.1 The [3+3] Cycloaddition of Nitrones and Donor-Acceptor Cyclopropanes

1.1.2.1.1 The Reaction Discovery and Development

The first example of a [3+3] cycloaddition of DA cyclopropanes with nitrones¹² was reported by Kerr and Young in 2003.¹¹a The reaction of an aldehyde-derived nitrone 1-5 with DA cyclopropane 1-4 in presence of catalytic Yb(OTf)₃ resulted in tetrahydro-1,2-oxazine 1-6 in good to excellent yields and diastereoselectivity (Scheme 1-2).

![Chemical structure](image)

**Scheme 1-2.** The [3+3] cycloaddition of DA cyclopropanes and nitrones.
In 2004, Kerr and co-workers further developed this reaction to encompass unstable nitrones via a three-component coupling of hydroxylamines, aldehydes, and DA cyclopropanes.\textsuperscript{11c} This multicomponent reaction allows the formation of a diverse array of tetrahydro-1,2-oxazines, which can then be transformed into congeners of FR900482 (similar to Scheme 1-5).

In 2005, Sibi and co-workers reported an asymmetric variant of this cycloaddition using bisoxazoline ligand 1-10 catalyzed by Ni(ClO\textsubscript{4})\textsubscript{2} (Scheme 1-3).\textsuperscript{11d} Excellent yields and enantiomeric excess was observed, but kinetic resolution remained elusive while using racemic cyclopropanes.

![Scheme 1-3. Sibi’s asymmetric [3+3] cycloaddition of DA cyclopropanes and nitrones.](image)

A few years later, in 2007, Tang and co-workers addressed the kinetic resolution problem using trisoxazoline ligand 1-14 in the Ni(ClO\textsubscript{4})\textsubscript{2}–catalyzed asymmetric [3+3] cycloaddition of nitrones with DA cyclopropanes.\textsuperscript{11g} As shown in the example in Scheme 1-4, both enantiomers of tetrahydro-1,2-oxazine 1-13 can be prepared from racemic DA cyclopropane 1-11 by either a direct cycloaddition with nitrone 1-12 in the presence of catalytic 1-14/Ni(ClO\textsubscript{4})\textsubscript{2} (eq 1, Scheme 1-4) or a 1-14/Ni(ClO\textsubscript{4})\textsubscript{2}-catalyzed kinetic resolution followed by cycloaddition with nitrone 1-12 (eq 2, Scheme 1-4).
Scheme 1-4. Kinetic resolution of racemic DA cyclopropane for the synthesis of both enantiomers of tetrahydro-1,2-oxazine.

1.1.2.1.2 Application in Target-oriented Synthesis

Although, the tetrahydro-1,2-oxazine structure is not abundant in nature, the core can be found in a few natural products\textsuperscript{13} as well as in pharmaceutical drugs\textsuperscript{14} (Figure 1-3).
Figure 1-3. Representative examples of tetrahydro-1,2-oxazine core in natural products and pharmaceutical drugs.

Although multiple methods exist for the synthesis of tetrahydro-1,2-oxazines, the [3+3] cycloaddition allows for the rapid generation of structural complexity from simple starting materials. For instance, in the same methodology paper, the authors demonstrated the utility of this elegant reaction in the synthesis of tricyclic skeleton of the antitumor agent FR-900482 (1-18). As shown in Scheme 1-5, nitrone 1-19 underwent a [3+3] cycloaddition with DA cyclopropane 1-20 to afford tetrahydro-1,2-oxazine 1-21 in 77% yield. In a similar manner to Danishefsky’s synthesis, oxazine 1-21 was converted into the desired tricyclic core 1-22 in 73% yield.

In 2006, Kerr and Carson showcased the [3+3] cycloaddition of nitrones with DA cyclopropanes, in their elegant total synthesis of a securinega alkaloid, (+)-phyllantidine (1-15, Scheme 1-6). The tetrahydro-1,2-oxazine core structure of (+)-phyllantidine (1-15) was efficiently accessed from a three component coupling of aldehyde 1-23, hydroxylamine 1-24, and enantiopure DA cyclopropane (R)-1-20 in 86% yield (Scheme 1-6). Oxazine 1-25 was then converted into the natural product (+)-phyllantidine (1-15) in a series of transformations. Thus the synthesis of (+)-phyllantidine was achieved in 6% overall yield over 12 linear steps from DA cyclopropane (R)-1-20.


Reissig and co-workers demonstrated the application of tetrahydro-1,2-oxazines in synthesis of pyrrolidines via a reductive cleavage of the N-O bond, followed by cyclization. Kerr and co-workers applied this strategy on tetrahydro-1,2-oxazine 1-28 accessed from a three component coupling of aldehyde 1-27, hydroxylamine 1-24, and enantiopure DA cyclopropane (R)-1-26 for the enantioselective synthesis of manzamine alkaloid (+)-nakadomarin A (1-32, Scheme 1-7).
As shown in Scheme 1-7 the three component coupling of aldehyde 1-27, hydroxylamine 1-24, and enantiopure DA cyclopropane (R)-1-26 (derived from D-mannose) gave oxazine 1-28 in 87% yield. The oxazine 1-28 was then converted into an advanced intermediate 1-29 through a series of transformations. Hydrogenolytic cleavage of the N-O bond of oxazine 1-29 gave the amino alcohol 1-30, which was selectively converted into O-mesylate and treated with base to afford pyrrolidine 1-31 in a 65% yield over three steps with inversion of configuration at reaction center. The pyrrolidine 1-31 was then carried on to (+)-nakadomarin A through a series of reactions. Thus the synthesis of (+)-nakadomarin A was achieved in 23 steps from DA cyclopropane (R)-1-26.

In 2012, Kerr and co-workers extended the applications of tetrahydro-1,2-oxazines towards synthesis Atorvastatin pyrrole (1-38, Scheme 1-8).\textsuperscript{19} As described in Scheme 1-8, the synthesis began with the [3+3] cycloaddition of nitrone 1-33 and DA cyclopropane 1-34 to afford oxazine 1-35 in 60% yield. Tsuji dehydrocarbonylation on the oxazine 1-35 provided the enolate 1-36 which was immediately treated with DBU to obtain pyrrole 1-37 in 70% yield over two steps.\textsuperscript{20} The pyrrole 1-37 was then converted into an advanced intermediate 1-38 through a series of transformations. Thus conversion of tetrahydro-1,2-oxazines to pyrroles was showcased in synthesis of Atorvastatin pyrrole (1-38).\textsuperscript{21}

In summary, the [3+3] cycloaddition of nitrones and DA cyclopropanes has proven to be an excellent method to construct tetrahydro-1,2-oxazines. The efficiency of the reaction has been well demonstrated in synthesis of natural products (+)-phyllantidine (1-15) and (+)-nakadomarin A (1-32). The tetrahydro-1,2-oxazines were also manipulated to congeners of pharmaceutical drug FR-900482 (1-18) and Atorvastatin pyrrole (1-38).
1.1.3 Donor-Acceptor Cyclobutanes

While the chemistry of DA cyclopropanes continues to mature, reports extending similar synthetic transformations to the homologous cyclobutanes are comparatively limited (Figure 1-4).22

![Figure 1-4](image)

**Figure 1-4.** Potential reactivity of DA cyclobutanes with generic dipolarophile $X=Y$.

1.1.3.1 Seminal Reports in DA Cyclobutane Chemistry

Even though the de Mayo reaction, in which the transient cyclobutane 1-42 undergoes a rapid ring opening to give 1,5-dicarbonyl compound 1-43, has been known in the literature since the 1960s (Scheme 1-9),23 attempts to explore the reactivity of DA cyclobutanes was not made until early 1990s.

![Scheme 1-9](image)

**Scheme 1-9.** Ring opening of the transient cyclobutane 1-42 in the de Mayo reaction.
The first report of formal cycloaddition of DA cyclobutanes was disclosed by Saigo and co-workers in 1991. In this work, amino-activated DA cyclobutanes \( \text{1-44} \) underwent [4+2] cycloadditions with carbonyl compounds \( \text{1-45} \) to generate tetrahydropyrans \( \text{1-46} \), albeit with low diastereoselectivity and modest yield (Scheme 1-10).

\[
\begin{align*}
\text{Me}_2\text{N} & \quad \text{CO}_2\text{R} \\
\text{Me} & \quad \text{Me} \\
\text{1-44} & \quad + \\
\text{O} & \quad \text{R}^1 \quad \text{R}^2 \\
\text{1-45} & \quad \text{1) TiCl}_4 \ (1.5 \text{ equiv}) \quad \text{CH}_2\text{Cl}_2, \text{ rt, 3 h} \quad \text{2) MeOH then aq. NaHCO}_3 \quad \text{3) MeOH, aq. HCl} \\
\text{HO} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{R}^1 \quad \text{R}^2 & \quad \text{CO}_2\text{R} \\
\text{1-46} & \quad \text{5 examples (47-72\%) 1:1-4:1 dr}
\end{align*}
\]

**Scheme 1-10.** The [4+2] cycloaddition of amino-activated DA cyclobutanes with carbonyl compounds.

A few years later, in 1997, Suzuki and co-workers observed a [4+2] cycloaddition of highly activated DA cyclobutane \( \text{1-47} \) with 2-oxazoline \( \text{1-48} \) without the need for a catalyst (Scheme 1-11).

\[
\begin{align*}
\text{EtO} & \quad \text{CN} \quad \text{CN} \quad \text{CO}_2\text{Me} \\
\text{CN} & \quad \text{CO}_2\text{Me} \\
\text{1-47} & \quad + \\
\text{N} & \quad \text{O} \\
\text{1-48} & \quad \text{no Lewis Acid} \quad \text{MeNO}_2, \text{ rt} \quad 24 \text{ h (45\%)} \\
\text{EtO} & \quad \text{N} \quad \text{CN} \quad \text{CN} \quad \text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{1-49} & \quad \text{1-47 with 2-oxazoline (1-48).}
\end{align*}
\]

**Scheme 1-11.** The [4+2] cycloaddition of DA cyclobutane \( \text{1-47} \) with 2-oxazoline \( \text{1-48} \).

The field remained relatively dormant for a decade, until 2008, when Matsuo and co-workers observed a conceptually similar [4+2] cycloaddition with 3-alkoxy cyclobutanones \( \text{1-50} \) and carbonyl compounds \( \text{1-52} \) (Scheme 1-12).
Scheme 1-12. The [4+2] cycloaddition of 3-alkoxycyclobutanones 1-50 with carbonyl compounds 1-52.

Shortly after the disclosure by Matsuo, the first catalytic cycloaddition of DA cyclobutanes with aldehydes that possessed a significantly broad substrate scope was reported by the research groups of Johnson\textsuperscript{28} and of Christie and Pritchard.\textsuperscript{31} The [4+2] cycloaddition with aldehydes 1-55 was found to proceed under mild conditions with good to excellent yields. In contrast to the work conducted by Saigo (Scheme 1-10), the DA cyclobutanes in these reports used carbon-based electron-donating groups (aryl, vinyl or cobalt-alkyne complex) and 1,1-diester substituents as the electron-accepting groups (Scheme 1-13).

Johnson found that Sc(OTf)$_3$ was able to catalyze the cycloaddition with loadings as low as 2 mol % (eq 1, Scheme 1-13). The cycloaddition was highly diastereoselective for the 2,6-cis-diastereomer with the majority of the aryl aldehydes investigated, but when cinnamaldehyde was used the diastereoselectivity dropped to 77:23, possibly due to the slow reactivity. The group was able to encompass aliphatic aldehydes with the more reactive and bulky Lewis acid, MADNTf$_2$.

The work by Christie and Pritchard reported a similar reactivity of cyclobutanes with a cobalt–alkyne complex as an electron-donor and 1,1-diesters as electron-acceptors (eq 2, Scheme 1-13). The group also found Sc(OTf)$_3$ as the best catalyst for this transformation. Most of the aryl aldehydes and other electron-rich aldehydes underwent the cycloaddition in good to excellent yields, forming the tetrahydropyran products as single diastereomers. When aliphatic aldehydes were used, the diastereoselectivity significantly dropped to 20-23% de.
It became apparent from the preceding examples that having 1,1-diesters as electron-acceptors enhanced the reactivity as well as the diastereoselectivity in cycloadditions as compared to a monoester. Inspired by these seminal reports and ongoing interest of Pagenkopf group (referred hereinafter as “we” or “our”) in alkoxy-activated cyclopropane chemistry,\textsuperscript{32} we were motivated to investigate the reactivity alkoxy-activated cyclobutane-1,1-dicarboxylates (AACDs).

1.1.3.2 Synthesis of Alkoxy-activated Cyclobutane-1,1-dicarboxylates

At the outset of our work, only two literature methods were available for the synthesis of AACDs (Scheme 1-14).

\begin{center}
\textbf{Scheme 1-14}. Literature methods for the synthesis of AACDs.
\end{center}

The use of a Michael induced ring closure of acyclic substrates (eq 1, Scheme 1-14) was not selected as a preparative route as it offers limited control over the stereochemistry, and requires multiple steps.\textsuperscript{33} On the other hand, a ZnBr\(_2\)-promoted [2+2] annulation reported by Roberts in 1986 appeared much more promising since the
required alkyl enol ethers are commercially available or can be readily prepared, and the methylidene malonates can be easily accessed through Knoevenagel condensation (eq 2, Scheme 1-14). Although this procedure could be utilized to prepare a number of AACDs containing 1,1-di-tert-butyl esters, this methodology could not be extended to prepare the more reactive ethyl- or methyl-substituted AACDs. To circumvent this challenge, a catalyst screening was explored, and it was revealed Yb(OTf)_3 as the best catalyst for this [2+2] cycloaddition. With the optimized conditions in hand, the scope of the cyclobutane synthesis was explored (Table 1-1).

Table 1-1. The synthesis of AACDs.

A range of cyclic and acyclic enol ethers were found to undergo cycloaddition with a variety of dialkyl methylidene malonates to generate AACDs in good to excellent yields as single diastereomers (1-67a-1-67g, Table 1-1). In addition to enol ethers,
electron-rich styrenes were also found to undergo efficient cycloaddition to yield AACDs in good yields (1-67h-1-67k, Table 1-1). With the AACDs at hand, the reactivity was explored with a variety of dipolarophiles

1.1.3.3 Reactivity of Alkoxy-activated Cyclobutane-1,1-dicarboxylates

1.1.3.3.1 The [4+2] Cycloaddition of AACDs with Aldehydes

Interestingly, initial investigations established that Yb(OTf)_3, which was used for the synthesis of AACDs (Table 1-1), was also a competent catalyst for the [4+2] cycloaddition with aldehydes. A wide range of aldehydes were found to undergo cycloadditions with AACDs in good to excellent yields, forming tetrahydropyrans as single diastereomers (Table 1-2). Aryl, heteroaryl, vinyl, and alkynyl aldehydes underwent smooth cycloadditions to afford tetrahydropyrans 1-69 in good to excellent yields (1-69a-1-69j). Finally, aliphatic aldehydes were also found to engage in cycloadditions, but only modest yields were observed (1-69k-1-69m).
Table 1-2. The [4+2] cycloaddition of AACDs with aldehydes.

\[
\begin{align*}
\text{AACD} (1-67b) + \text{Aldehyde} (1-68) \xrightarrow{\text{Yb(OTf)}_3 (10 \text{ mol\%})} \text{Product} (1-69)
\end{align*}
\]

\[
\begin{align*}
\text{1-69a: } X &= \text{OMe (80\%)} \\
\text{1-69b: } X &= \text{Cl (89\%)} \\
\text{1-69c: } X &= \text{CN (88\%)} \\
\text{1-69d: } X &= \text{NO}_2 (75\%)
\end{align*}
\]

\[
\begin{align*}
\text{1-69e (62\%)} \\
\text{1-69f: } R &= \text{Ph (87\%)} \\
\text{1-69g: } R &= \text{Me (51\%)}
\end{align*}
\]

\[
\begin{align*}
\text{1-69h: } X &= \text{O (71\%)} \\
\text{1-69i: } X &= \text{S (69\%)}
\end{align*}
\]

\[
\begin{align*}
\text{1-69j (81\%)} \\
\text{1-69k: } R &= \text{Me (51\%)} \\
\text{1-69l: } R &= \text{iPr (58\%)} \\
\text{1-69m: } R &= \text{nPr (56\%)}
\end{align*}
\]

1.1.3.3.2 The [4+2] Cycloaddition of AACDs with Imines

With the above example, the feasibility of cycloaddition chemistry with AACDs was confirmed. Our interest then shifted to further explore other possible dipolarophiles which could lead to desirable or novel structural architectures. Although imines were excellent dipolarophiles in cycloadditions with DA cyclopropanes, their reactivity with DA cyclobutanes was unexplored. Thus, we set out to investigate the reactivity of imines with AACDs. Upon exposure of cyclobutane 1-67 and imine 1-70 (prepared in situ) to catalytic Yb(OTf)3 at -50 °C, a mixture of bicyclic piperidine 1-71 and piperideine 1-72 were formed (Table 1-3). In order to converge on the piperideine product 1-72, the reaction was simply warmed to rt after the cyclobutane was consumed. Electron-rich
styrene derived cyclobutanes were also found to undergo cycloaddition to afford exclusive 2,6-trans-piperidines, but longer reaction times were necessary (1-71a-1-71d).

Table 1-3. The [4+2] cycloaddition of AACDs with imines.

![Diagram of the cycloaddition reaction]

1.1.3.3 The [4+3] Cycloaddition of AACDs with Nitrones

Having successfully expanded the reactivity of AACDs to imines, our interest turned to explore 3-atom dipolarophiles. Nitrones have previously been reported as excellent dipolarophiles in cycloadditions with DA cyclopropanes (see Section 1.1.2.1). Given this precedent, we investigated the reactivity of nitrones with AACDs.

After brief optimization studies, 5 mol % Yb(OTf)₃ was determined to be the best catalyst for this cycloaddition. Interestingly, cis-diastereomers were formed as thermodynamic products when the reaction was performed at rt; however a diastereomeric mixture containing significant amounts of the kinetic trans-diastereomer could be obtained at lower temperatures (Table 1-4). Additionally, when electron-deficient nitrone 1-73d was used, an inseparable third diastereomer was observed (entry
4), however, all three diastereomers would eventually converge to the single thermodynamic product. The heterocycle, 1,2-oxazepanes, are intriguing and unique structural motifs that are not naturally occurring, but they do display interesting antiviral and antiproliferative activity.

**Table 1-4.** The [4+3] cycloaddition of AACDs with nitrones.

<table>
<thead>
<tr>
<th>entry</th>
<th>1,2-oxazepane</th>
<th>at 0 °C yield (cis:trans:3rd)</th>
<th>at rt yield (cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-73a: Ar = C₆H₅</td>
<td>91% (31:69)</td>
<td>76%</td>
</tr>
<tr>
<td>2</td>
<td>1-73b: Ar = 4-C₆H₄Cl</td>
<td>82% (29:71)</td>
<td>73%</td>
</tr>
<tr>
<td>3</td>
<td>1-73c: Ar = 4-C₆H₄OMe</td>
<td>88% (37:63)</td>
<td>74%</td>
</tr>
<tr>
<td>4</td>
<td>1-73d: Ar = 4-C₆H₄CN</td>
<td>95% (15:57:27)</td>
<td>76%</td>
</tr>
</tbody>
</table>

**1.1.3.3 BF₃·OEt₂-promoted Reaction of AACDs with Terminal Alkynes**

Intrigued with the success of above discussed cycloadditions, we were then interested to study an all carbon dipolarophile, such as the alkynes. Terminal alkynes have previously been reported to undergo efficient [3+2] cycloadditions with DA cyclopropanes. After a multitude of unsuccessful attempts, it was discovered that stoichiometric BF₃·OEt₂ could promote the reaction to generate a peculiar 2,3-dihydrooxepine structure 1-76. This
structure originated from an addition/rearrangement sequence \textit{via} a highly strained bicyclic intermediate 1-79 (Scheme 1-15).\textsuperscript{46}

![Chemical Structure]

**Scheme 1-15.** BF$_3$·OEt$_2$-promoted reaction of AACDs with terminal alkynes.

Only arylacetylenes with electron-neutral and moderately electron-rich substituents proceeded through a productive reaction manifold, albeit in low yields (1-76a-1-76e, Scheme 1-15). Substrates with strong electron-donating substituents rapidly polymerized upon exposure to BF$_3$·OEt$_2$, whereas, electron-deficient alkynes failed to react.\textsuperscript{47} Interestingly, when silyloxy substituted phenylacetylene 1-75f was used, the reaction resulted in the expected [4+2] cycloadduct 1-80f (Scheme 1-16). This was the only case we observed cycloaddition instead of rearrangement, which could be due to the increased bulk on the aryl ring inhibiting the polymerization and/or rearrangement.
**Scheme 1-16.** The [4+2] cycloaddition of alkyne 1-75f with AACD 1-67b.

1.1.3.4 Additional Cyclobutane-1,1-dicarboxylates

In recent years, several other groups have reported interesting cycloadditions of DA cyclobutanes. Most recently, Tang and co-workers reported the enantioselective [4+3] cycloaddition of DA cyclobutanes and nitrones (Scheme 1-17).\(^{48}\) While contributing the first enantioselective variant, the group also added several new DA cyclobutanes to the library.

**Scheme 1-17.** Enantioselective [4+3] cycloaddition of DA cyclobutanes 1-81 with nitrones 1-83.

Waser and co-workers enhanced the family of DA cyclobutanes by developing a Fe(III)-catalyzed [2+2] cycloaddition of enimides 1-85 and alkylidene malonates 1-86 to access amino-activated cyclobutane-1,1-dicarboxylates 1-87 (Scheme 1-18).\(^{49}\)

The group also disclosed the reactivity of these DA cyclobutanes with aldehydes and silyl enolethers (Scheme 1-19).\(^{50}\) Interestingly, in the reaction with aldehydes 1-88 (eq 1, Scheme 1-19), the less substituted DA cyclobutanes 1-87 (R\(^2\) = R\(^3\) = H) could be activated with Sc(OTf)\(_3\), but the more substituted 1-87 (R\(^2\) = R\(^3\) ≠ H) required FeCl\(_3\)·Al\(_2\)O\(_3\). More interestingly, thymine- or fluorouracil-substituted cyclobutanes were also found to undergo cycloaddition with aldehydes under Hf(OTf)\(_4\) catalysis to access six-membered ring carbonucleoside analogues. In reaction with silyl enolethers, only less

substituted DA cyclobutanes 1-87 (R² = R³ = H) were found to undergo cycloadditions (eq 2, Scheme 1-19).

The first intramolecular cycloaddition of DA cyclobutanes⁵¹ was recently reported by France and co-workers.⁵²,⁵³ The authors described a Sc(OTf)₃-catalyzed [5+2] cycloaddition approach for the synthesis of azepino[1,2-a]indoles 1-94 via DA cyclobutane intermediates 1-95 (Scheme 1-20).


In summary, application of the long ignored DA cyclobutanes in cycloaddition chemistry have recently garnered significant attention. A number of reaction partners have been found to undergo efficient annulations with DA cyclobutanes to facilitate rapid access to structurally intriguing carbo- and heterocyclic frameworks. While initial examples lacked scope and stereochemical control, more recent examples have broadened the scope of the transformations, and have demonstrated the possibility of high level of stereo-control. Recently, asymmetric and intramolecular cycloaddition variants
have been reported, yet the chemistry of DA cyclobutanes is only in its infancy and further studies will surely prove fruitful.

Motivated by the successful cycloadditions of AACDs with aldehydes, imines, and nitrones, we became interested in exploring the reactivity of other dipolarophiles, as this would allow a better understanding of these fascinating systems. A successful cycloaddition would result in diverse structural motifs, depending on the dipolarophile, and would thus be useful in accessing a library of compounds for biological screening. In addition, as many natural products contain these cycloadducts as core structures, it would be very efficient to elaborate these cycloadducts for complex natural product synthesis. Thus, we chose nitrosoarenes as annulation partners to investigate it’s reactivity with AACDs.
1.2 Results and Discussion

1.2.1 Reactivity of Donor-Acceptor Cycloalkanes with Nitrosoarenes

Nitrosoarenes\textsuperscript{54} have been utilized in a variety of transformations\textsuperscript{55} such as dienophiles in hetero Diels-Alder cycloadditions\textsuperscript{56} and as enophiles in nitroso-ene reactions.\textsuperscript{57} The dichotomous capacity of nitroso functional group, to act as either nitrogen or oxygen transfer reagents, has been well studied in nitroso-aldol chemistry.\textsuperscript{58} Although the insertion of NO into the cyclopropane ring is known,\textsuperscript{59} surprisingly, nitrosoarenes have not yet seen application in annelation\textsuperscript{60} chemistry with either DA cyclopropanes or cyclobutanes.

1.2.1.1 The [4+2] Cycloaddition of AACDs with Nitrosoarenes

In collaboration with fellow grad student Andrew C. Stevens (Ph.D. 2013) and undergrad Tyler B. Schon (B.Sc. 2011), investigations into the reactivity of AACDs with nitrosoarenes began with the examination of the reaction between cyclobutane 1-67b and nitrosobenzene (1-96a) (Table 1-5).\textsuperscript{61} While a variety of Lewis acids were found to catalyze the reaction, maximum yields were obtained with Yb(OTf)\textsubscript{3}. Additionally, the product yield was dramatically improved by decreasing the catalyst loading from 10 to 2 mol % (compare entries 1, 6 and 8). The reaction could be effected with catalyst loadings as low as 0.5 mol % but in low yield (entry 9). Thus, 2 mol % Yb(OTf)\textsubscript{3} was selected as the optimized catalysts system for this reaction. Interestingly, among the two possible regioisomers (1-97a and 1-98a), the product obtained was always 1-97a, and no noticeable amount of 1-98a was observed, irrespective of the Lewis acid used. Thereby
demonstrating that the nitrogen of the nitroso functional group was acting as a nucleophile rather than oxygen.\textsuperscript{62}

**Table 1-5.** Catalyst screening for [4+2] cycloaddition of AACDs with nitrosoarenes.

<table>
<thead>
<tr>
<th>entry\textsuperscript{a}</th>
<th>Lewis acid</th>
<th>mol %</th>
<th>yield (%)\textsuperscript{b}</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yb(OTf)\textsubscript{3}</td>
<td>10</td>
<td>60</td>
<td>1-97a</td>
</tr>
<tr>
<td>2</td>
<td>Sc(OTf)\textsubscript{3}</td>
<td>10</td>
<td>55</td>
<td>1-97a</td>
</tr>
<tr>
<td>3</td>
<td>La(OTf)\textsubscript{3}</td>
<td>10</td>
<td>22</td>
<td>1-97a</td>
</tr>
<tr>
<td>4</td>
<td>Zn(OTf)\textsubscript{2}</td>
<td>10</td>
<td>61</td>
<td>1-97a</td>
</tr>
<tr>
<td>5</td>
<td>Pr(OTf)\textsubscript{3}</td>
<td>10</td>
<td>63</td>
<td>1-97a</td>
</tr>
<tr>
<td>6</td>
<td>Yb(OTf)\textsubscript{3}</td>
<td>5</td>
<td>72</td>
<td>1-97a</td>
</tr>
<tr>
<td>7</td>
<td>Sc(OTf)\textsubscript{3}</td>
<td>5</td>
<td>61</td>
<td>1-97a</td>
</tr>
<tr>
<td>8</td>
<td>Yb(OTf)\textsubscript{3}</td>
<td>2</td>
<td>92</td>
<td>1-97a</td>
</tr>
<tr>
<td>9</td>
<td>Yb(OTf)\textsubscript{3}</td>
<td>0.5</td>
<td>80</td>
<td>1-97a</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Typical reaction conditions: To a solution of Lewis acid in CH\textsubscript{2}Cl\textsubscript{2} (3 mL) at rt, was added nitroso benzene 1-96a (0.30 mmol) followed by cyclobutane 1-67b (0.36 mmol). Reactions were monitored until 1-96a was consumed by TLC.\textsuperscript{b}Isolated yield.

With optimal conditions in hand, the scope of the reaction was examined (Table 1-6). It was discovered that nitrosoarenes with halogen substituents were excellent reaction partners regardless of the position on the aryl ring (entries 2-7).\textsuperscript{63} Substrates with moderately deactivating ketone (entries 8 and 9) or ester (entry 10) substituents were
competent in the reaction affording the product in good yields. Electron-deficient nitrosoarenes afforded moderate yields (entries 11 and 12); however, the other possible regioisomer (Figure 1-6) was also formed, comprising up to 25% of the isolated yield. Nitrosoarene with a weakly electron donating methyl substituent resulted in a substantially decreased yield (entry 13). Upon incorporation of a strongly electron donating group no reaction was observed (entries 14 and 15). The arrest in reactivity is likely due to the sequestration of the ytterbium catalyst by the electron-rich nitrosoarene.
Table 1-6. Reaction scope of the [4+2] cycloaddition of AACDs with nitrosoarenes.

<table>
<thead>
<tr>
<th>entry</th>
<th>nitrosoarene</th>
<th>product</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ar = C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>1-97a</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>Ar = 4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Br</td>
<td>1-97b</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>Ar = 4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Cl</td>
<td>1-97c</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>Ar = 3-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Br</td>
<td>1-97d</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>Ar = 3-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Cl</td>
<td>1-97e</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>Ar = 2,4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;Br&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1-97f</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>Ar = 3,4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1-97g</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>Ar = 4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;C(O)Me</td>
<td>1-97h</td>
<td>69</td>
</tr>
<tr>
<td>9</td>
<td>Ar = 3-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;C(O)Me</td>
<td>1-97i</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>Ar = 4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td>1-97j</td>
<td>76</td>
</tr>
<tr>
<td>11</td>
<td>Ar = 4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;CN</td>
<td>1-97k, 1-98k (3:1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>61</td>
</tr>
<tr>
<td>12</td>
<td>Ar = 4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1-97l, 1-98l (4:1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>59</td>
</tr>
<tr>
<td>13</td>
<td>Ar = 4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Me</td>
<td>1-97m</td>
<td>29</td>
</tr>
<tr>
<td>14</td>
<td>Ar = 4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;OMe</td>
<td>-</td>
<td>no reaction&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td>Ar = 4-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;NMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>-</td>
<td>no reaction&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Ratio of 1-97:1-98 of isolated overall yield, <sup>b</sup>Isolated yield.

<sup>c</sup>Yb(OTf)<sub>3</sub> 2 mol % or 10 mol %

Fortuitously, X-ray quality crystals of compounds 1-97b (entry 2, Table 1-6) and 1-97k (entry 11, Table 1-6) were obtained and the ORTEP structures are depicted in
Figure 1-5. These crystal structures unambiguously establish both the regiochemistry of the cyclization and the relative stereochemistry at the ring fusion.\textsuperscript{64}

![ORTEP structures of 1-97b and 1-97k.](image)

(Reproduced with permissions from ref. 61)

Extensive 2D NMR analysis was used to support the structural assignments of the isomers formed with electron deficient nitrosoarenes (entries 11 and 12, Table 1-6). The major isomer in each case was found to have nOe and \textsuperscript{1}H-\textsuperscript{15}N HMBC interactions that were consistent with those observed for 1-97b and 1-97k (Figure 1-6). The minor isomer showed nOe interactions suggesting a \textit{cis} ring fusion, and \textsuperscript{1}H-\textsuperscript{15}N HMBC data indicated that it is a regioisomer, rather than a diastereomer, was formed. Similar nOe and \textsuperscript{1}H-\textsuperscript{15}N HMBC correlations were observed for 1-97l and 1-98l also. This lack of selectivity could be due to delocalization of the nitrogen lone pair of electrons into the aromatic ring, leading to competition between nitrogen and oxygen for dominant nucleophilicity.
Figure 1-6. Key nOe and $^1\text{H}$$^{15}\text{N}$ HMBC correlations for structural assignment of 1-97k and 1-98k.

As electron-rich nitrosoarenes were found not to participate in the Yb(OTf)$_3$-catalyzed cycloaddition, we reinvestigated the reaction conditions in attempts to find an alternative. Employing 1-methoxy-4-nitrosobenzene 1-96n as a model substrate, a thorough screening of catalysts was undertaken. In most cases, either no reaction or decomposition of the cyclobutane was observed (Table 1-7). However, a number of catalysts did afford the reaction product in small quantities.
Table 1-7. Catalyst screening for electron-rich nitrosoarenes.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>mol %</th>
<th>temp, time</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yb(OTf)(_3)</td>
<td>50</td>
<td>rt, 30 min</td>
<td>19%(^c)</td>
</tr>
<tr>
<td>2</td>
<td>Zn(OTf)(_2)</td>
<td>10</td>
<td>rt, 20 h</td>
<td>13%(^c)</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl(_2)</td>
<td>10</td>
<td>rt, 6 h</td>
<td>26%(^c)</td>
</tr>
<tr>
<td>4</td>
<td>Zn(NTf(_2))(_2)</td>
<td>10</td>
<td>rt, 2 h</td>
<td>1-98n-15%</td>
</tr>
<tr>
<td>5</td>
<td>AlCl(_3)</td>
<td>10</td>
<td>rt, 23 h</td>
<td>1-98n-9%</td>
</tr>
<tr>
<td>6</td>
<td>AlBr(_3)</td>
<td>10</td>
<td>rt, 72 h</td>
<td>no reaction(^f)</td>
</tr>
<tr>
<td>7</td>
<td>AlMe(_3)</td>
<td>20</td>
<td>rt, 24 h</td>
<td>no reaction(^f)</td>
</tr>
<tr>
<td>8</td>
<td>MADNTf(_2)</td>
<td>100</td>
<td>rt, 72 h</td>
<td>no reaction(^f)</td>
</tr>
<tr>
<td>9</td>
<td>Et(_2)AlCl</td>
<td>20</td>
<td>0 °C, 2 h; rt, 18 h</td>
<td>decomposition(^e)</td>
</tr>
<tr>
<td>10</td>
<td>Sc(OTf)(_3)</td>
<td>10</td>
<td>rt, 30 min</td>
<td>decomposition(^e)</td>
</tr>
<tr>
<td>11</td>
<td>CuI</td>
<td>10</td>
<td>rt, 52 h</td>
<td>no reaction(^f)</td>
</tr>
<tr>
<td>12</td>
<td>Cu(OTf)(_2)</td>
<td>10</td>
<td>rt, 30 min</td>
<td>1-98n-14%</td>
</tr>
<tr>
<td>13</td>
<td>SnCl(_2)</td>
<td>10</td>
<td>rt, 46 h</td>
<td>no reaction(^f)</td>
</tr>
<tr>
<td>14</td>
<td>SnCl(_4)</td>
<td>10</td>
<td>0 °C, 1 h</td>
<td>decomposition(^f)</td>
</tr>
<tr>
<td>15</td>
<td>Sn(OTf)(_2)</td>
<td>10</td>
<td>rt, 18 h</td>
<td>1-98n-10%</td>
</tr>
<tr>
<td>16</td>
<td>Bu(_2)BOTf</td>
<td>10</td>
<td>0 °C, 2 h; rt, 30 min</td>
<td>decomposition(^e)</td>
</tr>
<tr>
<td>17</td>
<td>BF(_3)OEt(_2)</td>
<td>10</td>
<td>0 °C, 4 h; rt, 18 h</td>
<td>decomposition(^e)</td>
</tr>
<tr>
<td>18</td>
<td>AgOTf</td>
<td>10</td>
<td>rt, 15 min</td>
<td>decomposition(^e)</td>
</tr>
<tr>
<td>19</td>
<td>AgCl</td>
<td>10</td>
<td>rt, 18 h</td>
<td>decomposition(^e)</td>
</tr>
<tr>
<td>20</td>
<td>ZrCl(_4)</td>
<td>10</td>
<td>0 °C, 3 h; rt, 18 h</td>
<td>decomposition(^e)</td>
</tr>
<tr>
<td>21</td>
<td>TiCl(_4)</td>
<td>10</td>
<td>0 °C, 3 h; rt, 18 h</td>
<td>decomposition(^e)</td>
</tr>
<tr>
<td>22</td>
<td>In(NTf(_2))(_3)</td>
<td>10</td>
<td>rt, 30 min</td>
<td>1-98n-20%</td>
</tr>
<tr>
<td>Entry</td>
<td>Lewis Acid</td>
<td>Temp.</td>
<td>Time</td>
<td>Product</td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>-------</td>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>23</td>
<td>In(OTf)$_3$</td>
<td>rt</td>
<td>3.5 h</td>
<td>1-98n</td>
</tr>
<tr>
<td>24</td>
<td>MgCl$_2$</td>
<td>rt</td>
<td>100 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>25</td>
<td>MgBr$_2$</td>
<td>rt</td>
<td>120 h</td>
<td>1-98n</td>
</tr>
<tr>
<td>26</td>
<td>Mg(ClO$_4$)$_2$</td>
<td>0 °C</td>
<td>4 h; rt, 2 h</td>
<td>decomposition</td>
</tr>
<tr>
<td>27</td>
<td>MgI$_2$</td>
<td>rt</td>
<td>23 h</td>
<td>1-98n</td>
</tr>
<tr>
<td>28</td>
<td>MgI$_2$</td>
<td>5</td>
<td>rt</td>
<td>24 h</td>
</tr>
<tr>
<td>29</td>
<td>MgI$_2$</td>
<td>10</td>
<td>0 °C, 40 h</td>
<td>1-98n</td>
</tr>
<tr>
<td>30</td>
<td>MgI$_2$</td>
<td>10</td>
<td>-20 °C, 72 h</td>
<td>1-98n-20%</td>
</tr>
<tr>
<td>31</td>
<td>MgI$_2$</td>
<td>50</td>
<td>0 °C, 15 min</td>
<td>1-98n-26%</td>
</tr>
</tbody>
</table>

*aTypical reaction conditions:* To a solution of Lewis acid in CH$_2$Cl$_2$ (3 mL) at specified temp, was added nitrosoarene 1-96n (0.30 mmol) followed by cyclobutane 1-67b (0.36 mmol). Reactions were monitored until 1-96n was consumed by TLC.


*f*Cyclobutane 1-67b recovered with some decomposition based on TLC and/or crude $^1$H NMR spectroscopy.

Among all the Lewis acids tested, MgI$_2$ was found to be functional for this reaction; however only low yields of product were obtained (entries 27-31, Table 1-7). Interestingly the regioisomer isolated under these conditions was the acetal 1-98n and not the aminal 1-97n as expected (compare with Table 1-6). This reversal in regioselectivity could be rationalized by the proposed mechanism (Scheme 1-21), in which the electron donating methoxy group on the aryl ring enhances the nucleophilicity of the nitroso oxygen, causing the oxygen to act as the nucleophile instead of nitrogen. Nucleophilic addition of the oxygen of the nitroso on the oxocarbenium ion 1-99 followed by cyclization via intermediate 1-100 would yield 1-98n.
Scheme 1-21. Proposed mechanism for the formation of 1-98n.

During the course studying this reaction, a peculiar observation was noted. When the reaction was left to stir for 2 days at rt or when 1-98n was treated with 50 mol % MgI₂ at rt overnight, pyrrolidine 1-101n was formed with trace amounts of lactone 1-102n (Scheme 1-22).

Scheme 1-22. Formation of pyrrolidine 1-101n and lactone 1-102n.

The structural assignment for the deoxygenated pyrrolidine product 1-101n was made based on extensive 2D NMR analysis (Figure 1-7). The nOe correlations were
consistent with those observed for aminal regioisomer of oxazine 1-97 (See Figure 1-6) suggesting a cis ring fusion and an aminal linkage. The presence of $^1$H-$^{15}$N HMBC correlations of nitrogen with all of the pyrrolidine protons, and a $^1$H-$^{13}$C HMBC correlation between aminal proton and quaternary carbon supported the proposed structure which was in agreement with the observed mass in HRMS.

![Diagram of nOe, $^1$H-$^{15}$N HMBC, and $^1$H-$^{13}$C HMBC correlations](image)

**Figure 1-7.** Key nOe, $^1$H-$^{15}$N HMBC, and $^1$H-$^{13}$C HMBC correlations for structural assignment of 1-101n.

A postulated mechanism to explain this redox transformation is depicted in Scheme 1-23.
Scheme 1-23. Proposed mechanism for the formation of 1-101n and 1-102n.

Coordination of MgI₂ to the oxygen of tetrahydro-1,2-oxazine 1-103 polarizes both the C-O and N-O bonds indicated. Cleavage of the C-O bond (Path A, Scheme 1-23) generates an oxocarbenium ion 1-104, which could then undergo nucleophilic attack by the pendant nitrogen, forming pyrrolidinium intermediate 1-105. Finally, the initially displaced iodide reacts with the side chain on the nitrogen, resulting in N-O bond reduction, and concomitantly producing I₂, MgO, and pyrrolidine 1-101n. Lactone 1-102n can be formed via N-O bond cleavage of 1-103 (Path B) leading to intermediate 1-106 followed by 1,5-hydride shift.

Based on the proposed mechanism it is clear that stoichiometric MgI₂ was necessary for complete conversion of 1-98n to 1-101n, but disappointingly the yields were further lowered with considerable decomposition of cyclobutane under such conditions.
With these interesting results we proceeded to investigate if other nitrosoarenes would follow a similar reaction manifold under MgI₂-promoted conditions. Thus, the reaction of electron-rich nitrosoarene 1-96o directly afforded pyrrolidine 1-101o (entry 2, Table 1-8), without observation of the anticipated tetrahydro-1,2-oxazine 1-98o. Interestingly, the substrate 1-96k, which afforded aminal 1-97k as the major product under Yb(OTf)₃ catalysis (entry 11, Table 1-6), resulted in reversal of regioselectivity albeit in low yield (entry 3, Table 1-8). Also, the isolated aminal 1-107k was found to be the trans-diastereomer (confirmed by single-crystal X-ray diffraction; see, Figure 1-8), rather than cis. Nitrosobenzene 1-96a, which is electronically sandwiched between 1-96n and 1-96k, produced aminal 1-97a as the exclusive product, ruling out the possibility of Mg-enolate aldol reaction mechanism. The nitroso-heteroarenes 2-nitrosopyridine (1-96p) and N-Boc-5-nitrosoindole (1-96q), which did not react under Yb(OTf)₃ conditions, provided exclusive acetal products (1-98 and 1-98q respectively) in low yields (entries 5 and 6, Table 1-8).
Table 1-8. Scope of MgI$_2$-promoted cycloaddition.

<table>
<thead>
<tr>
<th>entry$^a$</th>
<th>nitrosoarene</th>
<th>product</th>
<th>MgI$_2$ (mol %)</th>
<th>yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>1-96n</strong> Ar = 4-C$_6$H$_4$OMe</td>
<td><strong>1-101n</strong></td>
<td>50</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td><strong>1-96o</strong> Ar = 4-C$_6$H$_4$NMe$_2$</td>
<td><strong>1-101o</strong></td>
<td>50</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td><strong>1-96k</strong> Ar = 4-C$_6$H$_4$CN</td>
<td><strong>1-98k</strong>, <strong>1-107k</strong>($2:1)^b$</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td><strong>1-96a</strong> Ar = C$_6$H$_5$</td>
<td><strong>1-97a</strong></td>
<td>10</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td><strong>1-96p</strong> Ar = 2-pyridine</td>
<td><strong>1-98p</strong></td>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td><strong>1-96q</strong> Ar = N-Boc-5-nitrosoindole</td>
<td><strong>1-98q</strong></td>
<td>10</td>
<td>19</td>
</tr>
</tbody>
</table>

$^a$Typical reaction conditions: To a solution of MgI$_2$ in CH$_2$Cl$_2$ (3 mL) at specified temp, was added nitrosoarene **1-96** (0.30 mmol) followed by cyclobutane **1-67b** (0.36 mmol). Reactions were monitored until nitrosoarene **1-96** was consumed by TLC.

$^b$Ratio of isolated overall yields. $^c$Isolated yields.
Additional AACDs were explored under both Yb(OTf)$_3$ and MgI$_2$ reaction conditions (Table 1-9). AACD 1-67a gave a moderate yield with nitrosobenzene (1-96a) under Yb(OTf)$_3$ catalysis, while electron-rich nitrosoarenes 1-96n and 1-96o resulted in low yields of exclusive pyrrolidine products 1-110an and 1-110ao respectively (entries 2 and 3). The AACD 1-67g smoothly reacted with nitrosobenzene (1-96a) and 1-chloro-4-nitrosobenzene 1-96c to furnish tetrahydro-1,2-oxazines 1-108ga and 1-108gc respectively in good yields (entries 4 and 5). Disappointingly the AACD 1-67f gave a poor yield with nitrosobenzene (1-96a), while electron-rich nitrosoarene 1-96n resulted in a low yield of acetal product 1-109fn (entry 7).
**Table 1-9.** Reaction scope of additional AADCs in [4+2] cycloaddition.

<table>
<thead>
<tr>
<th>entry</th>
<th>cyclobutane</th>
<th>nitrosoarene</th>
<th>isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-96a Ar = C₆H₅</td>
<td>1-108aa, 45%</td>
<td>Yb(OTf)₃ Mgl₂</td>
</tr>
<tr>
<td>2</td>
<td>1-96n Ar = 4-C₆H₄OMe</td>
<td>-</td>
<td>1-110an, 35%</td>
</tr>
<tr>
<td>3</td>
<td>1-96o Ar = 4-C₆H₄N(CH₃)₂</td>
<td>-</td>
<td>1-110ao, 18%</td>
</tr>
<tr>
<td>4</td>
<td>1-96a Ar = C₆H₅</td>
<td>1-108ga, 73%</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>1-96c Ar = 4-C₆H₄Cl</td>
<td>1-108gc, 70%</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>1-96a Ar = C₆H₅</td>
<td>1-108fa, 21%</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>1-96n Ar = 4-C₆H₄OMe</td>
<td>-</td>
<td>1-109fn, 38%</td>
</tr>
</tbody>
</table>

Crystals of **1-110an** were obtained and the X-ray structure was able to unambiguously confirm the structure of the pyrrolidine product (Figure 1-9).
Knowing that 1-98n could be converted into pyrrolidine 1-101n via MgI₂ mediated reaction (Scheme 1-22), 1-109fn was subjected 50 mol % of MgI₂ in attempts to form pyrrolidine 1-110fn. However, ester 1-111fn was the only product formed, and pyrrolidine 1-110fn was not observed (Scheme 1-24).

In summary, we have developed the first example of [4+2] cycloaddition between AACDs and nitrosoarenes. The regiochemistry and relative stereochemistry of aminal products have been assigned by 2D NMR spectroscopy correlations and ultimately confirmed by single crystal X-ray diffraction. The reaction proceeds well with electron-neutral and deficient nitrosoarenes but, electron-rich nitrosoarenes required much strong
Lewis acid, MgI₂. Furthermore, a procedure to convert tetrahydro-1,2-oxazines into pyrrolidines was discovered. The regiochemistry and stereochemistry of the unexpected pyrrolidine products was assigned based on 2D NMR correlations and ultimately confirmed by single-crystal X-ray diffraction. Future work includes gaining mechanistic insights into the formation of pyrrolidines which will surely bring about new and exciting opportunities for furthering the efficiency of the process.
1.2.1.2 Cascade Reaction of Donor-Acceptor Cyclopropanes: Mechanistic Studies on Cycloadditions with Nitrosoarenes and cis-Diazenes

The interesting results observed in cycloadditions of nitrosoarenes with AACDs spurred the investigation of similar reactivity with alkoxy-activated cyclopropanes. Unfortunately, the initial investigation only resulted in either no reaction or decomposition of the cyclopropane 1-12 despite a variety of conditions employed (Scheme 1-25).

![Scheme 1-25. Anticipated [3+2] cycloaddition of DA cyclopropane 1-112 with nitrosobenzene (1-96a).](image)

While investigating for the best cycloaddition conditions, the Studer group reported an elegant [3+2] cycloaddition of DA cyclopropanes with nitrosoarenes. The reaction proceeds with complete retention of configuration and perfect control of regioselectivity (an example shown in Scheme 1-26).

![Scheme 1-26. Studer's [3+2] cycloaddition of DA cyclopropanes with nitrosoarenes.](image)
The observed stereospecificity and regioselectivity (which is opposite to what was observed with AACDs, see Section 1.2.1.1), was rationalized by Studer and co-workers through the mechanism proposed below (Scheme 1-27).

Scheme 1-27. Studer’s proposed mechanism for the [3+2] cycloaddition.

As per the authors, the catalyst MgBr$_2$ first coordinates to the DA cyclopropane (S)-1-115a, providing the MgBr$_2$-activated cyclopropane 1-118a. The bromide anion then opens the cyclopropane ring at the benzylic position in an $S_N$2 fashion, generating Mg-enolate 1-119a. This enolate 1-119a then undergoes a nitroso-aldol reaction with the nitrosobenzene (1-96a) likely via the 6-membered transition state 1-120a, to generate magnesiated hydroxylamine 1-121. Intermediate 1-121 then cyclizes through an intramolecular $S_N$2 substitution to close the catalytic cycle, providing the isoxazole (S)-1-116a with net retention at the stereogenic center with respect to the starting cyclopropane (S)-1-115a.

Motivated by this reaction and previously reported Yb(OTf)$_3$-catalyzed cycloadditions of DA cyclopropanes, we set out to investigate alternative reactivity of
DA cyclopropanes with nitrosoarenes under Yb(OTf)_3 catalysis, aiming to secure the opposite regioisomer 1-123a. To our surprise, the reaction resulted in the formation of tetrahydro-1,2-oxazine 1-124aa instead of the anticipated isoxazolidine (1-123a, Scheme 1-28).

Scheme 1-28. Yb(OTf)_3-catalyzed reaction of nitrosobenzene (1-96a) with DA cyclopropane 1-122a.

Interestingly, the yield of the reaction was slightly below 50%, but rose to 87% when two equiv of cyclopropane were used. After additional experimentation, it appeared that the reaction was consuming two equiv of the cyclopropane. A plausible mechanism that accounts for the observed stoichiometry requirements shown in Scheme 1-29.
Scheme 1-29. Proposed mechanism for the formation of tetrahydro-1,2-oxazine 1-124aa.

As described in Scheme 1-29, the nitrogen of the nitrosobenzene (1-96a) opens the Yb(OTf)$_3$-activated DA cyclopropane 1-125 resulting in intermediate 1-126, which instead of undergoing ring closure to give the expected cycloadduct isoxazolidine 1-123a (Path A), expels dimethyl 2-methylene malonate (1-127a) producing nitrone 1-128a (Path B). This \textit{in situ} generated nitrone 1-128a then undergoes a well-known [3+3] cycloaddition with another equiv of Yb(OTf)$_3$-activated DA cyclopropane 1-125 to furnish tetrahydro-1,2-oxazine 1-124aa (see Section 1.1.2.1). Interestingly, no evidence of recombination of nitrone 1-128a and dimethyl 2-methylene malonate (1-127a) to form isoxazolidine 1-128a was observed. This could be due to the rapid polymerization of dimethyl 2-methylene malonate (1-127a) under Yb(OTf)$_3$ conditions.

In order to substantiate the proposed mechanism and gain insights into this unique reaction, a crossover experiment was designed with two similar cyclopropanes, 1-122a and 1-122b, with nitrosobenzene (1-96a, Scheme 1-30).
Scheme 1-30. Crossover experiment for the reaction of DA cyclopropanes, 1-122a and 1-122b, with nitrosobenzene (1-96a).

(Experiment was conducted by Tristan Chidley)

As expected, crossover products 1-124ba and 1-124ab were observed, supporting the formation of nitrone intermediates 1-128a and 1-128b (Scheme 1-30). These products were identical to standards independently synthesized from literature procedures.\textsuperscript{11c}

It is interesting to note that this remarkable transformation has a reasonable substrate scope and could be used as a general method for the synthesis of tetrahydro-1,2-oxazines (Table 1-10).\textsuperscript{13} Nitrosoarenes with halogen substituents resulted in good yields regardless of the position on the aryl ring (entries 2-4). Nitrosoarenes with a moderately
electron-withdrawing ketone (entry 5) or ester (entries 6-7) substituent were also found to be good reaction partners. Disappointingly, nitrosoarenes with strong electron-withdrawing (entry 8) or electron-donating (entry 9) substituent resulted in decomposition products. Finally, a thiophene-substituted cyclopropane 1-122c was also shown to be a suitable reaction partner (entry 10).
Table 1-10. Scope of the cascade reaction.

![Diagram](image)

1-122a, Ar\(^1\) = Ph
1-122c, Ar\(^1\) = 2-thienyl

<table>
<thead>
<tr>
<th>entry(^a)</th>
<th>Ar(^1)</th>
<th>Ar</th>
<th>time (h)</th>
<th>yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>1-96a, C(_6)H(_5)</td>
<td>13</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>1-96d, 3-C(_6)H(_4)Br</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>1-96b, 4-C(_6)H(_4)Br</td>
<td>24</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>1-96g, 3,4-C(_6)H(_3)Cl(_2)</td>
<td>12</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>1-96i, 3-C(_6)H(_4)C(O)Me</td>
<td>20</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>1-96r, 3-C(_6)H(_4)CO(_2)Et</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>1-96j, 4-C(_6)H(_4)CO(_2)Et</td>
<td>23</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>1-96k, 4-C(_6)H(_4)CN</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>1-96n, 4-C(_6)H(_4)OMe</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>2-thienyl</td>
<td>1-96a, C(_6)H(_5)</td>
<td>7</td>
<td>69</td>
</tr>
</tbody>
</table>

(Conducted in collaboration with Tristan Chidley)

\(^a\)Reaction conditions: To a solution of cyclopropane 1-122 and nitrosoarene 1-96 in (CH\(_2\))\(_2\)Cl\(_2\) at rt, was added Yb(OTf)\(_3\)·H\(_2\)O, and then heated at reflux for specified time.

\(^b\)Isolated yields.
With the mechanistic insight in hand, we began to reconsider the curious products isolated by the de Meijere group in GaCl₃-catalyzed cycloadditions of diazene derivatives with DA cyclopropanes. We believe that the unusual product 1-132aa formed from cis-diazene, 4-phenyl-1,2,4-triazoline-3,5-dione (1-130a, PTAD) and DA cyclopropane 1-129a might have resulted through a similar mechanism via azomethine imine intermediate 1-133a (Scheme 1-31).

Scheme 1-31. Proposed mechanism for de Meijere’s report on cycloaddition of cis-diazene 1-130a with GaCl₃-activated DA cyclopropane 1-129aa.

As depicted in Scheme 1-31, one of the nitrogens of PTAD 1-130a opens the GaCl₃-activated cyclopropane 1-129aa to form zwitterionic intermediate 1-131. This intermediate could then undergo either a cyclization to yield normal cycloadduct 1-132a (Path A) or fragment into azomethine imine 1-133a and diethyl 2 methylenemalonate (1-
134a, Path B). Recombination of these latter two fragments would provide the cycloadduct 1-132aa. To validate this hypothesized mechanism, a crossover experiment was designed with two similar cyclopropanes, 1-129a and 1-129d, with PTAD 1-130a (Scheme 1-32).\textsuperscript{72}

Scheme 1-32. Crossover experiment for the reaction of DA cyclopropanes, 1-129a and 1-129b, with *cis*-diazene 1-130a.

(Experiment was conducted by Tristan Chidley)
As anticipated, the reaction did yield crossover products 1-132ad, 1-132dd, 1-132aa, and 1-132da, thus providing strong evidence for the formation of azomethine imines 1-133a and 1-133d in the reaction. All of the crossover products were identical with standards independently synthesized from de Meijere’s method. The gas chromatogram in Figure 1-10 shows relative ratios of all six products in the crude mixture of a representative crossover experiment.

![Chemical Structures]

**Figure 1-10.** Gas chromatogram of the crude product of crossover experiment of cycloaddition of DA cyclopropanes, 1-129a and 1-129d, with cis-diazene 1-130a.

In summary, we discovered a cascade process in reactions of DA cyclopropanes with nitrosoarenes. The reaction results in tetrahydro-1,2-oxazines *via* nitrone intermediates in good to excellent yields as single diastereomers. Mechanistic insights gained by crossover experiments on this unique transformation enabled a better rationale
for peculiar products formed in GaCl₃-catalyzed cycloaddition of PTAD with DA cyclopropanes. As the chemistry of DA cyclopropanes is constantly expanding, we believe this mechanistic observation serves as a caution for the cascade processes. Additionally, this study reveals new opportunities for reaction design in DA cyclopropane chemistry.
1.2.2 The [4+2] Cycloaddition of AACDs with cis-Diazenes

Diazenes are well-known in the literature largely for use as dienophiles for hetero Diels-Alder chemistry. Also, diazenes are competent dipolarophiles in GaCl₃-catalyzed [3+2] cycloadditions with DA cyclopropanes furnishing pyrazolidine derivatives **1-135** (eq 1, Scheme 1-33). Given this precedent, and our ongoing interest in DA cyclobutane chemistry (see Section 1.1.3.3), we sought to access hexahydropyridazines **1-136** through Lewis acid-catalyzed [4 + 2] cycloaddition of AACDs and diazenes (eq 2, Scheme 1-33). The resulting hexahydropyridazine derivatives are of interest for their prevalence in biologically relevant and structurally interesting molecules (Figure 1-11).

**Scheme 1-33.** Cycloaddition of diazenes with DA cyclopropanes and DA cyclobutanes.
Figure 1-11. Representative examples of hexahydropyridazine core in synthetic pharmaceuticals and natural products.

In collaboration with fellow graduate student Tristan Chidley, we began our studies by examining the reactivity of AACD 1-67b with commercially available trans-diazenes diethyl azodicarboxylate (DEAD) and azobenzene, with either Yb(OTf)₃ or GaCl₃ catalysis with a variety of conditions, but unfortunately these attempts only resulted in slow decomposition of AACD 1-67b. Fortunately, the cis-diazene PTAD (1-130a) was found to engage in cycloaddition to yield hexahydropyridazine 1-136b as a single diastereomer albeit in poor yield (Scheme 1-34).

Scheme 1-34. Cycloaddition of cis-diazene 1-130a with AACD 1-67b.
Quick optimization established 5 mol % GaCl₃ as optimal to catalyze the reaction (Table 1-11). With the optimal conditions in hand, we then investigated the scope of the reaction using PTAD 1-130a and a variety of AACDs (Table 1-11).

**Table 1-11.** The [4+2] cycloaddition of *cis*-diazene 1-130a with AACDs.

![Reaction Scheme]

**Reaction conditions:** To a solution of cyclobutane 1-67 (0.40 mmol, 2.0 equiv) and PTAD 1-130a (0.20 mmol, 1.0 equiv) in DCE (2 mL) at rt was added a solution of GaCl₃ (0.01 mmol, 0.05 equiv) in DCE (1 mL) and stirred until 1-130a was fully consumed (by TLC).

The pyran-fused cyclobutane 1-67a resulted in a 78% isolated yield while the ethoxy substituted cyclobutane 1-67f afforded hexahydropyridazine in 90% yield. Densely functionalized cyclobutanes 1-67g and 1-67l also caused excellent conversions
to hexahydropyridazines 1-136g and 1-136l respectively. Finally, an aryl substituted cyclobutane 1-67h was also found to engage in the cycloaddition.

Due to thermal instability and short shelf-life of the other reported cis-diazenes, we were unable to expand the scope of the reaction to additional cis-diazenes.

Fortuitously, X-ray quality crystals of cycloadduct 1-136a (Table 1-11) were obtained and the ORTEP structure depicted in Figure 1-12.78 The crystal structure shows the relative cis stereochemistry at the ring fusion.

![ORTEP structure of hexahydropyridazine 1-136a.](image)

**Figure 1-12. ORTEP structure of hexahydropyridazine 1-136a.**

In summary, we have developed the first example of a [4+2] cycloaddition between AACDs and cis-diazene. The relative cis stereochemistry at ring fusion has been assigned based on nOe correlations and confirmed by single crystal X-ray diffraction. The reaction proceeds smoothly with alkoxy activated cyclobutanes as well as aryl activated cyclobutanes to form hexahydropyridazines in good to excellent yields.
1.2.3 Spiroketals from AACDs

Spiroketals are abundant substructures of natural products from many sources, including but not limited to, insects, microbes, plants, fungi, and marine organisms (Figure 1-13).\textsuperscript{79} Interesting pharmacological properties of these compounds resulted in significant research in both their synthesis and chemical reactivity.\textsuperscript{80}

![Figure 1-13. Representative examples of spiroketal-containing natural products.](image)

Two of the most common strategies towards the synthesis of spiroketals is acid-catalyzed dehydration of dihydroxy ketones (eq 1, Scheme 1-35)\textsuperscript{79e} and transition metal-mediated cyclizations of internal alkynes (eq 2, Scheme 1-35).\textsuperscript{81} Although these methods efficiently construct spiroketals, additional methods would be desirable for regio- and stereoselective synthesis of spiroketals.
Recently, our group reported a cycloaddition between AACDs and a wide range of aldehydes under Yb(OTf)$_3$ catalysis to generate fused acetals with exclusive cis-stereochemistry (see Section 1.1.3.3.1). Now we anticipated that the same chemistry could be applied to spirocyclic AACDs to efficiently access spiroketals (Scheme 1-36).

**Scheme 1-36.** Proposed synthesis of spiroketals from spirocyclic AACDs.

We set out to synthesize the spirocyclic AACDs under previously successful conditions with AACDs (see Section 1.1.3.2). The required enol ethers were prepared from β-elimination of corresponding chloroethyl ethers using literature procedures.$^{82}$ Initial investigation established 5 mol % of Zn(OTf)$_2$ at -78 °C in dichloromethane as the
best conditions for this reaction (Scheme 1-37). Nevertheless, both preventing the formation of the decomposition product 1-149a in the reaction or purification of the product 1-143a turned out to be insurmountable and ultimately partially purified product 1-143a was carried forwarded to the next step.\textsuperscript{83}

![Scheme 1-37. Synthesis of spirocyclic ACD 1-143a.](image)

In order to examine the proposed synthesis of spiroketals, we tested the reactivity of partially purified 1-143a with benzaldehyde (1-150a) under Yb(OTf)\textsubscript{3} conditions. Satisfyingly the reaction did produce the spiroketal as a single diastereomer in moderate 45\% yield (Scheme 1-38).

![Scheme 1-38. Synthesis of spiroketal 1-145a via a [4+2] cycloaddition of ACD 1-143a and benzaldehyde (1-150a).](image)

In summary, we accomplished the spiroketal 1-145a synthesis from spirocyclic ACD 1-143a. Although the yield is moderate, this result serves as a proof of concept.
Efforts are now underway to isolate the AACD 1-43a in pure form to further optimize the reaction conditions and to examine the reaction scope.
1.3 Conclusions and Outlook

In summary, we have developed the first example of a [4+2] cycloaddition between DA cyclobutanes and nitrosoarenes. The regiochemistry and relative stereochemistry of the cycloadducts have been assigned based on $^1$H-$^{15}$N HMBC spectroscopy and confirmed by single crystal X-ray diffraction. The reaction proceeds well with electron neutral and deficient nitrosoarenes to form tetrahydro-1,2-oxazines. We have also discovered the formation of unexpected pyrrolidine products in the MgI$_2$ promoted [4+2] cycloaddition between DA cyclobutanes and electron-rich nitrosoarenes. Furthermore, a procedure to make pyrrolidines from tetrahydro-1,2-oxazines was reported. The regiochemistry and stereochemistry of the unexpected pyrrolidine product has been unambiguously assigned by single-crystal X-ray diffraction. Future work includes mechanistic insights into the unexpected formation of pyrrolidines, and to further increase the efficiency of this transformation. In short, the reaction of DA cyclobutanes and nitrosoarenes could be used as a general method to access either tetrahydro-1,2-oxazine or pyrrolidine products, depending on the electronics of the nitrosoarenes.

A cascade process was discovered in Yb(OTf)$_3$-catalyzed reactions of nitrosoarenes with DA cyclopropanes. The reaction underwent a tandem ring-opening, elimination, and cyclization sequence to form tetrahydro-1,2-oxazines via nitrone intermediates in good to excellent yields as single diastereomers. Mechanistic insights gained by crossover experiments on this unique transformation enabled a better rationale for peculiar products formed in GaCl$_3$-catalyzed cycloaddition of cis-diazene PTAD with DA cyclopropanes. Overall, this study serves as a warning for the cascade processes in DA cyclopropane chemistry and reveals new opportunities for reaction design.
We have also developed the first example of a [4+2] cycloaddition between AACDs and cis-diazenes. The relative cis stereochemistry of the cycloadducts has been assigned based on single crystal X-ray diffraction. The reaction proceeds efficiently with all the AACDs investigated to form hexahydropyridazines in good to excellent yields, suggesting the potential use as a general method. Expansion of the substrate scope to additional cis-diazenes and application towards the synthesis of synthetic pharmaceutical Pralnacasan are currently under investigation.

Finally, we demonstrated the application of spirocyclic AACC in spiroketal synthesis. Although, we only disclosed one example, this serves as a proof of concept to motivate further studies.

To conclude, exploitation of ring strain in carbocycles to generate dipolar intermediates for cycloaddition chemistry, has become an efficient strategy in modern organic synthesis. Despite the plethora of discoveries already made in DA cyclopropane chemistry, there are still opportunities for new chemistries to uncover (such as the cascade reaction we discovered). On the other hand, the long ignored DA cyclobutanes has only recently garnered attention. Regardless of the reactions disclosed, elaboration of these cycloaddition adducts remains to be exploited for the synthesis of complex natural products. Overall, the chemistry of DA cyclobutanes is only in its infancy and further investigation will surely benefit the synthetic community.
1.4 Experimental

1.4.1 General Considerations

All reactions were run under argon atmosphere unless otherwise indicated. Flasks were oven dried at approximately 120 °C and cooled in a dessicator prior to use. Solvents and reagents were purified by standard methods.\(^{84}\) Yb(OTf)\(_3\) used as mono hydrate as obtained from Sigma-Aldrich\(^\circledR\). All other chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. The progress of reactions were monitored by thin layer chromatography (TLC) performed on F254 silica gel plates. The plates were visualized by UV light (254 nm) or by staining with ceric ammonium molybdate (CAM). Column chromatography was performed with Silica Flash P60 60 Å silica gel from SiliCycle\(^\circledR\) according to the Still method.\(^{85}\)

The \(^1\)H and \(^{13}\)C NMR data were obtained on either 400 or 600 MHz spectrometers. All spectra were obtained in deuterated chloroform and were referenced to the residual chloroform at 7.26 ppm for \(^1\)H spectra and the center signal of the triplet at 77.0 ppm for \(^{13}\)C spectra. Scalar coupling was eliminated from nOe experiments by using acquisition delays of 500 ms. Electron ionization mass spectra were obtained on a Finnigan MAT 8400 spectrometer at an ionizing voltage of 70 eV. GC/MS analyses of the samples were performed on a Shimadzu GCMS-QP2010 Chromatography-Ion trap mass spectrometer. A DB-5MS (J&W Scientific) (30 m X 0.25 mm i.d. and 0.25 (m film thickness) capillary column was used; carrier gas helium (1 mL/min). Temperature program for the oven: 200 °C (3 min), 320 °C at 6 °C/min. Ion source temp 250 °C; interface temp 250 °C; solvent cut time 0.5 min; time 2-28 min; scan, m/z 45-600. The microwave reaction was conducted in an Initiator reactor from Biotage\(^\circledR\).
1.4.2 Cycloadditions of AACDs and Nitrosoarenes

Nitrosoarenes, which are not commercially available, were prepared from the corresponding anilines according to literature methods.\textsuperscript{86} AACDs were prepared according to the literature procedure, except 5 mol % of Zn(OTf)\textsubscript{2} was used instead of 10 mol % Yb(OTf)\textsubscript{3}.\textsuperscript{87}

General Cycloaddition Procedure A

To a mixture of nitrosoarene (0.30 mmol, 1.0 equiv) and Yb(OTf)\textsubscript{3}·H\textsubscript{2}O (4 mg, 0.006 mmol, 2 mol %) in CH\textsubscript{2}Cl\textsubscript{2} (3 mL) at rt was added cyclobutane (0.36 mmol, 1.2 equiv). After complete consumption of the nitrosoarene (as indicated by TLC) the reaction mixture (RM) was layered directly onto a silica gel column and purified by flash chromatography (0-25% EtOAc/hexanes).

General Cycloaddition Procedure B

To a stirred solution of MgI\textsubscript{2} (41.5 mg, 0.15 mmol, 50 mol %) in CH\textsubscript{2}Cl\textsubscript{2} (3 mL) at 0 °C was added nitrosoarene (0.30 mmol, 1.0 equiv) followed by cyclobutane (0.36 mmol, 1.2 equiv). After complete consumption of the nitrosoarene (as indicated by TLC) the RM was layered directly onto a silica gel column and purified by flash chromatography (0-25% EtOAc/hexanes).

Compounds 1-97b, 1-97f, 1-97h, and 1-97m were prepared either by Andrew C. Stevens (Ph.D. 2013) or Tyler B. Schon (B.Sc. 2011) and are not shown below.
Characterization Data

![Chemical Structure](image)

**Compound 1-97a**

The title compound was prepared according to the general cycloaddition procedure A to afford pale yellow oil (96 mg, 92%).

\[ R_f = 0.27 \text{ (30\% EtOAc/hexanes).} \]

\[^1H\text{ NMR (400 MHz, CDCl}_3\delta 7.26 - 7.35 (m, 4 H), 6.97 - 7.02 (m, 1 H), 5.44 (d, J = 5.9 Hz, 1 H), 4.25 - 4.33 (m, 2 H), 4.15 - 4.24 (m, 2 H), 4.09 (td, J = 6.8, 8.5 Hz, 1 H), 3.93 (td, J = 3.9, 8.2 Hz, 1 H), 2.80 - 2.90 (m, 1 H), 2.60 (dd, J = 6.6, 14.1 Hz, 1 H), 2.16 (dq, J = 8.2, 12.7 Hz, 1 H), 2.04 (dd, J = 8.6, 14.1 Hz, 1 H), 1.83 - 1.92 (m, 1 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.18 (t, J = 7.2 Hz, 3 H).} \]

\[^13C\text{ NMR (101 MHz, CDCl}_3\delta 167.9, 167.6, 146.7, 128.5, 123.0, 117.5, 88.6, 83.6, 67.0, 62.2, 62.0, 33.3, 30.6, 29.6, 14.0, 13.9.} \]

**HRMS (m/z):** 349.1525 (calcd for C\textsubscript{18}H\textsubscript{23}NO\textsubscript{6}, 349.1525).

![Chemical Structure](image)

**Compound 1-97c**

The title compound was prepared according to the general cycloaddition procedure A to afford colorless oil (109 mg, 93%).
\( R_f = 0.30 \) (30% EtOAc/hexanes).

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.21 - 7.29 (m, 4 H), 5.37 (d, \( J = 5.9 \) Hz, 1 H), 4.14 - 4.33 (m, 4 H), 4.05 - 4.10 (m, 1 H), 3.92 (td, \( J = 8.3, 3.8 \) Hz, 1 H), 2.80 - 2.88 (m, 1 H), 2.58 (dd, \( J = 14.1, 6.4 \) Hz, 1 H), 2.15 (dq, \( J = 12.4, 8.2 \) Hz, 1 H), 2.07 (dd, \( J = 14.1, 8.2 \) Hz, 1 H), 1.85 - 1.92 (m, 1 H), 1.28 (t, \( J = 7.3 \) Hz, 3 H), 1.18 (t, \( J = 7.0 \) Hz, 3 H).

\(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 167.7, 167.5, 145.4, 128.5, 128.1, 118.9, 88.7, 83.6, 67.1, 62.2, 62.1, 33.4, 30.5, 29.4, 14.0, 14.0.

HRMS (m/z): 383.1128 (calcd for C\(_{18}\)H\(_{22}\)ClNO\(_6\), 383.1136).

**Compound 1-97d**

The title compound was prepared according to the general cycloaddition procedure A to afford a colorless thick mass (112 mg, 87%).

\( R_f = 0.32 \) (30% EtOAc/hexanes).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.52 - 7.55 (m, 1 H), 7.17 - 7.23 (m, 1 H), 7.10 - 7.14 (m, 2 H), 5.40 (d, \( J = 5.9 \) Hz, 1 H), 4.25 - 4.36 (m, 2 H), 4.16 - 4.25 (m, 2 H), 4.09 (td, \( J = 8.3, 6.8 \) Hz, 1 H), 3.93 (td, \( J = 8.2, 3.9 \) Hz, 1 H), 2.78 - 2.90 (m, 1 H), 2.60 (dd, \( J = 14.3, 6.5 \) Hz, 1 H), 2.04 - 2.21 (m, 2 H), 1.84 - 1.93 (m, 1 H), 1.30 (t, \( J = 7.0 \) Hz, 3 H), 1.21 (t, \( J = 7.2 \) Hz, 3 H).

\(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 167.7, 167.4, 147.9, 129.8, 125.7, 122.5, 120.5, 115.5, 88.5, 83.6, 67.2, 62.3, 62.2, 33.3, 30.5, 29.3, 14.0, 13.9.

HRMS (m/z): 427.0621 (calcd for C\(_{18}\)H\(_{22}\)BrNO\(_6\), 427.0631).
The title compound was prepared according to the general cycloaddition procedure A to afford pale yellow color oil (111 mg, 95%).

\[ R_f = 0.30 \) (30% EtOAc/hexanes).

\[^1\text{H NMR}\] (600 MHz, CDCl\(_3\)) \( \delta \) 7.38 - 7.41 (m, 1 H), 7.14 - 7.22 (m, 2 H), 6.97 (dd, \( J = 7.6, 1.8 \) Hz, 1 H), 5.42 (d, \( J = 5.9 \) Hz, 1 H), 4.26 - 4.36 (m, 2 H), 4.16 - 4.26 (m, 2 H), 4.07 - 4.13 (m, 1 H), 3.94 (td, \( J = 8.2, 4.1 \) Hz, 1 H), 2.82 - 2.89 (m, 1 H), 2.61 (dd, \( J = 14.1, 6.4 \) Hz, 1 H), 2.16 (dq, \( J = 12.6, 8.1 \) Hz, 1 H), 2.10 (dd, \( J = 14.1, 7.6 \) Hz, 1 H), 1.87 - 1.94 (m, 1 H), 1.31 (t, \( J = 7.0 \) Hz, 3 H), 1.21 (t, \( J = 7.0 \) Hz, 3 H).

\[^{13}\text{C NMR}\] (101 MHz, CDCl\(_3\)) \( \delta \) 167.7, 167.5, 147.9, 134.4, 129.5, 122.8, 117.8, 115.1, 88.6, 83.7, 67.2, 62.3, 62.2, 33.4, 30.5, 29.3, 14.0, 13.9.

\text{HRMS (m/z):} 383.1132 (calcd for C\(_{18}\)H\(_{22}\)ClNO\(_6\), 383.1136).

The title compound was prepared according to the general cycloaddition procedure A to afford a pale yellow color paste (114 mg, 91%).

\[ R_f = 0.25 \) (30% EtOAc/hexanes).
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, $J$ = 2.3 Hz, 1 H), 7.32 (d, $J$ = 8.8 Hz, 1 H), 7.15 (dd, $J$ = 8.8, 2.3 Hz, 1 H), 5.37 (d, $J$ = 6.4 Hz, 1 H), 4.26 - 4.35 (m, 2 H), 4.17 - 4.26 (m, 2 H), 4.06 - 4.11 (m, 1 H), 3.94 (td, $J$ = 8.3, 4.4 Hz, 1 H), 2.81 - 2.89 (m, 1 H), 2.59 (dd, $J$ = 14.1, 6.4 Hz, 1 H), 2.09 - 2.20 (m, 2 H), 1.87 - 1.94 (m, 1 H), 1.31 (t, $J$ = 7.3 Hz, 3 H), 1.22 (t, $J$ = 7.0 Hz, 3 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.6, 167.3, 146.3, 132.4, 130.0, 126.0, 119.5, 116.6, 88.7, 83.7, 67.3, 62.4, 62.2, 33.5, 30.4, 29.2, 14.0, 14.0.

HRMS (m/z): 417.0737 (calcd for C$_{18}$H$_{21}$Cl$_2$NO$_6$, 417.0746).

The title compound was prepared according to the general cycloaddition procedure A to afford pale yellow colored oil (103 mg, 87%).

R$_f$ = 0.39 (30% EtOAc/hexanes, double elution).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.87 - 7.91 (m, 1 H), 7.55 - 7.62 (m, 2 H), 7.34 - 7.41 (m, 1 H), 5.49 (d, $J$ = 5.9 Hz, 1 H), 4.25 - 4.35 (m, 2 H), 4.20 (q, $J$ = 7.0 Hz, 2 H), 4.05 - 4.13 (m, 1 H), 3.94 (td, $J$ = 8.4, 3.9 Hz, 1 H), 2.81 - 2.92 (m, 1 H), 2.59 - 2.65 (m, 1 H), 2.58 (s, 3 H), 2.02 - 2.23 (m, 2 H), 1.84 - 1.95 (m, 1 H), 1.30 (t, $J$ = 7.0 Hz, 3 H), 1.18 (t, $J$ = 5.9 Hz, 3 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 198.0, 167.7, 167.4, 147.1, 137.5, 128.8, 122.9, 122.1, 117.0, 88.6, 83.7, 67.1, 62.3, 62.1, 33.3, 30.5, 29.4, 26.7, 14.0, 13.9.

HRMS (m/z): 391.1636 (calcd for C$_{20}$H$_{25}$NO$_7$, 391.1631).
The title compound was prepared according to the general cycloaddition procedure A to afford pale yellow oil (104 mg, 76%).

$R_f = 0.21$ (30% EtOAc/hexanes).

$^1H$ NMR (600 MHz, CDCl$_3$) $\delta$ 7.95 - 7.98 (m, 2 H), 7.31 - 7.34 (m, 2 H), 5.55 (d, $J = 5.9$ Hz, 1 H), 4.27 - 4.36 (m, 4 H), 4.15 - 4.24 (m, 2 H), 4.08 - 4.13 (m, 1 H), 3.94 (td, $J = 8.2$, 4.1 Hz, 1 H), 2.84 - 2.91 (m, 1 H), 2.63 (dd, $J = 14.1$, 6.5 Hz, 1 H), 2.17 (dq, $J = 12.6$, 8.1 Hz, 1H), 2.11 (dd, 14.4, 7.9 Hz, 1H), 1.88 - 1.94 (m, 1 H), 1.37 (t, $J = 7.3$ Hz, 3 H), 1.31 (t, $J = 7.0$ Hz, 3 H), 1.15 - 1.18 (m, 3 H).

$^{13}C$ NMR (101 MHz, CDCl$_3$) $\delta$ 167.6, 167.2, 166.4, 150.4, 130.3, 124.2, 115.8, 88.0, 83.6, 67.2, 62.3, 62.1, 60.5, 33.1, 30.5, 29.2, 14.3, 13.9, 13.9.

HRMS ($m/z$): 421.1742 (calcd for C$_{18}$H$_{23}$NO$_6$, 421.1737).

The title compound was prepared according to the general cycloaddition procedure A to afford a cream colored solid (67 mg, 46%).

$R_f = 0.22$ (30% EtOAc/hexanes).
\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.55 - 7.58 (m, 2 H), 7.37 - 7.40 (m, 2 H), 5.52 (d, \(J = 5.9\) Hz, 1 H), 4.27 - 4.36 (m, 2 H), 4.16 - 4.25 (m, 2 H), 4.07 - 4.12 (m, 1 H), 3.94 (td, \(J = 8.2, 4.1\) Hz, 1 H), 2.85 - 2.92 (m, 1 H), 2.61 (dd, \(J = 14.7, 6.5\) Hz, 1 H), 2.14 - 2.22 (m, 2 H), 1.90 - 1.96 (m, 1 H), 1.31 (t, \(J = 7.0\) Hz, 3 H), 1.18 (t, \(J = 7.0\) Hz, 3 H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.4, 167.0, 150.2, 132.8, 119.3, 116.6, 105.1, 87.9, 83.7, 67.4, 62.5, 62.3, 33.3, 30.4, 29.0, 14.0, 13.9.

HRMS \((m/z)\): 374.1482 (calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_6\), 374.1478).

![Compound 1-98k](image)

The title compound was isolated as a byproduct along with 1-97k as yellow oil (22 mg, 15%).

R\(_f\) = 0.22 (30% EtOAc/hexanes).

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.46 - 7.50 (m, 2 H), 7.09 - 7.13 (m, 2 H), 5.57 (d, \(J = 5.3\) Hz, 1 H), 4.28 (q, \(J = 7.0\) Hz, 2 H), 4.10 - 4.21 (m, 3 H), 4.02 (td, \(J = 8.2, 3.5\) Hz, 1 H), 2.65 - 2.70 (m, 1 H), 2.60 - 2.65 (m, 1 H), 2.54 - 2.59 (m, 1 H), 2.08 - 2.18 (m, 1 H), 1.87 - 1.94 (m, 1 H), 1.25 (t, \(J = 7.0\) Hz, 3 H), 1.13 (t, \(J = 7.3\) Hz, 3 H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.2, 168.2, 150.6, 132.4, 119.5, 116.0, 104.9, 104.0, 72.9, 68.7, 62.7, 62.4, 35.4, 33.0, 29.6, 13.9, 13.8.

HRMS \((m/z)\): 374.1489 (calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_6\), 374.1478).
The title compound was prepared according to the general cycloaddition procedure A to afford a yellow solid (56 mg, 47%).

\( R_f = 0.19 \) (30% EtOAc/hexanes).

\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.14 - 8.20 (m, 2 H), 7.38 - 7.42 (m, 2 H), 5.58 (d, \( J = 6.3 \) Hz, 1 H), 4.28 - 4.36 (m, 2 H), 4.17 - 4.24 (m, 2 H), 4.11 (q, \( J = 7.9 \) Hz, 1 H), 3.95 (td, \( J = 8.2, 4.3 \) Hz, 1 H), 2.86 - 2.94 (m, 1 H), 2.63 (dd, \( J = 14.1, 6.3 \) Hz, 1 H), 2.15 - 2.24 (m, 2 H), 1.91 - 1.98 (m, 1 H), 1.32 (t, \( J = 7.2 \) Hz, 3 H), 1.18 (t, \( J = 7.0 \) Hz, 3 H).

\( ^13C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \) 167.3, 167.0, 152.0, 142.3, 124.7, 115.8, 88.0, 83.7, 67.5, 62.6, 62.4, 33.4, 30.3, 28.9, 14.0, 13.9.

HRMS (m/z): 394.1377 (calcd for C\(_{18}\)H\(_{22}\)N\(_2\)O\(_8\), 394.1376).

The title compound was isolated as a byproduct along with \textbf{1-97l} as yellow colored oil (14 mg, 12%).

\( R_f = 0.19 \) (30% EtOAc/hexanes).

\( ^1H \) NMR (600 MHz, CDCl\(_3\)) \( \delta \) 8.08 - 8.11 (m, 2 H), 7.05 - 7.09 (m, 2 H), 5.59 (d, \( J = 5.3 \) Hz, 1 H), 4.26 - 4.34 (m, 2 H), 4.17 - 4.23 (m, 2 H), 4.10 - 4.15 (m, 1 H), 4.04 (td, \( J = \)}
8.2, 3.5 Hz, 1 H), 2.63 - 2.69 (m, 2 H), 2.54 - 2.58 (m, 1 H), 2.10 - 2.18 (m, 1 H), 1.88 - 1.92 (m, 1 H), 1.27 (t, J = 7.0 Hz, 3 H), 1.15 (t, J = 7.0 Hz, 3 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.8, 167.8, 152.0, 140.9, 124.3, 114.2, 105.0, 72.4, 68.5, 62.8, 62.5, 35.3, 32.9, 29.7, 13.8, 13.7.

HRMS (m/z): 394.1377 (calcd for C$_{18}$H$_{22}$N$_2$O$_8$, 394.1376).

**Compound 1-98n**

The title compound was prepared according to the general cycloaddition procedure B to afford a pale yellow paste (30 mg, 26%).

$R_f$ = 0.41 (50% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.24 – 7.26 (m, 2 H), 6.75 – 6.77 (m, 2 H), 5.55 (d, J = 5.3 Hz, 1 H), 4.20 – 4.24 (m, 1 H), 4.15 – 4.19 (m, 1 H), 4.07 – 4.13 (m, 2 H), 4.01 – 4.06 (m, 1 H), 3.96 (td, J = 8.1, 5.0 Hz, 1 H), 3.76 (s, 3 H), 2.61 – 2.72 (m, 2 H), 2.50 – 2.57 (m, 1 H), 2.01 – 2.09 (m, 1 H), 1.95 (dq, J = 12.2, 6.3 Hz, 1 H), 1.14 (t, J = 7.0 Hz, 3 H), 1.10 (t, J = 7.0 Hz, 3 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.0, 168.8, 156.6, 140.7, 122.7, 113.0, 104.5, 74.3, 68.8, 61.9, 61.6, 55.4, 35.1, 32.3, 28.9, 13.8, 13.8.

HRMS (m/z): 379.1635 (calcd for C$_{19}$H$_{25}$NO$_7$, 379.1631).
To a stirred solution of MgI$_2$ (44 mg, 0.16 mmol, 0.5 equiv) in 10 mL CH$_2$Cl$_2$ at rt was added 1-98n (120 mg, 0.32 mmol). The RM was stirred for about 18 h at rt (complete consumption of starting material by TLC) then the RM was layered directly onto a silica gel column and purified by flash chromatography (0-25% EtOAc/hexanes) to a brown oil (57 mg, 50%).

$R_f = 0.37$ (50% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.90 – 6.94 (m, 2 H), 6.75 – 6.78 (m, 2 H), 5.62 (d, $J = 5.9$ Hz, 1 H), 4.15 – 4.25 (m, 4 H), 3.91 – 4.00 (m, 2 H), 3.74 (s, 3 H), 3.00 – 3.07 (m, 1 H), 2.70 (dd, $J = 12.9$, 8.8 Hz, 1 H), 2.39 (dd, $J = 13.5$, 8.8 Hz, 1 H), 2.00 – 2.08 (m, 1 H), 1.72 (dd, $J = 12.6$, 5.0 Hz, 1 H), 1.21 (t, $J = 7.3$ Hz, 3 H), 1.18 (t, $J = 7.3$ Hz, 3 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.7, 169.9, 153.4, 138.3, 117.6, 113.9, 98.6, 74.8, 65.5, 61.8, 61.8, 55.5, 40.6, 40.1, 32.0, 14.0, 14.0.

HRMS ($m/z$): 363.1692 (calcd for C$_{19}$H$_{25}$NO$_6$, 363.1682).

The title compound was isolated in trace amount along with 1-101n as a pale brown oil.

$R_f = 0.24$ (70% hexanes/EtOAc).
$^1$H NMR (600 MHz, CDCl$_3$) δ 6.75 – 6.72 (m, 2 H), 6.65 – 6.62 (m, 2 H), 4.89 (s, 1 H), 4.29 – 4.15 (m, 5 H), 4.06 (ddd, $J = 11.2$, 9.1, 6.2 Hz, 1 H), 3.72 (s, 3 H), 3.09 (dd, $J = 15.3$, 3.5 Hz, 1 H), 2.67 – 2.60 (m, 1 H), 2.44 (dd, $J = 15.3$, 10.0 Hz, 1 H), 2.34 – 2.27 (m, 1 H), 1.78 (qd, $J = 11.7$, 8.8 Hz, 1 H), 1.21 – 1.16 (m, 6 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 178.8, 169.9, 169.2, 153.3, 137.5, 116.9, 114.7, 67.9, 66.4, 62.5, 55.5, 35.2, 33.7, 29.7, 13.9.

HRMS ($m/z$): 379.1639 (calcd for C$_{19}$H$_{25}$NO$_7$, 379.1631).

Compound 1-101o

The title compound was prepared according to the general cycloaddition procedure B at rt for 4 h to afford a yellow colored oil (25 mg, 22%).

$R_f = 0.33$ (40% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$) δ 6.90 – 6.94 (m, 2 H), 6.66 – 6.70 (m, 2 H), 5.62 (d, $J = 5.9$ Hz, 1 H), 4.13 – 4.24 (m, 4 H), 3.91 – 3.98 (m, 2 H), 2.99 – 3.06 (m, 1 H), 2.82 (s, 6 H), 2.68 (dd, $J = 13.5$, 8.8 Hz, 1 H), 2.37 (dd, $J = 13.2$, 8.5 Hz, 1 H), 1.98 – 2.06 (m, 1 H), 1.70 (dd, $J = 12.6$, 4.4 Hz, 1 H), 1.15 – 1.21 (m, 6 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.9, 170.0, 145.3, 136.0, 118.2, 114.3, 98.7, 74.8, 65.4, 61.7, 61.6, 41.7, 40.5, 40.0, 32.2, 14.0, 14.0.

HRMS ($m/z$): 376.2044 (calcd for C$_{20}$H$_{28}$N$_2$O$_5$, 376.1998).
**Compound 1-107k**

The title compound was prepared along with 1-98k according to the general cycloaddition procedure B, employing MgI₂ (10 mol %) at rt for 2 h to afford a pale brown solid (15 mg, 13%).

\[ R_f = 0.44 \text{ (30\% EtOAc/hexanes).} \]

\(^1\text{H NMR}\ (600\text{MHz, CDCl}_3) \delta 7.60 - 7.63 (m, 2\text{H}), 7.54 - 7.59 (m, 2\text{H}), 4.22 - 4.34 (m, 5\text{H}), 4.06 - 4.15 (m, 2\text{H}), 2.98 (dd, J = 12.9, 3.5 Hz, 1\text{H}), 2.24 - 2.32 (m, 1\text{H}), 2.19 - 2.24 (m, 1\text{H}), 1.87 (t, J = 12.9 Hz, 1\text{H}), 1.70 - 1.79 (m, 1\text{H}), 1.30 (t, J = 7.0 Hz, 3\text{H}), 1.24 (t, J = 7.0 Hz, 3\text{H}).

\(^{13}\text{C NMR}\ (101\text{MHz, CDCl}_3) \delta 167.0, 166.2, 151.9, 132.5, 119.4, 119.2, 107.2, 94.5, 84.0, 67.7, 62.6, 62.3, 41.4, 34.1, 27.9, 14.0, 14.0.

**HRMS (m/z):** 374.1480 (calcd for C\(_{19}\)H\(_{22}\)N\(_2\)O\(_6\), 374.1478).

**Compound 1-98p**

The title compound was prepared according to the general cycloaddition procedure B at rt for 2 h to afford a yellow syrup (30 mg, 28%).

\[ R_f = 0.34 \text{ (30\% EtOAc/hexanes).} \]
$^1$H NMR (600 MHz, CDCl$_3$) δ 8.01 – 8.04 (m, 1 H), 7.55 – 7.60 (m, 1 H), 7.19 – 7.23 (m, 1 H), 6.75 – 6.79 (m, 1 H), 5.58 (d, $J = 4.7$ Hz, 1 H), 4.22 – 4.32 (m, 2 H), 4.19 (q, $J = 7.0$ Hz, 1 H), 4.10 – 4.17 (m, 1 H), 3.93 (q, $J = 8.0$ Hz, 1 H), 2.68 – 2.77 (m, 2 H), 2.53 – 2.60 (m, 1 H), 1.98 – 2.10 (m, 2 H), 1.22 – 1.27 (m, 3 H), 1.13 – 1.17 (m, 3 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.9, 168.7, 159.3, 145.6, 137.5, 116.7, 109.8, 104.1, 69.9, 69.1, 62.0, 61.6, 36.1, 31.8, 27.6, 13.8, 13.7.

HRMS (m/z): 350.1470 (calcd for C$_{17}$H$_{22}$N$_2$O$_6$, 350.1478).

The title compound was prepared according to the general cycloaddition procedure B, employing MgI$_2$ (10 mol %) at rt for 4 h to afford a pale yellow oil (28 mg, 19%).

$R_f =$ 0.29 (30% EtOAc/hexanes).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.94 (d, $J = 8.6$ Hz, 1 H), 7.52 (d, $J = 3.5$ Hz, 1 H), 7.50 (d, $J = 2.3$ Hz, 1 H), 7.26 (dd, $J = 9.0$, 2.3 Hz, 1 H), 6.47 (d, $J = 3.5$ Hz, 1 H), 5.60 (d, $J = 5.5$ Hz, 1 H), 3.94 – 4.28 (m, 6 H), 2.64 – 2.77 (m, 2 H), 2.51 – 2.62 (m, 1 H), 2.02 – 2.13 (m, 1 H), 1.92 – 2.02 (m, 1 H), 1.65 (s, 9 H), 1.12 (t, $J = 7.0$ Hz, 3 H), 1.04 (t, $J = 7.0$ Hz, 3 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.0, 168.9, 142.9, 130.1, 126.1, 118.0, 114.1, 112.9, 107.5, 104.5, 83.4, 74.4, 68.8, 62.0, 61.6, 35.3, 32.6, 29.0, 28.2, 13.8, 13.7.

HRMS (m/z): 488.2153 (calcd for C$_{25}$H$_{32}$N$_2$O$_8$, 488.2159).
The title compound was prepared according to the general cycloaddition procedure A for 4 h to afford a pale yellow solid (50 mg, 45%).

R<sub>f</sub> = 0.25 (30% EtOAc/hexanes).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.22 – 7.31 (m, 4 H), 7.00 (t, J = 7.0 Hz, 1 H), 4.88 (d, J = 2.9 Hz, 1 H), 4.26 – 4.33 (m, 2 H), 4.14 – 4.26 (m, 2 H), 4.04 – 4.10 (m, 1 H), 3.50 (td, J = 11.7, 1.8 Hz, 1 H), 2.42 – 2.49 (m, 1 H), 2.22 – 2.35 (m, 2 H), 1.87 – 1.95 (m, 1 H), 1.76 – 1.86 (m, 2 H), 1.31 (t, J = 7.0 Hz, 3 H), 1.16 (t, J = 7.0 Hz, 3 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 168.0, 166.9, 146.6, 128.5, 122.9, 117.4, 84.4, 67.9, 62.1, 61.8, 29.9, 28.5, 27.5, 20.1, 14.1, 14.0.

HRMS (m/z): 363.1688 (calcd for C<sub>19</sub>H<sub>25</sub>NO<sub>6</sub>, 363.1682).

The title compound was prepared according to the general cycloaddition procedure B to afford a pale brown solid (40 mg, 35%).

R<sub>f</sub> = 0.26 (30% EtOAc/hexanes).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 6.90 – 6.94 (m, 2 H), 6.72 – 6.77 (m, 2 H), 5.03 (d, J = 3.5 Hz, 1 H), 4.15 – 4.25 (m, 4 H), 3.90 – 3.96 (m, 1 H), 3.73 (s, 3 H), 3.44 (td, J = 11.3,
2.1 Hz, 1 H), 2.84 (t, $J = 12.3$ Hz, 1 H), 2.43 (dd, $J = 12.0$, 6.8 Hz, 1 H), 2.33 – 2.40 (m, 1 H), 1.85 – 1.94 (m, 1 H), 1.69 – 1.80 (m, 2 H), 1.38 – 1.44 (m, 1 H), 1.22 (t, $J = 7.0$ Hz, 3 H), 1.16 (t, $J = 7.0$ Hz, 3 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.1, 153.3, 137.8, 118.0, 113.8, 90.0, 74.0, 63.9, 61.7, 61.7, 55.5, 38.2, 35.1, 23.7, 20.7, 14.0, 13.9.

HRMS ($m$/z): 377.1837 (calcd for C$_{20}$H$_{27}$NO$_6$, 377.1838).

The title compound was prepared according to the general cycloaddition procedure B for 1 h, followed by 1 h at rt to afford a yellow oil (22 mg, 19%).

$R_f$ = 0.43 (50% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.92 – 6.96 (m, 2 H), 6.65 – 6.68 (m, 2 H), 5.01 (d, $J = 4.1$ Hz, 1 H), 4.15 – 4.21 (m, 4 H), 3.92 (d, $J = 11.2$ Hz, 1 H), 3.42 (td, $J = 11.0$, 2.1 Hz, 1 H), 2.82 (s, 6 H), 2.39 – 2.44 (m, 1 H), 2.33 – 2.39 (m, 1 H), 1.83 – 1.93 (m, 1 H), 1.68 – 1.80 (m, 2 H), 1.37 – 1.43 (m, 1 H), 1.24 – 1.30 (m, 1 H), 1.21 (t, $J = 7.3$ Hz, 3 H), 1.15 (t, $J = 7.0$ Hz, 3 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 171.4, 170.4, 145.5, 135.5, 118.9, 114.3, 90.2, 74.1, 63.8, 61.6, 61.5, 41.8, 38.1, 35.2, 23.8, 20.8, 14.0, 13.9.

HRMS ($m$/z): 390.2167 (calcd for C$_{21}$H$_{30}$N$_2$O$_5$, 390.2155).
The title compound was prepared according to the general cycloaddition procedure A for 15 min to afford a pale yellow oil (85 mg, 73%).

$R_f = 0.59$ (30% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.18 - 7.24 (m, 4 H), 6.98 - 7.01 (m, 1 H), 4.11 - 4.22 (m, 4 H), 3.13 (s, 3 H), 2.60 (t, $J = 12.6$ Hz, 1 H), 2.14 (dd, $J = 12.6$, 3.8 Hz, 1 H), 1.95 - 2.00 (m, 1 H), 1.66 - 1.75 (m, 2 H), 1.60 - 1.65 (m, 1 H), 1.43 - 1.48 (m, 2 H), 1.21 - 1.35 (m, 3 H), 1.12 - 1.18 (m, 6 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.8, 167.9, 148.8, 127.6, 123.3, 120.5, 101.4, 76.3, 62.1, 61.0, 48.1, 40.6, 33.8, 29.3, 27.6, 25.5, 22.5, 13.9, 13.7.

HRMS ($m$/z): 391.1987 (calcd for C$_{21}$H$_{29}$NO$_6$, 391.1995).

The title compound was prepared according to the general cycloaddition procedure A to afford a pale yellow oil (90 mg, 70%).

$R_f = 0.65$ (30% EtOAc/hexanes).
\[ ^1H \text{NMR} \ (600 \text{ MHz, CDCl}_3) \ \delta \ 7.16 \ (s, \ 4 \ \text{H}), \ 4.11 - 4.23 \ (m, \ 4 \ \text{H}), \ 3.10 \ (s, \ 3 \ \text{H}), \ 2.58 \ (t, \ J = 12.6 \ \text{Hz}, \ 1 \ \text{H}), \ 2.12 \ (dd, \ J = 12.6, \ 3.8 \ \text{Hz}), \ 1.93 - 1.99 \ (m, \ 1 \ \text{H}), \ 1.60 - 1.75 \ (m, \ 3 \ \text{H}), \ 1.42 - 1.52 \ (m, \ 3 \ \text{H}), \ 1.26 - 1.36 \ (m, \ 1 \ \text{H}), \ 1.19 - 1.26 \ (m, \ 1 \ \text{H}), \ 1.14 - 1.19 \ (m, \ 6 \ \text{H}). \]

\[ ^{13}C \text{NMR} \ (101 \text{ MHz, CDCl}_3) \ \delta \ 168.6, \ 167.8, \ 147.5, \ 127.6, \ 122.0, \ 101.6, \ 76.4, \ 62.2, \ 61.2, \ 48.0, \ 40.6, \ 33.7, \ 29.3, \ 27.6, \ 25.5, \ 22.5, \ 14.0, \ 13.7. \]

\textbf{HRMS (m/z):} 425.1607 (calcd for C\text{\textsubscript{21}}H\text{\textsubscript{28}}ClNO\text{\textsubscript{6}}, 425.1605).

\textbf{Compound 1-108fa}

The title compound was prepared according to the general cycloaddition procedure A to afford a yellow oil (29 mg, 21%).

\[ R_f = 0.40 \ (30\% \ \text{EtOAc/hexanes}). \]

\[ ^1H \text{NMR} \ (600 \text{ MHz, CDCl}_3) \ \delta \ 7.16 - 7.24 \ (m, \ 4 \ \text{H}), \ 6.99 - 7.03 \ (m, \ 1 \ \text{H}), \ 5.03 \ (dd, \ J = 7.9, \ 3.8 \ \text{Hz}, \ 1 \ \text{H}), \ 4.19 - 4.25 \ (m, \ 2 \ \text{H}), \ 4.11 - 4.19 \ (m, \ 2 \ \text{H}), \ 3.94 \ (dq, \ J = 9.9, \ 7.1 \ \text{Hz}, \ 1 \ \text{H}), \ 3.61 \ (dq, \ J = 9.9, \ 7.1 \ \text{Hz}, \ 1 \ \text{H}), \ 2.58 \ (dt, \ 13.5, \ 4.7 \ \text{Hz}, \ 1 \ \text{H}), \ 2.44 \ (ddd, \ 13.4, \ 12.2, \ 4.4 \ \text{Hz}, \ 1 \ \text{H}), \ 1.97 \ (dq, \ J = 13.4, \ 4.2 \ \text{Hz}, \ 1 \ \text{H}), \ 1.76 - 1.84 \ (m, \ 1 \ \text{H}), \ 1.22 \ (t, \ J = 7.0 \ \text{Hz}, \ 3 \ \text{H}), \ 1.18 \ (t, \ J = 7.0 \ \text{Hz}, \ 3 \ \text{H}), \ 1.13 \ (t, \ J = 7.0 \ \text{Hz}, \ 3 \ \text{H}). \]

\[ ^{13}C \text{NMR} \ (101 \text{ MHz, CDCl}_3) \ \delta \ 168.4, \ 168.1, \ 148.3, \ 127.7, \ 123.3, \ 119.5, \ 102.5, \ 74.8, \ 64.7, \ 61.9, \ 61.6, \ 30.8, \ 27.0, \ 15.1, \ 13.8, \ 13.7. \]

\textbf{HRMS (m/z):} 351.1679 (calcd for C\text{\textsubscript{18}}H\text{\textsubscript{25}}NO\text{\textsubscript{6}}, 351.1682).
The title compound was prepared according to the general cycloaddition procedure B to afford a yellow oil (43 mg, 38%).

\[ R_f = 0.36 \] (30% EtOAc/hexanes)

**\(^1\)H NMR** (600 MHz, CDCl\(_3\)) \( \delta \): 7.19 – 7.23 (m, 2 H), 6.75 – 6.79 (m, 2 H), 5.00 (dd, \( J = 8.2, 3.5 \) Hz, 1 H), 4.06 – 4.23 (m, 4 H), 3.83 – 3.90 (m, 1 H), 3.77 (s, 3 H), 3.53 – 3.60 (m, 1 H), 2.57 (dt, \( J = 13.5, 4.7 \) Hz, 1 H), 2.44 (td, \( J = 12.6, 4.7 \) Hz, 1 H), 1.95 (dq, \( J = 13.4, 4.2 \) Hz, 1 H), 1.73 – 1.83 (m, 1 H), 1.17 – 1.22 (m, 6 H), 1.13 (t, \( J = 7.0 \) Hz, 3 H).

**\(^13\)C NMR** (101 MHz, CDCl\(_3\)) \( \delta \): 168.3, 168.1, 156.4, 141.3, 122.7, 112.8, 102.3, 75.2, 64.6, 61.8, 61.5, 55.4, 27.1, 37.7, 15.1, 13.9, 13.8.

**HRMS (m/z):** 381.1778 (calcd for C\(_{19}\)H\(_{27}\)NO\(_7\), 381.1788).

**Compound 1-111fn**

To a stirred solution of MgI\(_2\) (47 mg, 0.17 mmol) in 6 mL CH\(_2\)Cl\(_2\) at rt was added 1-109fn (130 mg, 0.34 mmol). The RM was stirred for about 30 min at rt (complete consumption of starting material by TLC) then the RM was layered directly onto a silica gel column and purified by flash chromatography (0-25% EtOAc/hexanes) to afford a yellow oil (50 mg, 38%).

\[ R_f = 0.43 \] (30% EtOAc/hexanes).
$^1$H NMR (400 MHz, CDCl$_3$) δ 6.70 - 6.75 (m, 2 H), 6.58 - 6.64 (m, 2 H), 4.81 (s, 1 H), 4.16 - 4.26 (m, 4 H), 4.04 (q, $J = 7.2$ Hz, 2 H), 3.73 (s, 3 H), 2.61 - 2.68 (m, 2 H), 2.22 - 2.29 (m, 2 H), 1.19 (t, $J = 7.0$ Hz, 9 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 196.3, 172.7, 169.6, 153.2, 137.6, 116.9, 114.6, 68.1, 62.4, 60.5, 55.6, 28.7, 27.4, 14.1, 13.9.

HRMS (m/z): 381.1789 (calcd for C$_{19}$H$_{27}$NO$_7$, 381.1788).
1.4.3 Cascade Reaction of Donor-Acceptor Cyclopropanes: Mechanistic Studies in Cycloadditions with Nitrosoarenes and cis-Diazenes

Majority of the experimental work done by Tristan Chidley (M.Sc. 2015) and only representative examples are shown in here.\textsuperscript{88}

![Compound 1-124aa](image)

**Compound 1-124aa**

To a solution of cyclopropane **1-122a** (100 mg, 0.43 mmol) and nitrosobenzene (**1-96a**, 21 mg, 0.20 mmol) in (CH\textsubscript{2})\textsubscript{2}Cl\textsubscript{2} (3 mL) at rt was added Yb(OTf)\textsubscript{3}\cdot H\textsubscript{2}O (12 mg, 0.02 mmol) and stirred for about 15 min. The RM was then heated to reflux until complete consumption of nitrosobenzene (3 h, as indicated by TLC). Then the RM was cooled to rt and directly layered onto a silica gel column and purified by flash chromatography (0-10\% EtOAc/hexanes) to afford the title compound as a yellow oil, which was recrystallized with CH\textsubscript{2}Cl\textsubscript{2}/hexanes to give a white solid (75 mg, 87\%). The characterization data is in agreement with literature values.\textsuperscript{89}
Crossover Experiment 1

To a solution of cyclopropanes 1-122a (0.43 mmol, 1.0 equiv), 1-122b (0.43 mmol, 1.0 equiv) and nitrosobenzene (1-96a, 0.43 mmol, 1.0 equiv) in (CH\(_2\)\(_2\))Cl\(_2\) (3 mL) was added Yb(OTf)\(_3\)·H\(_2\)O (0.02 mmol, 0.1 equiv) and stirred for 15 min. The mixture was then refluxed for about 22 h. After compete consumption of nitrosobenzene (as indicated by TLC) the RM was directly layered onto a silica gel column and isolated all 4 compounds in pure form by flash chromatography (0-10% EtOAc/hexanes).

These 4 isolated compounds are identical with the standards independently synthesized from literature methods.\(^90\)

**Compound 1-124bb**

The title compound was isolated in crossover experiment 1 as yellow oil, which was recrystallized with CH\(_2\)Cl\(_2\)/hexanes to give a white solid (73 mg, 35%).

\(R_f = 0.58\) (25% EtOAc/hexanes).
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.43 - 7.49\) (m, app dd, \(J = 8.2, 6.6\) Hz, 4 H), 7.27 (app d, \(J = 8.2\) Hz, 2 H), 7.07 - 7.17 (m, 4 H), 6.98 (d, \(J = 8.2\) Hz, 2 H), 6.80 (app tt, \(J = 7.0, 1.6\) Hz, 1 H), 5.76 (s, 1 H), 4.99 (dd, \(J = 12.1, 2.3\) Hz, 1 H), 4.38 (q, \(J = 7.0\) Hz, 2 H), 3.84 – 4.02 (app dddd, \(J = 7.0, 7.0, 7.0, 10.5\) Hz, 2 H), 2.87 (app dd, \(J = 14.5, 12.5\) Hz, 1 H), 2.75 (app dd, \(J = 14.5, 2.3\) Hz, 1 H), 2.41 (s, 3 H), 2.22 (s, 3 H), 1.35 (t, \(J = 7.0\) Hz, 3 H), 1.06 (t, \(J = 7.0\) Hz, 3 H).

\(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 169.7, 168.0, 148.7, 138.1, 137.5, 136.6, 131.9, 130.4, 129.2, 128.6, 128.5, 126.5, 121.3, 115.7, 78.7, 65.4, 62.2, 61.7, 59.4, 31.6, 21.2, 21.0, 14.2, 13.7.

HRMS (m/z): 487.2348 (Calcd for C\(_{30}\)H\(_{33}\)NO\(_5\), 487.2359).
1.4.4 Cycloadditions of Donor-Acceptor Cyclobutanes and cis-Diazenes

Known AACDs 1-53a – 1-53f were prepared according to literature procedures.\textsuperscript{38}

\[ \text{Compounds 1-67l} \]

Following a reported procedure,\textsuperscript{38} to a stirring solution of Yb(OTf)\textsubscript{3}·H\textsubscript{2}O (415 mg, 0.05 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (25 mL) at rt was slowly added, a cold solution (maintained at –78 °C) of 1-methoxycyclohept-1-enc\textsuperscript{91} (2.0 g, 15.85 mmol, 1.2 equiv), and diethyl 2-methylenemalonate (2.3 g, 13.36 mmol, 1.0 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (25 mL). After addition, the RM was stirred until appeared complete by TLC (~30 min). Pyridine (1 mL) was added and the reaction was filtered through a bilayer pad of silica gel (2 cm) and Celite® (1 cm) open to the atmosphere. The filtrate was concentrated \textit{in vacuo} and the residue was purified by silica gel flash chromatography (0-5% EtOAc/hexanes, buffered with 1% Et\textsubscript{3}N) to afford the title compound as a colorless oil (1.60 g, 40%).

\( \text{R}_f = 0.41 \) (20% EtOAc/hexanes).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \): 4.21 (dq, \( J = 14.3, 7.2 \) Hz, 4 H), 3.27 (s, 3 H), 2.63 - 2.75 (m, 1 H), 2.43 - 2.55 (m, 2 H), 2.00 (dt, \( J = 13.9, 7.1 \) Hz, 1 H), 1.75 - 1.85 (m, 1 H), 1.63 - 1.74 (m, 2 H), 1.54 - 1.63 (m, 1 H), 1.34 - 1.52 (m, 2 H), 1.25 - 1.32 (m, 6 H), 1.08 - 1.25 (m, 3 H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \): 169.6, 87.0, 61.4, 60.8, 60.3, 50.8, 43.0, 31.7, 28.5, 27.9, 26.1, 24.3, 23.3, 14.1, 14.0.

HRMS \( (m/z) \): 298.1792 (calcd for C\textsubscript{16}H\textsubscript{26}O\textsubscript{5}, 298.1780).
The [4+2] cycloadditions of AACDs with cis-diazene (PTAD) were performed by Tristan Chidley (M.Sc. 2015) and only a representative example is shown in here.\textsuperscript{88}

![Compound 1-136b](image)

**Compound 1-136b**

To a solution of cyclobutane 1-67b (141 mg, 0.58 mmol, 2.0 equiv) and PTAD (1-30a,50 mg, 0.29 mmol, 1.0 equiv) in (CH\(_2\))\(_2\)Cl\(_2\) (3 mL) at rt was added a solution of GaCl\(_3\) (2.6 mg, 0.015 mmol, 0.05 equiv) in (CH\(_2\))\(_2\)Cl\(_2\) (0.5 mL) and stirred for about 30 min. Then the RM directly loaded onto a SiO\(_2\) column and was purified by flash chromatography (30-50% EtOAc/hexanes) to afford the title compound as a white solid. (111 mg, 92%).

R\(_f\) = 0.50 (50% EtOAc/hexanes).

\textsuperscript{1}H NMR (400 MHz, CDCl\(_3\)) 7.45 - 7.53 (m, 4 H), 7.38 (app t, J = 7.0 Hz, 1 H), 5.78 (d, J = 4.3 Hz, 1 H), 4.29 - 4.37 (m, 4 H), 4.18 - 4.23 (m, 2 H), 4.08 (td, J = 9.4, 2.0 Hz, 1 H), 2.64 (dd, J = 13.3, 5.9 Hz, 1 H), 2.40 - 2.48 (m, 1 H), 2.28 - 2.36 (m, 1 H), 2.24 (dd, J = 13.3, 12.1 Hz, 1 H), 1.90 (ddd, J = 6.6, 6.6, 2.0 Hz, 1 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.32 (t, J = 7.0 Hz, 3 H).

\textsuperscript{13}C NMR (101 MHz, CDCl\(_3\)) 166.2, 165.8, 153.7, 151.0, 131.0, 129.1, 128.3, 125.7, 77.6, 70.4, 65.0, 63.2, 63.0, 26.5, 25.6, 15.0, 14.1, 13.8.

HRMS (m/z): 417.1530 (Calcd for C\(_{20}\)H\(_{23}\)N\(_3\)O\(_7\), 417.1536).
1.4.5 Spiroketalts from AACDs

**Compound 1-143a**

To a stirring solution of Zn(OTf)$_2$ (216 mg, 0.05 equiv) in CH$_2$Cl$_2$ (10 mL) at -78 °C was simultaneously added (over 1 h), a rt solution of 2-methylenetetrahydrofuran (1.0 g, 11.89 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (3 mL) and diethyl 2-methylenemalonate (3.1 g, 17.83 mmol, 1.5 equiv) in CH$_2$Cl$_2$ (3 mL). After addition, the RM was stirred for about 15 min, and pyridine (0.3 mL) was added. Stirring was continued for 5 more min, then RM was filtered through a bilayer pad of silica gel (2 cm) and Celite® (1 cm) open to the atmosphere and the filtrate was concentrated *in vacuo*. After two unsuccessful attempts to purify the residue by flash column chromatography on silica gel (0-1% EtOAc/hexanes, buffered with 2% Et$_3$N), the partially purified compound carried forward to next step without characterization.

**Compound 1-145a**

To a solution of Yb(OTf)$_3$·H$_2$O (29 mg, 0.04 mmol, 0.1 equiv) in CH$_2$Cl$_2$ (1 mL) at 0 °C was added benzaldehyde (145 mg, 0.57 mmol, 1.0 equiv) followed by cyclobutane 1-143a (50 mg, 0.47 mmol, 1.2 equiv). After 15 min the RM passed through a plug of silica gel (2 cm), washed with CH$_2$Cl$_2$ (5 mL), and the solvent concentrated *in vacuo* to obtain the title compound as a colorless oil in a reasonably pure form (77 mg, 45%).

$R_f = 0.24$ (20% EtOAc/hexanes).
\textbf{H NMR} (600 MHz, CDCl\textsubscript{3}) \(\delta\) 7.43 (d, \(J = 7.0\) Hz, 2 H), 7.19-7.25 (m, 3 H), 5.50 (s, 1 H), 4.14 (q, \(J = 7.4\) Hz, 2 H), 4.01 (dq, \(J = 10.9, 7.1\) Hz, 1 H), 3.91 (td, \(J = 8.2, 5.9\) Hz, 1 H), 3.79-3.85 (m, 2 H), 2.39-2.45 (m, 2 H), 2.30-2.36 (m, 1 H), 2.09-2.16 (m, 1 H), 1.98-2.06 (m, 1 H), 1.82-1.90 (m, 1 H), 1.71-1.80 (m, 2 H), 1.16 (t, \(J = 7.3\) Hz, 3 H), 0.93 (t, \(J = 7.3\) Hz, 3 H).

\textbf{13C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 170.9, 169.1, 139.9, 127.6 (2 C), 127.1, 127.0 (2 C), 106.2, 73.4, 67.4, 61.1, 60.4, 58.2, 37.4, 29.1 (2 C), 23.5, 13.9, 13.5.

\textbf{HRMS} (m/z): 385.1612 (calcd for C\textsubscript{20}H\textsubscript{26}O\textsubscript{6} + Na, 385.1627).

\begin{center}
\includegraphics[width=0.2\textwidth]{compound1-149a.png}
\end{center}

\textbf{Compound 1-149a}

The title compound was isolated as a byproduct in [2+2] cycloaddition reaction.

R\textsubscript{f} = 0.43 (30% EtOAc/hexanes).

\textbf{H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 4.18 (app qd, \(J = 7.0, 1.6\) Hz, 6 H), 4.07 (t, \(J = 6.8\) Hz, 1 H), 3.40 (t, \(J = 7.6\) Hz, 1 H), 2.63 (app t, \(J = 7.6\) Hz, 2 H), 2.45 (td, \(J = 7.5, 1.4\) Hz, 2 H), 2.93 (quin, \(J = 7.1\) Hz, 2 H), 1.25 (t, \(J = 7.0\) Hz, 6 H).

\textbf{13C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 169.3, 157.1, 90.3, 70.5, 61.0, 52.3, 28.8, 24.8, 24.8, 14.0.

\textbf{HRMS} (m/z): 256.1310 (calcd for C\textsubscript{13}H\textsubscript{20}O\textsubscript{5}, 256.1311).
1.5 Notes and References


4. In majority of the cases, the dipolarophile will intercept the polarized DA cyclopropane before it converts into 1,3-zwitterionic intermediate so the stereochemical information will be intact.


26. Although 3-alkoxycyclobutanones do undergo annulation reactions through a 1,4-zwitterionic intermediate, they are not formally defined as DA cyclobutanes. For more examples of cyclobutanones, see Ref. 22b.
29. More strong Lewis acid, Hf(OTf)₄ was used for this example.


39. Plausible mechanism for the conversion of piperidine to piperideine:


41. Conditions that allow for exclusive formation of the trans-diastereomer were not found to date, despite exploring various temperatures, catalysts, and solvents.


46. Machin, B. P.; Pagenkopf, B. L. *Synlett* **2011**, 2799.
54. Vančík, H. *Aromatic C-Nitroso Compounds*; Springer: New York, **2013**.
60. Although “annelation” is the appropriate term for ring-forming reactions of DA cyclopropanes and cyclobutanes, the term “cycloaddition” is widely accepted, and thus used throughout this thesis.


62. Atomic charges derived from the electrostatic potentials for the nitrosobenzene were in agreement with the results observed. CHelpG charges (a.u.); nitrogen (-0.228) and oxygen (-0.163). Geometry: B3LYP/6-31G*; Density: B3LYP/6-311++G(3df,3pd). Also see Chapter 1 in Ref. 54.

63. The low yield of the 1-97f could be due to the steric of bromine at 2-position.

64. The regiochemistry and relative stereochemistry of the other products were assigned by analogy.


66. Studer group observed Mg-enolate aldol mechanism in reaction of DA cyclopropanes with nitrosoarenes: See ref. 68.

67. Most of the previously successful Lewis acids were employed. Such as, TMSOTf, TiCl$_4$, SnCl$_4$…etc.


69. Imines underwent efficient cycloadditions with DA cyclopropanes under Yb(OTf)$_3$-catalysys. See: Ref. 37f.

70. Previous results with AACDs showed that strong electron-withdrawing or donating substituents on the nitrosoarene alters the chemo-selectivity of the nitroso functional group (See Section 1.2.1.1).


72. Different cyclopropanes were chosen for experimental convenience.

73. GC/MS was used to analyse the products due to separation problems in flash chromatography. See Experimental for complete details.


78. CCDC-1498473 contains the crystal data for compound **1-136a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


83. Neither trimethylamine saturated column chromatography nor fractional distillation help purify the compound.


87. Decomposition of the AACDs was minimal with Zn(OTf)$_2$ compared to Yb(OTf)$_3$.


Chapter 2. Studies Towards the Synthesis of Streptorubin B

This chapter describes synthetic efforts towards the prodigiosin alkaloid streptorubin B using our group developed [3+2] cycloaddition of DA cyclopropanes and nitriles. An overview of this methodology along with relevant background information as well as reported studies directed towards the synthesis of streptorubin B and related prodigiosins has been discussed.
2.1 Introduction

The prodigiosin family of alkaloids have been of interest to both chemists and biologists for their unique molecular architecture and range of biological properties.\(^1\) Even though, prodigiosins share a common tripyrrole skeleton, they are diverse in molecular connectivity (Figure 2-1).\(^2\) Some of them have unique pyrrolophane core structure (such as 2-1) and some are distinctive macrocycles (such as 2-2). They display a characteristic deep-red color which has been misinterpreted in certain religious or symbolic contexts as the miraculous appearance of blood in certain foods.\(^2b\)

![Figure 2-1. Representative members of prodigiosin family of alkaloids.](image-url)
2.1.1 Biological Activity of Prodigiosins

The natural prodigiosins have impressive array of biological activities, and have inspired many medicinal chemists to synthesize hundreds of structural congeners for their potential as active ingredients in immunosuppressant and anti-cancer therapeutics. As a result of these studies, Pharmacia-Upjohn discovered a synthetic congener PNU156804 (2-7, Figure 2-2), which had impressive immunosuppressive properties, and was selected as a drug candidate for further studies. Gemin X (which was later acquired by Cephalon) discovered Obatoclax (2-8, Figure 2-2) for the treatment of various types of cancers, which is currently in Phase II clinical trials for the treatment of leukemia, lymphoma, myelofibrosis, and mastocytosis.

![Figure 2-2. Structures of PNU156804 (2-7) and Obatoclax (2-8).](image)

2.1.2 Streptorubin B

Streptorubin B (2-1) was first isolated in 1964 by Thirumalachar and co-workers from *Streptomyces caespitosus* bacteria, found in soil samples in Pimpri, India. In 1975, Gerber and co-workers reported isolation of a red pigment from *Streptomyces* sp. Y-42 and *Streptomyces abikoensis*, which was structurally assigned as butylcycloheptylprodigiosin (2-3). Due to the structural similarities between 2-1 and 2-3, which differ only in connectivity of the pyrrole ring, there was confusion regarding the
structures of these compounds. Later in 1978, Gerber expressed the need to revise the structure of 2-3 to 2-1 without elaborating the reasons behind this revision. A few years later, in 1985, Floss and co-workers assigned the structure of 2-3 to a pink pigment isolated from a strain of *Streptomyces coelicolor*. In 1991, Weyland and co-workers reported the isolation of a red pigment from an actinomycete strain B 4358, which was assigned as 2-1 based on 2D NMR data. Weyland also stated that the assignment of 2-3 assigned by Gerber and Floss should be revised to 2-1. In 2005, Fürstner reported the synthesis of 2-3, followed by Reeves in 2007, who stated 2-3 is in fact the natural product isolated by Gerber and Floss, against Weyland claims. Furthermore, in 2008, Challis and co-workers isolated 2-1 from *Streptomyces coelicolor*, the organism from which Floss isolated red pigment, and they found no evidence for the production of 2-3. The debate was continued until 2013, when Thomson and co-workers conducted mass spectral analysis and proposed biosynthesis hypotheses to eliminate butylcycloheptylprodigiosin (2-3) as a known natural product. The compound Floss isolated from *Streptomyces coelicolor* and Gerber from *Streptomyces* sp. Y-42 and *Streptomyces abikoensis* was in fact streptorubin B (2-1).

From a synthetic chemist point of view, streptorubin B (2-1) is very interesting target for its unique 10-membered 2,4-pyrrolophane structure with possible atropisomerism and its potent cytotoxicity against tumor cells, it has been shown to selectively kill 100% breast cancer cells at 1 µM doses.
2.1.3 Biosynthesis of Streptorubin B and Related Prodigiosins

It was widely accepted that a key step in the biosynthesis of the prodigiosins is the non-enzymatic condensation of 4-methoxy-2,2'-bipyrrrole-5-carboxaldehyde (2-9) with a substituted pyrrole moiety 2-10 (Scheme 2-1).²

\[
\begin{align*}
\text{2-9} & \quad + \quad \text{2-10} & \quad \rightarrow \quad \text{2-11}
\end{align*}
\]

**Scheme 2-1.** Biosynthesis of the prodigiosins from condensation of aldehyde 2-9 with pyrrole 2-10.

Biosynthetic studies including \(^{13}\)C labelled feeding studies established that each pyrrole was derived in a series of enzymatic reactions from different amino acids and alkyl chains formed from several acetyl units.¹⁸

From a structural standpoint, streptorubin B (2-1) and streptorubin A (2-5, widely known as metacyclprodigiosin) are very similar (Figure 2-3). It was understood that these highly strained pyrrolophane natural products were formed by oxidative ring closure mediated by Rieske oxygenase-like enzymes from a common intermediate, undecylprodigiosin (2-12).¹⁹ This biosynthesis proposal was supported by the fact that undecylprodigiosin (2-12) has been isolated from the same strains of bacteria as metacyclprodigiosin (2-5) and streptorubin B (2-1).⁸a,⁹
Figure 2-3. Biosynthesis of streptorubin B (2-1) and streptorubin A (2-5) from undecylprodigiosin (2-12) catalyzed by enzymes RedG and McpG respectively.

2.1.4 Published Studies Towards the Streptorubin B and Related Prodigiosins

There have been many synthetic studies reported towards aldehyde 2-9. The first successful synthesis of aldehyde 2-9 was reported by Rapoport and co-workers in 1962.\textsuperscript{20} Rapoport’s synthesis of aldehyde 2-9 was straightforward, consisting of seven linear steps (Scheme 2-2). The synthesis began with the condensation of ethyl N-(ethoxycarbonyl)glycinate (2-13) with diethyl ethoxymethyleneomalonate (2-14) followed by conversion of the resulting alcohol 2-15 to methyl ether 2-16 with diazomethane. Selective dealkoxy-carbonylation with H\textsubscript{2}SO\textsubscript{4} and heat followed by condensation with 1-pyrroline (2-18) led to pyrrolidinylpyrrole 2-19 which was dehydrogenated to 2,2\textprime{}-bipyrrrole 2-20. Bipyrrrole ester 2-20 was then converted to the corresponding aldehyde 2-9 under McFadyen-Stevens conditions. Acid catalyzed condensation of this aldehyde with 2-methyl-3-pentylpyrrole (2-21, which was made in five steps from 3-octanone) resulted in synthetic prodigiosin (2-4).
In 2004, Wasserman and co-workers reported a short synthesis of aldehyde 2-9. The report described the synthesis of the tert-butyl analogue 2-25 (Scheme 2-3) of Rapoport’s intermediate 2-20 via addition of singlet oxygen to certain pyrrole compounds (Scheme 2-3). The transient imino hydroperoxide intermediate 2-23 has been shown to react with a number of nucleophiles, such as pyrrole to give 2,2'-bipyrrrole 2-25. Subsequent McFadyen-Stevens reduction produced aldehyde 2-9 (see Scheme 2-2).
Although this route allows for the structural modifications on the pyrrole, it is limited by the low yields of both the singlet oxygen reaction as well as the McFadyen-Stevens reduction.


In 2006, Lavallèe and Tripathy reported the shortest synthesis of aldehyde 2-9 to date.\textsuperscript{22} Commercially available 4-methoxy-3-pyrolin-2-one (2-26) was treated with the Vislmeier–Haack reagent derived from diethylformamide\textsuperscript{23} to produce bromopyrrole enamine 2-27 in 70% yield. Suzuki cross-coupling reaction of 2-27 with N-Boc-2-pyrroleboronic acid (2-28) followed by aq work-up led to the aldehyde 2-9 in 95% yield (Scheme 2-4). Furthermore, the authors applied this methodology towards the efficient synthesis of Obatoclax (2-8).\textsuperscript{24}

Scheme 2-4. Lavallèe and Tripathy's synthesis of aldehyde 2-9.

The first total synthesis of metacycloprodigiosin (2-5) was reported by Wassermann and co-workers in 1969, following its isolation and structural
determination.\textsuperscript{25} As described in Scheme 2-5, the synthesis began with enolate ethylation of 2-29 followed by protection of the carbonyl as spiroketal 2-30 in a 32% yield. Regioselective bromination followed by E2 elimination with DBU establishes enone 2-31 in a 91% yield. Deprotection of the carbonyl, epoxidation, followed by acidic hydrazine-promoted rearrangement of α,β-epoxyketone to allylic alchol 2-32 was achieved in 30% yield. Oxidation of alcohol 2-32 followed by 1,4-addition of cyanide to the resulting enone was accomplished in 91% yield. Protection of the ketone followed by DIBAL-H reduction of nitrile 2-33 led to aldehyde 2-34. Deprotection of the ketone followed by Paal-Knorr cyclization with ammonium carbonate completed the synthesis of pyrrole 2-35 in 3.5% overall yield over 13 linear steps. This pyrrole moiety was then condensed with the known aldehyde 2-9 to complete the synthesis of metacycloprodigiosin (2-5).
Scheme 2-5. Wasserman’s total synthesis of metacycloprodigiosin (2-5).

A few years later, in 1998, Fürstner and co-workers reported an efficient synthesis of the pyrrolophane core (2-35) of metacycloprodigiosin (2-5) via enyne metathesis.\(^{26}\)

As depicted in Scheme 2-6, the synthesis began with an ene-type reaction on the cyclodecene (2-36) with an \textit{in situ} generated diimino-selenium reagent.\(^{27}\) Alkylation of allyl amine 2-37 with propargyl bromide, and a subsequent acylation of the resulting terminal alkyne 2-38 with acetyl chloride established the enyne 2-39 required for the
The enyne metathesis reaction on 2-39 was initiated with either 
BF$_3$·OEt$_2$ or PtCl$_2$ to afford ring-expanded product 2-40 in moderate yield. The enone of bicycle 2-40 was reduced to 2° alcohol 2-41, which was thionylated with O-Phenyl chlorothionoformate followed by Barton-McCombie dehydroxylation to give 2-43. Compound 2-43 was then converted into pyrrolophane 2-35 by a one pot detosylation and aromatization with potassium 3-aminopropylamide (KAPA). Thus, the formal synthesis of metacycloprodigiosin 2-5 was achieved in 5% overall yield from commercially available cyclodecene.

Scheme 2-6. Fürstner's synthesis of Wasserman’s pyrrole 2-35 via enyne metathesis.
The first synthesis of the pyrrolophane core (2-52) of streptorubin B (2-1) was accomplished by the Fürstner group (Scheme 2-7). The required precursor 2-47 for the enyne metathesis reaction was prepared from cyclooctene by a series of transformations similar to those discussed earlier (vide supra). The PtCl₂-catalyzed enyne metathesis reaction on 2-47 resulted in ring expanded product 2-48 in 94% yield, which was then converted into pyrrolophane 2-52 through previously described transformations. Thus, the first synthesis of pyrrolophane core (2-52) of streptorubin B (2-1) was achieved in about 16% overall yield in nine steps from cyclooctene.

Scheme 2-7. Fürstner’s first synthesis of pyrrolophane core (2-52) of streptorubin B (2-1).

In an effort to synthesize a library of prodigiosin derivatives for drug discovery, Murthy and co-workers completed the first total synthesis of streptorubin B along with
several structural congeners using Fürstner’s route.\textsuperscript{30} They used chiral catalyst Ru$_2$Cl$_4$((S)-BINAP)$_2$(NEt$_3$) to reduce the ketone 2-49 to a pair of alcohols 2-50a and 2-50b, which were separated and carried on independently according to Fürstner’s route to pyrrolophanes 2-52a and 2-52b (Scheme 2-8). These pyrrolophanes were then condensed independently with the known aldehyde 2-9 to access both enantiomers of streptorubin B.

\begin{center}
\textbf{Scheme 2-8.} Murthy's asymmetric syntheses of both enantiomers of streptorubin B.
\end{center}

In 2005, Chang and co-workers reported a synthesis of intermediate 2-51 using ring closing metathesis (RCM).\textsuperscript{31} The synthesis began with the commercially available trans-4-hydroxy-L-proline (2-53). Esterification of the acid and tosylation of the amine followed by silylation of the 2° alcohol and reduction of the ester resulted in prolinol 2-55 in 90\% yield over four steps. Swern oxidation, Wittig reaction on the resulting aldehyde, followed by two reductions gave 1° alcohol 2-57. Oxidation of this alcohol by PCC, followed by Wittig reaction installed the alkene required for the RCM reaction. Deprotection of the alcohol followed by PCC oxidation gave ketone 2-59. Grignard addition into this ketone followed by RCM with Grubbs II catalyst resulted in 2-62 as a
mixture of geometrical isomers and diastereomers. This mixture was then converted to Fürstner’s intermediate 2-51 by hydrogenation of the alkene followed by dehydration of the 3° alcohol.

Scheme 2-9. Chang’s synthesis of Fürstner’s intermediate 2-51 of streptorubin B.

Even though the total synthesis of the streptorubin B has been achieved, no comparison was made between synthetic and natural samples of streptorubin B to
establish the absolute and relative configuration. It was not until 2010 when the Thompson group established the correct absolute and relative stereochemistry of streptorubin B through an enantioselective total synthesis and comparisons of circular dichroism (CD) spectra.\(^{\text{32}}\)

As described in Scheme 2-10, the synthesis began with the oxidative cleavage of cycloheptene (2-63) to afford the dialdehyde necessary for an asymmetric intramolecular aldol reaction.\(^{\text{33}}\) An (S)-proline catalyzed aldol followed by Witting reaction with ylide 2-66 gave the homoallylic alcohol 2-67 with high diasterecontrol. Oxidation of alcohol 2-67 followed by addition of vinyl anion 2-68 installed the functional handles required for an anionic Cope rearrangement. Upon exposure of alcohol 2-69 to KHMDS and 18-crown-6 produced the desired 10-membered ring in 85% yield with excellent stereochemical transfer. This cyclic ketone was then efficiently converted into pyrrole 2-52a following reduction of the alkene with concomitant cleavage of the benzyl ether, Dess-Martin oxidation of the resulting alcohol, and Paal-Knorr pyrrole synthesis. Pyrrole 2-52a was converted into streptorubin B (2-1) through an acid-promoted condensation with aldehyde 2-72, followed by deprotection of Boc group via basic methanolysis. Interestingly, the isolated product was a 10:1 mixture of two compounds of which the major compound is not the streptorubin B (possibly atropisomer of streptorubin B). However, over time (10 days), the mixture completely transformed into the natural product, making this route the shortest to date, in nine linear steps with 20% overall yield from cycloheptene (2-63).
Scheme 2-10. Thompson's enantioselective total synthesis of streptorubin B (2-1).

In summary, the synthesis of streptorubin B (2-1) was achieved and its absolute and relative stereochemistry was firmly established with X-ray crystallography. The above discussed syntheses (and a few unsuccessful studies) are efficient in their own way, but they are linear and rather lengthy. Thus, a convergent approach to streptorubin B, which would also allow the expedited synthesis of structural congeners is warranted.
2.2 Project Plans and Goals

Our goal for this project was to achieve the total synthesis of streptorubin B in a modular approach, which would allow for late stage functionalization. As shown in Scheme 2-11, the butyl side chain of the streptorubin B could be attained via a Wittig reaction followed by an asymmetric hydrogenation of compound 2-73.\(^{35}\) We envisioned the pyrrolophane core structure can be prepared via our group developed [3+2] cycloaddition between DA cyclopropanes and nitriles (see Section 2.3). Therefore, compound 2-73 can come from a Lewis acid catalyzed [3+2] cycloaddition of bicyclic DA cyclopropane 2-74 and functionalized nitrile 2-75.

![Scheme 2-11. Retrosynthesis of streptorubin B (2-1).](image)

The bicyclic DA cyclopropane 2-74 can be accessed from a known cyclononane-1,3-dione (2-77)\(^{36}\) via enolate O-alkylation followed by cyclopropanation (Scheme 2-12). The cyclononane-1,3-dione (2-77) could be prepared from commercially available dimethyl octanedioate (2-80) using a known 3-step procedure\(^{36}\) via acyloin condensation of 2-80, followed by Simmons-Smith cyclopropanation and subsequent oxidative ring-expansion.
One of the major advantages of this synthesis would be the ease of late stage functionalization. Also, this strategy, if ideally executed, could be a short synthesis of streptorubin B in five linear steps from a known 1,3-dione 2-77.

**Scheme 2-12.** Retrosynthesis of bicyclic DA cyclopropane 2-74.
2.3 Cycloaddition of DA Cyclopropanes and Nitriles

2.3.1 The [3+2] Cycloaddition of DA Cyclopropanes and Nitriles

The first example of [3+2] cycloaddition between DA cyclopropanes and nitriles was reported by Pagenkopf and Yu in 2003. The report disclosed a novel TMSOTf-promoted [3+2] cycloaddition of carbohydrate-derived DA cyclopropanes 2-81 with a wide range of nitriles 2-82 to produce 1-pyrrolines (2-83) in good to excellent yields (Scheme 2-13).


A few years later, in 2010, Trushkov and co-workers extended this methodology to aryl-activated DA cyclopropanes. In this report, only alkyl nitriles were examined in cycloadditions with DA cyclopropanes under excess-stoichiometric SnCl₄ conditions. The cycloaddition afforded 1-pyrrolines in good yields (Scheme 2-14).

In 2011, Srinivasan and co-workers further extended Trushkov’s methodology to a highly activated DA cyclopropane 2-86 under stoichiometric SnCl₄ conditions (Scheme 2-15). Both alkyl and aryl nitriles were reported to undergo efficient cyclizations with DA cyclopropane 2-68 affording 1-pyrrolines in good yields.

**Scheme 2-15.** SnCl₄-promoted [3+2] cycloaddition of highly activated DA cyclopropane 2-86 with nitriles.

In an attempt to prepare enantiopure 1-pyrrolines via [3+2] cycloaddition of DA cyclopropanes and nitriles, Trushkov and co-workers subjected an enantiopure DA cyclopropane (S)-2-88 to previously reported cycloaddition conditions (see Scheme 2-14). The reaction with acetonitrile (2-89) resulted in racemic 1-pyrrole 2-90 suggesting that the reaction is going through an achiral zwitterionic intermediate 2-91 (Scheme 2-16). Changing the solvent or temp did not help improve the stereoselectivity.

Recently, Wang and co-workers reported a TfOH-promoted [3+2] cycloaddition of DA cyclopropanes with nitriles. The cycloaddition reported to have a broad substrate scope including aryl, allyl, or alkyl activated DA cyclopropanes with a wide range of nitriles (Scheme 2-17).

Scheme 2-17. TfOH-promoted [3+2] cycloaddition of DA cyclopropanes with nitriles
2.3.2 Pyrroles from DA Cyclopropanes and Nitriles

During the efforts to expand TMSOTf-promoted [3+2] cycloaddition of DA cyclopropanes and nitriles (see Scheme 2-13), Pagenkopf and Yu made an interesting observation. When the reaction was conducted in either toluene or dichloromethane, only rearranged products 2-95 and/or 2-96 were formed (eq 1, Scheme 2-18), but when highly polar solvents, such as nitromethane or nitroethane were used, the reaction underwent a tandem [3+2] cycloaddition, elimination, and tautomerization sequence to produce pyrroles 2-98 (eq 2, Scheme 2-18).\(^{41}\)

![Scheme 2-18](image.png)

**Scheme 2-18.** The effect of solvent in reaction of DA cyclopropanes with nitriles.

Gratifyingly, this cascade reaction has a broad substrate scope (Table 2-1).\(^{42}\) A wide range of DA cyclopropanes, irrespective of the substitution around the ring, were found to undergo efficient cyclizations with a variety of nitriles in good to excellent yields (2-98a-2-98m). Interestingly, substrates with silyl protecting groups, were also tolerated by the reaction conditions to afford pyrroles (2-98n-2-98p).
A year later, in 2004, Pagenkopf and co-workers applied this methodology towards the synthesis of unsymmetrical 2,2'-bipyrroles and 2,2'-thienylpyrroles. A series of DA cyclopropanes were reported to undergo cycloadditions with 2-cyanopyrroles and 2-cyanothiophenes, to afford 2,2'-bipyrroles and 2,2'-thienylpyrroles, respectively (Table 2-2).
Table 2-2. Synthesis of 2.2'-bipyroles and 2.2'-thienylpyrroles from cycloadditions of DA cyclopropanes and nitriles.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Reaction Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-100a</td>
<td><img src="image1" alt="Structure" /></td>
<td>TMSOTf (1 equiv)</td>
<td>67%</td>
</tr>
<tr>
<td>2-100b</td>
<td><img src="image2" alt="Structure" /></td>
<td>MeNO₂/EtNO₂, -25 °C - 0 °C</td>
<td>72%</td>
</tr>
<tr>
<td>2-100c</td>
<td><img src="image3" alt="Structure" /></td>
<td>TMSOTf (1 equiv)</td>
<td>61%</td>
</tr>
<tr>
<td>2-100d</td>
<td><img src="image4" alt="Structure" /></td>
<td>TMSOTf (1 equiv)</td>
<td>81%</td>
</tr>
<tr>
<td>2-100e</td>
<td><img src="image5" alt="Structure" /></td>
<td>MeNO₂/EtNO₂, -25 °C - 0 °C</td>
<td>78%</td>
</tr>
<tr>
<td>2-100f</td>
<td><img src="image6" alt="Structure" /></td>
<td>TMSOTf (1 equiv)</td>
<td>52%</td>
</tr>
<tr>
<td>2-100g</td>
<td><img src="image7" alt="Structure" /></td>
<td>MeNO₂/EtNO₂, -25 °C - 0 °C</td>
<td>45%</td>
</tr>
<tr>
<td>2-100h</td>
<td><img src="image8" alt="Structure" /></td>
<td>TMSOTf (1 equiv)</td>
<td>48%</td>
</tr>
<tr>
<td>2-100i</td>
<td><img src="image9" alt="Structure" /></td>
<td>MeNO₂/EtNO₂, -25 °C - 0 °C</td>
<td>75%</td>
</tr>
<tr>
<td>2-100j</td>
<td><img src="image10" alt="Structure" /></td>
<td>TMSOTf (1 equiv)</td>
<td>49%</td>
</tr>
<tr>
<td>2-100k</td>
<td><img src="image11" alt="Structure" /></td>
<td>MeNO₂/EtNO₂, -25 °C - 0 °C</td>
<td>46%</td>
</tr>
<tr>
<td>2-100l</td>
<td><img src="image12" alt="Structure" /></td>
<td>TMSOTf (1 equiv)</td>
<td>34%</td>
</tr>
<tr>
<td>2-100m</td>
<td><img src="image13" alt="Structure" /></td>
<td>TMSOTf (1 equiv)</td>
<td>85%</td>
</tr>
<tr>
<td>2-100n</td>
<td><img src="image14" alt="Structure" /></td>
<td>MeNO₂/EtNO₂, -25 °C - 0 °C</td>
<td>82%</td>
</tr>
<tr>
<td>2-100o</td>
<td><img src="image15" alt="Structure" /></td>
<td>TMSOTf (1 equiv)</td>
<td>52%</td>
</tr>
<tr>
<td>2-100p</td>
<td><img src="image16" alt="Structure" /></td>
<td>MeNO₂/EtNO₂, -25 °C - 0 °C</td>
<td>61%</td>
</tr>
<tr>
<td>2-100q</td>
<td><img src="image17" alt="Structure" /></td>
<td>TMSOTf (1 equiv)</td>
<td>52%</td>
</tr>
<tr>
<td>2-100r</td>
<td><img src="image18" alt="Structure" /></td>
<td>MeNO₂/EtNO₂, -25 °C - 0 °C</td>
<td>67%</td>
</tr>
</tbody>
</table>

In 2010, Moustafa and Pagenkopf further developed this methodology towards the synthesis of 5-azaindoles via oxidation of the cycloadducts obtained through cycloadditions between functionalized DA cyclopropane 2-101 and nitriles (Scheme 2-19).

2.3.3 Application in Total Synthesis

Pagenkopf and co-workers demonstrated the utility of [3+2] cycloaddition of DA cyclopropanes and nitriles in their total syntheses of (±)-goniomitine (2-107)\(^5\) and (±)-quebrachamine (2-108, Scheme 2-20).\(^6\) As shown in Scheme 2-20 the [3+2] cycloaddition of DA cyclopropane 2-104 with functionalized nitrile 2-105 (which was prepared from commercially available δ-valerolactam in 48% yield over 5 steps) afforded the pyrrole 2-106 in 74% yield. This pyrrole 2-106 was then converted into (±)-goniomitine (2-107) in 11% yield over 10 steps. The pyrrole 2-106 was also transformed into (±)-quebrachamine (2-108) in 33% yield over 7 steps. Thus the syntheses of aspidosperma alkaloids (±)-goniomitine (2-107) and (±)-quebrachamine (2-108) were efficiently achieved via a [3+2] cycloaddition of DA cyclopropane 2-104 and nitrile 2-105.

\[\text{Scheme 2-20. Total synthesis of (±)-goniomitine (2-107) and (±)-quebrachamine (2-108) via [3+2] cycloaddition of DA cyclopropane 2-104 and nitrile 2-105.}\]
In summary, cycloadditions of DA cyclopropanes with nitriles have been revealed to be an efficient method to prepare 1-pyrrolines. The diversity oriented synthesis of pyrroles via [3+2] cycloaddition, dehydration and tautomerization sequence, proved to be an excellent method with a broad substrate scope. The efficiency and practicality of this method has been shown in synthesis of 2,2'-bipyroles, 2,2'-thienylpyrroles and 5-azaindoles. Finally, this methodology has been showcased in the total synthesis of aspidosperma alkaloids (±)-goniomitine and (±)-quebrachamine.
2.4 General Introduction to Medium-sized Rings

Molecules with medium-sized rings (MRs, 8-11 atoms)\(^{47}\) are present in a large number of biologically active natural products and are an important class of synthetic targets in drug discovery (Figure 2-4).\(^ {48}\)

![Representative examples of medium-sized rings in biologically important molecules.](image)

**Figure 2-4.** Representative examples of medium-sized rings in biologically important molecules.

In contrast to larger rings (>11 atoms), the MRs have inherent strain associated with them.\(^ {49}\) While Baeyer strain is predominant in small rings, transannular and Pitzer strains are severe in MRs compared to both smaller and larger rings.\(^ {50}\) As shown in Figure 2-5, the measured experimental strain energies for MRs are quite high compared to other cycloalkanes (exempting cyclopropane and cyclobutane).\(^ {51}\)
Figure 2-5. Relative strain energies of cycloalkanes.

(Energies are referenced to the chair-confirmation of cyclohexane at 0 Kcal/mol)

The conformational properties of cyclooctane have been extensively studied, and it was revealed that the conformational preference for “boat-chair” at rt is the result of avoidance of unfavorable transannular interactions at the expense of Pitzer strain (Figure 2-6).\textsuperscript{52}

Figure 2-6. Boat-chair conformation of cyclooctane (2-112, eclipsed bonds shown).

Because of these unique structural features, any synthesis of MRs must overcome both enthalpic (increasing strain in the transition state) and entropic (probability of the
chain ends meeting) energy barriers. Thus the synthesis of MRs is relatively difficult compared to smaller or larger rings.\textsuperscript{53}
2.5 Results and Discussion

2.5.1 Attempted Synthesis DA Cyclopropane 2-74

In order to attempt the proposed synthesis (see Scheme 2-11), we set out to synthesize cyclononane-1,3-dione (2-77). Following a reported synthesis,\(^3\) 1,3-dione 2-77 was prepared in \(\sim 25\%\) yield over three steps from commercially available dimethyl octanedioate (2-80, Scheme 2-21). Acyloin condensation of 2-80 followed by trapping the intermediate with TMSCl afforded cyclooctene 2-79 in moderate yields. Furukawa modified Simmons-Smith cyclopropanation\(^5\) of 2-79 followed by oxidative ring expansion with FeCl\(_3\) afforded the cyclononane-1,3-dione (2-77).

![Scheme 2-21. Synthesis of cyclononane-1,3-dione (2-77).](image)

Having 1,3-dione 2-77 at hand, \(O\)-methylation was attempted under TsOH catalyzed conditions. Disappointingly, 2-77 underwent a retro-Claisen reaction instead of \(O\)-methylation (Scheme 2-22). This could be due to the severe strain associated with the 9-membered ring (see Section 2.4).
Scheme 2-22. Retro-Claisen condensation of 1,3-dione 2-77.

We then examined base-mediated \(O\)-methylation with a variety of bases and methylating agents and were pleased to find KH and methyl Meerwein salt in DME afforded the vinylogous ester 2-76 in a 69\% yield (Scheme 2-23). After unsuccessful attempts at cyclopropanation of vinylogous ester 2-76, we decided to reduce the ketone to an alcohol prior to cyclopropanation.

Scheme 2-23. \(O\)-Methylation of cyclononane-1,3-dione (2-77)

According to the revised plan (Scheme 2-24), the ketone of 2-76 was reduced to allylic alcohol 2-117 with LiAlH\(_4\) in excellent yield. Furukawa modified Simmons-Smith cyclopropanation of allylic alcohol resulted in bicyclic cyclopropyl alcohol 2-118 in an
80% yield. Disappointingly, the 2° alcohol could not be oxidized back to the ketone despite extensive efforts, as only ring expansion products 2-119 and 2-120 were observed (Scheme 2-24).

![Scheme 2-24. Synthesis of bicyclic cyclopropane 2-118.](image)

A plausible mechanism for this ring expansion is shown in Scheme 2-25. Typical activation of cyclopropyl alcohol 2-118 (with DMSO shown in this case) results in 2-121. Instead of undergoing deprotonation with base to yield ketone 2-74 (Path A), the more favorable pathway is ring expansion55 to give 2-122 which eventually deprotonates to diene 2-120. Any formation of desired ketone 2-74 quickly undergoes ring expansion to yield 1,4-diketone 2-119.
Scheme 2-25. Proposed mechanism for the formation of ring expansion products 2-119 and 2-120.

In order to investigate if this ring expansion is solely due to severe ring strain associated with medium sized ring, we wanted to examine a macrocycle. Thus, 13-membered cyclopropyl alcohol 2-123 was prepared using similar steps discussed above. Unfortunately, this compound also resulted in ring expansion products as discussed above (Scheme 2-26).

Scheme 2-26. Attempted oxidation of cyclopropyl alcohol 2-123.

We then wanted to replace the methoxy functionality with acetoxy, hoping it would reduce the electron-density on oxygen, impeding the cyclopropane ring from
expanding (see Scheme 2-25). Thus, the cyclotridecane-1,3-dione (2-126) was converted into vinylogous anhydride 2-128 using isopropenyl acetate (2-127, Scheme 2-27).

Scheme 2-27. Acetylation of cyclotridecane-1,3-dione (2-126).

As 2-128 is less electron rich compared to its methoxy analogue, we attempted a Corey-Chaykovsky cyclopropanation, and were surprised to isolate thiabenzene 1-oxide 2-131.57


Thiabenzene 1-oxides are known in the literature since the 1960s for their appreciable aromatic conjugation,58 and have been used in synthesis of coordination complexes.59

The structure of the thiabenzene 2-131 was assigned based on single crystal X-ray diffraction and the ORTEP structure is depicted in Figure 2-7.60
A plausible mechanism accounting the formation of 2-131 is depicted in Scheme 2-29. Nucleophilic attack of the *in situ* generated ylide 2-132 on 2-128 results in intermediate 2-133. Which instead of undergoing a ring closure to give cyclopropane 2-130 (Path A) eliminates acetate to give enone 2-134. Deprotonation of the methyl of the sulfoxide followed by 1,2-addition on the carbonyl 2-135 results in intermediate 2-136. Protonation of the alkoxide, followed by dehydration and aromatization results in thiabenzene 1-oxide 2-131.
Scheme 2-29. Proposed mechanism for the formation of thiabenzene 1-oxide 2-131.

After numerous unsuccessful attempts to oxidize the cyclopropyl alcohols 2-118 and 2-123 to bicyclic DA cyclopropanes to test our methodology, this route was terminated.
2.5.2 Progress Towards the Formal Synthesis

As our initial strategy did not allow us to try our anticipated [3+2] cycloaddition, we revised our strategy to make streptorubin B (2-1) via an intramolecular DA cyclopropane/nitrile cycloaddition (Scheme 2-30).

Scheme 2-30. Retrosynthesis of streptorubin B (2-1) via an intramolecular DA cyclopropane/nitrile cycloaddition.

As shown in Scheme 2-30, the target can be achieved from a condensation reaction of pyrrolophane 2-52 with known aldehyde 2-72. This has been well established by the Thompson group in their enantioselective synthesis (see Scheme 2-10). Thus, we chose pyrrolophane 2-52 as a target for our synthesis. Our idea was to proceed through an intramolecular cycloaddition of DA cyclopropane/nitrile 2-140. Dealkoxy-carbonylation of the ester in 2-139 would result in target molecule 2-52. Intermediate 2-140 is proposed to be made from known oxonan-2-one 2-145 (Scheme 2-31).
Scheme 2-31. Retrosynthesis of intermediate 2-140.

As shown in Scheme 2-31, we anticipated that the nitrile functionality could come from an S<sub>N</sub>2 displacement of mesylated alcohol 2-141. The DA cyclopropane could come from cyclopropanation of enol ether 2-143 with ethyl diazoacetate. Enol ether 2-143 could be made from a reductive ring opening of lactone 2-144 followed by a Wittig reaction of the resulting aldehyde. Ultimately, lactone 2-144 could be generated from a base mediated butylation of known oxonan-2-one 2-145.

As an intramolecular variant of [3+2] cycloaddition between DA cyclopropanes and nitriles is unknown, we thought it would be practical to perform a model study prior to our intended late stage [3+2] cycloaddition. Thus, we targeted model compound 2-146, which can be prepared from known aldehyde 2-149 via a Wittig reaction, cyclopropanation, followed by cyanation of alkyl chloride (2-147, Scheme 2-34).
The forward synthesis began with the oxidation of commercially available alcohol 2-150 to give aldehyde 2-149 (Scheme 2-33). Wittig reaction of the aldehyde 2-149 with the ylide in situ generated from 2-151 gave the enol ether 2-148 as a 1:0.7 mixture of E and Z isomers in 91% yield. Surprisingly, cyclopropanation of enol ether 2-148 with ethyl diazoacetate (2-152) was unsuccessful under either Cu(II) or Rh(II) catalysis.

We then converted the alkyl chloride 2-148 to nitrile 2-153 and subjected it to cyclopropanation conditions. Disappointingly the cyclopropanation was unsuccessful despite a variety of conditions employed.
We hypothesized having an alkyl chloride or nitrile functionality in the molecule might be causing the problem in cyclopropanation, and thus we decided to pursue the originally proposed strategy towards streptorubin B (see Scheme 2-30 and Scheme 2-31). But, unfortunately, due to time constraints this project was suspended.
2.6 Conclusions and Outlook

Unfortunately, we never got to try our anticipated [3+2] cycloaddition of DA cyclopropane and nitrile towards the synthesis of streptorubin B. Herein we described the two different strategies investigated towards the synthesis of streptorubin B. Although the synthesis was not complete, the described synthesis of bicyclic cyclopropyl alcohols, 2-118 and 2-123, could potentially be of use for future studies. The proposed formal synthesis seems much simpler, but many challenging synthetic steps need to be overcome. The intramolecular cycloaddition of DA cyclopropanes/nitriles, if ideally executed, could be an efficient way to make pyrrole macrocycles.
2.7 Experimental

2.7.1 General Considerations

Same as in section 1.4.1.

2.7.2 Experimental Procedures and Characterization Data

Following literature protocol, a three neck round bottom flask (RBF) containing a magnetic stir bar was fitted with a Liebig condenser and a pressurized addition funnel. The system was flame dried under vacuum and purged with argon twice. Toluene (600 mL) was charged into the flask through the third neck of the flask followed by pentane washed sodium (24.00 g, 1043.93 mmol, 4.8 equiv) in pieces. The solution was refluxed for about 1 h to produce a sodium dispersion. The addition funnel was charged with toluene (200 mL), dimethyl suberate (50.00 g, 217.10 mmol, 1 equiv), and chlorotrimethylsilane (152 mL, 1197.64 mmol, 5.5 equiv). The solution in the addition funnel was mixed via argon ebullition and added dropwise over 3 h to the refluxing RM, with stirring. The RM turned purple upon addition. After addition, stirring and reflux were continued for 16 h. After being cooled to rt, the mixture was vacuum filtered through a plug of glass wool and then vacuum filtered through a pad of Celite® (3 cm) on a glass frit to remove residual sodium particles (about 200 mL of hexane/s were used for washings). The resulting light yellow filtrate was distilled to yield the title compound as a colorless oil (31.65 g, 0.11 mol, 51%): bp 92-97 °C/1 mbar. 

\[ R_f = 0.29 \] (10% EtOAc/hexanes).

\[ ^1H \text{ NMR} \] (400 MHz, CDCl3) \( \delta \) 2.14 - 2.19 (m, 4 H), 1.56 - 1.62 (m, 4 H), 1.49 - 1.54 (m,
4 H), 0.18 (s, 18 H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 133.1, 31.2, 28.8, 26.4, 1.1.

$^1$H and $^{13}$C NMR spectra were in agreement with previously reported data.$^{61}$

![Compound 2-78](image)

Following literature protocol,$^{36b}$ to a degassed solution of 2-79 (63.30 g, 0.221 mol, 1.0 equiv) and CH$_2$I$_2$ (159.75 g, 0.596 mol, 2.7 equiv) in toluene (750 mL) at -15 °C, was slowly added (over a period of 1 h) a solution of Et$_2$Zn (79.12 g, 0.64 mol, 2.9 equiv)$^{62}$ in toluene (250 mL). After addition, the RM was stirred for 1 h, then warmed up to rt, and stirred for about 16 h. The RM was then cooled to -15 °C and carefully was added a satd. NH$_4$Cl aq solution (300 mL). Salts filtered by passing through a pad of Celite® (5 cm) and washing with ether (200 mL). Layers separated, and aq layer extracted with ether (2 x 300 mL). Combined organic extractions were dried over anhyd. MgSO$_4$, filtered, and concentrated in vacuo. The resulting pale yellow oil was distilled to yield the title compound as a colorless oil (54.00 g, 0.18 mol, 81%): bp 110-115 °C/1 mbar.

$R_f$ = 0.59 (10% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$) δ 2.13 (dt, $J = 14.8$, 3.7 Hz, 2 H), 1.72 – 1.80 (m, 2 H), 1.57 – 1.65 (m, 2 H), 1.27 – 1.35 (m, 4 H), 1.09 (ddd, $J = 15.1$, 13.1, 3.5 Hz, 2 H), 0.76 (d, $J = 6.5$ Hz, 1 H), 0.38 (d, $J = 6.5$ Hz, 1 H), 0.16 (s, 18 H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 59.9, 34.9, 26.3, 25.5, 24.7, 1.4.

$^1$H NMR spectrum was in agreement with previously reported data.$^{36b}$
Following literature protocol, to a degassed solution of Compound 2-78 (54.00 g, 0.180 mol, 1.0 equiv) in DMF (540 mL) at rt, was added anhyd. FeCl₃ (64.11 g, 0.395 mol, 2.2 equiv) in 10 equal portions. After addition, the RM was heated to 60 °C and maintained for 18 h. RM then cooled down to rt and transferred into a vigorously stirring aq solution of 1 N HCl (500 mL) and stirred for 3 h. RM then extracted with CHCl₃ (2 x 500 mL, 2 x 250 mL), dried over anhyd. MgSO₄, and concentrated in vacuo. The crude compound was then purified on silica gel flash chromatography (15% EtOAc/hexanes) to afford the title compound as a pale brown syrup (19.10 g, 0.12 mol, 69%).

\[ R_f = 0.28 \text{ (30\% EtOAc/hexanes).} \]

\[ ^1\text{H NMR (600 MHz, CDCl₃)} \delta 3.68 \text{ (s, 2 H), 2.52 – 2.56 (m, 4 H), 1.77 – 1.84 (m, 4 H), 1.43 – 1.49 (m, 4 H).} \]

\[ ^{13}\text{C NMR (151 MHz, CDCl₃)} \delta 204.9, 61.3, 42.4, 25.1, 23.5. \]

\[ ^1\text{H NMR spectrum was in agreement with previously reported data.} \]

To a solution of Compound 2-77 (260 mg, 1.69 mmol, 1 equiv) and CH(OMe)₃ (197 mg, 1.86 mmol, 1.1 equiv) in MeOH (1 mL) at rt, was added TsOH·H₂O (3 mg, 0.02 mmol, 0.01 equiv).
RM was then heated to 50 °C and maintained for 5 h. Cooled down to rt, concentrated \textit{in vacuo}, and the residue was diluted in CH$_2$Cl$_2$ (2 mL) and passed through a plug of silica gel and concentrated \textit{in vacuo}. The crude compound purified on silica gel flash chromatography (15% EtOAc/hexanes) to afford the title compound as a colorless oil (200 mg, 1.07 mmol, 64%).

$R_f = 0.24$ (20% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$) δ 3.66 (s, 3 H), 2.42 (t, $J = 7.3$ Hz, 2 H), 2.30 (t, $J = 7.6$ Hz, 2 H), 2.13 (s, 3 H), 1.54 – 1.66 (m, 4 H), 1.27 – 1.36 (m, 4 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 208.5, 173.7, 51.0, 43.2, 33.6, 29.5, 28.5, 28.4, 24.4, 23.2.

$^1$H NMR spectrum was in agreement with previously reported data.$^{64}$

\[ \begin{array}{c}
\text{O}
\end{array} \]

\text{Compound 2-76}

To a suspension of KH [(30% in mineral oil) 5.20 g, 38.91 mmol, 2 equiv] in a RBF at 0 °C was slowly added DME (90 mL). To this dark brown RM, was slowly added a solution of 2-77 (3.00 g, 19.45 mmol, 1.0 equiv) in DME (10 mL) (syringe pump addition, 0.5 mL/min). After addition, the RM stirred at the same temp for about 10 min, then warmed up to rt and stirred for 1 h.$^{65}$ RM then cooled down to 0 °C, at which time a fine powder of Me$_3$O·BF$_4$ (5.75 g, 38.90 mmol, 2.0 equiv) was added in 2 equal portions with a 5 min interval. After addition, RM was stirred at the same temp for 1 h, and at rt for 14 h. Cooled down to 0 °C and carefully was added H$_2$O (30 mL). Warmed up to rt,
stirred for 15 min, DME removed \textit{in vacuo}, and aq layer extracted into EtOAc (50 mL, 2 x 25 mL). Combined organic extractions were dried over anhyd. MgSO$_4$ and concentrated \textit{in vacuo}. The crude compound was purified on silica gel flash chromatography (0-20% EtOAc/hexanes) to afford the title compound as a pale brown oil, which turned into a cake upon cooling in the freezer at around -5 °C (2.27 g, 13.49 mmol, 69%).

$R_f = 0.29$ (30% EtOAc/hexanes).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.48 (s, 1 H), 3.61 (s, 3 H), 2.72 (dt, $J = 9.1, 3.1$ Hz, 4 H), 1.75 – 1.84 (m, 2 H), 1.55 – 1.68 (m, 4 H), 1.44 – 1.52 (m, 2 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 203.7, 172.8, 107.3, 55.4, 40.6, 31.2, 29.1, 28.7, 26.7, 25.0.

HRMS ($m/z$): 168.1147 (Calcd for C$_{10}$H$_{16}$O$_2$, 168.1150).

Following literature protocol,$^{66}$ to a suspension of LiAlH$_4$ (1.96 g, 51.65 mmol, 1.1 equiv) in Et$_2$O (100 mL) at -78 °C was added a solution of \textbf{2-76} (7.90 g, 46.96 mmol, 1.0 equiv) in Et$_2$O (50 mL) over a period of 1 h. After addition, RM stirred at the same temp for 1 h and carefully was added H$_2$O (3 mL) followed by 10% aq NaOH (2 mL) and finally with more H$_2$O (10 mL). RM then warmed up to rt and stirred until the RM turned into a white slurry. Salts filtered by passing through a pad of Celite® (3 cm) washing with Et$_2$O (20 mL). Et$_2$O dried over anhyd. MgSO$_4$ and concentrated \textit{in vacuo} to afford the title compound as a pale yellow syrup (7.50 g, 44.05 mmol, 94%) which was
reasonably pure and forwarded to next step without further purification.

\[ R_f = 0.32 \] (50% EtOAc/hexanes).

\[^1\text{H NMR}\] (600 MHz, CDCl\textsubscript{3}) \( \delta \) 4.61 (td, \( J = 9.0, 4.4 \) Hz, 1 H), 4.39 (d, \( J = 8.8 \) Hz, 1 H), 3.52 (s, 3 H), 2.23 – 2.30 (m, 1 H), 2.12 – 2.18 (m, 1 H), 1.79 – 1.87 (m, 1 H), 1.67 – 1.77 (m, 2 H), 1.49 – 1.57 (m, 3 H), 1.41 – 1.49 (m, 3 H), 1.32 – 1.41 (m, 2 H).

\[^{13}\text{C NMR}\] (101 MHz, CDCl\textsubscript{3}) \( \delta \) 158.3, 101.0, 70.0, 54.4, 37.7, 32.1, 27.2, 27.0, 24.8, 23.5.

\textbf{HRMS (m/z):} 170.1308 (Calcd for C\textsubscript{10}H\textsubscript{18}O\textsubscript{2}, 170.1307).

\begin{center}
\includegraphics[width=0.2\textwidth]{Compound_2-118.png}
\end{center}

\textbf{Compound 2-118}

Following literature protocol\textsuperscript{67} to a degassed solution of \textbf{2-117} (7.50 g, 44.05 mol, 1.0 equiv) and CH\textsubscript{2}I\textsubscript{2} (35.40 g, 132.16 mol, 3.0 equiv) in toluene (130 mL) at -15 °C, was slowly added (over a period of 1 h) a solution of Et\textsubscript{2}Zn (16.32 g, 132.16 mol, 3.0 equiv) in toluene (120 mL). After addition, the RM was stirred for 1 h, then warmed up to rt, and stirred for about 18 h. The RM was then cooled to -15 °C and carefully added a half satd. NH\textsubscript{4}Cl aq solution (250 mL). RM warmed up to rt, and stirred for 15 min. Salts filtered by passing through a pad of Celite\textsuperscript{®} (5 cm) washing with ether (200 mL). Layers separated, and aq layer extracted with ether (2 x 300 mL). Combined organic extractions were dried over anhyd. MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The residue was purified on silica gel flash chromatography (0-20% EtOAc/hexanes, buffered with 1% Et\textsubscript{3}N) to afford the title compound as a pale yellow syrup (6.50 g, 35.27 mmol, 80%).
$R_f = 0.19$ (50% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 3.41 (td, $J = 10.3, 4.1$ Hz, 1 H), 3.23 (s, 3 H), 2.56 (ddd, $J = 15.8, 7.0, 1.2$ Hz, 1 H), 1.79 – 1.87 (m, 2 H), 1.65 – 1.77 (m, 2 H), 1.48 – 1.65 (m, 4 H), 1.33 – 1.41 (m, 1 H), 1.19 – 1.28 (m, 1 H), 1.17 (td, $J = 10.1, 6.8$ Hz, 1 H), 0.93 (ddd, $J = 15.8, 10.6, 2.4$ Hz, 1 H), 0.88 (dd, $J = 10.0, 5.3$ Hz, 1 H), 0.16 (dd, $J = 7.0, 5.3$ Hz, 1 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 72.8, 64.7, 52.8, 37.2, 34.4, 29.6, 27.8, 26.4, 21.6, 20.1, 13.9.

HRMS ($m/z$): 184.1461 (Calcd for C$_{11}$H$_{20}$O$_2$, 184.1463).

![Compound 2-154](attachment:Compound_2-154.png)

Following literature protocol,$^{36b}$ a three neck round bottom flask containing a magnetic stir bar was fitted with a Liebig condenser and a pressurized addition funnel. The system was flame dried under vacuum and purged with argon twice. Xylenes (900 mL) was charged into the flask through the third neck of the flask followed by pentane washed sodium (24.00 g, 1043.93 mmol, 5.4 equiv) in pieces. The solution was heated to 100 °C and maintained for about 1 h to produce a sodium dispersion. The pressurized addition funnel was charged with xylenes (300 mL), dimethyl dodecanedioate$^{68}$ (50.00 g, 193.53 mmol, 1 equiv), and chlorotrimethylsilane (115.64 g, 1064.41 mmol, 5.5 equiv). The solution in the addition funnel was mixed via argon ebullition and then added dropwise over 6 h to the RM, with stirring. The RM turned pale brown upon addition. After addition, RM heated to reflux and maintained for 4 h before being cooled to rt. The
mixture was vacuum filtered through a plug of glass wool and then vacuum filtered through a pad of Celite® (3 cm) on a glass frit to remove residual sodium particles (about 200 mL of hexane/s were used for washings). The resulting brownish yellow filtrate was distilled to yield the title compound as a colorless oil (23.50 g, 68.67 mmol, 35%): bp 125-135 °C/1.5 mbar.

Rf = 0.29 (10% EtOAc/hexanes).

1H NMR (600 MHz, CDCl3) δ 2.09 - 2.12 (t, J = 7.0 Hz, 4 H), 1.52 - 1.57 (m, 4 H), 1.35 - 1.38 (m, 8 H), 1.26 - 1.32 (m, 4 H), 0.18 (s, 18 H).

HRMS (m/z): 342.2416 (Calcd for C18H38O2Si2, 342.2410).

1H spectrum was in agreement with previously reported data.36b

Compound 2-155

Following literature protocol,36b to a degassed solution of 2-154 (30.00 g, 0.088 mol, 1.0 equiv) and CH2I2 (63.39 g, 0.268 mol, 2.7 equiv) in toluene (260 mL) at -15 °C, was slowly added (over a period of 1 h) a solution of Et2Zn (31.40 g, 0.254 mol, 2.9 equiv) in toluene (160 mL). After addition, the RM was stirred for 1 h, then warmed up to rt, and stirred for about 12 h. The RM was then cooled to -15 °C and carefully was added a satd. aq solution of NH4Cl (300 mL). RM warmed up to rt and stirred for 30 min. Salts filtered by passing through a pad of Celite® (5 cm) washing with ether (200 mL). Layers separated, and aq layer extracted with ether (2 x 300 mL). Combined organic extractions were dried over anhyd. MgSO4 and concentrated in vacuo to afford the title compound as a pale yellow oil in reasonable purity (31.00 g, 0.087 mol, 98% crude yield). The crude
compound was directly forwarded to next step without further purification.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.77 – 1.87 (m, 4 H), 1.20 – 1.64 (m, 16 H), 0.81 (d, $J = 6.5$ Hz, 1 H), 0.44 (d, $J = 6.5$ Hz, 1 H). 0.17 (s, 18 H).

$^1$H spectrum was in agreement with previously reported data.$^{36b}$

Following literature protocol,$^{36b}$ to a degassed solution of 2-155 (31.00 g, 0.087 mol, 1.0 equiv) in DMF (300 mL) at rt, was added anhyd. FeCl$_3$ (31.01 g, 0.191 mol, 2.2 equiv) in 10 equal portions. After addition, RM heated to 60 °C and maintained for 14 h. RM then cooled down to rt and transferred into a vigorously stirring aq solution of 1 N HCl (300 mL) and stirred for 3 h. RM then extracted with CHCl$_3$ ($2 \times 200$ mL, $2 \times 100$ mL). Combined organic extractions were dried over MgSO$_4$, concentrated in vacuo and the residue purified on silica gel flash chromatography (15% EtOAc/hexanes) to afford the title compound as a pale brown syrup (0.3:1 mixture of keto, enol tautomers, 16.60 g, 0.079 mol, 90%).

$R_f = 0.45$ (20% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$)

Signals correspond to keto-tautomer: $\delta$ 3.60 (s, 2 H), 2.59 - 2.63 (m, 4 H), 1.66 (dt, $J = 11.9$, 6.1 Hz, 4 H), 1.36 (quin, $J = 6.6$ Hz, 8 H), 1.01 – 1.10 (m, 4 H).

Signals correspond to enol-tautomer: $\delta$ 5.70 (s, 1 H), 2.26 – 2.31 (m, 4 H), 1.69 – 1.74 (m, 4 H), 1.20 – 1.32 (m, 12 H).

$^1$H NMR spectrum was in agreement with previously reported data.$^{63}$
To a solution of **2-126** (3.10 g, 14.74 mmol, 1.0 equiv) and **CH(OMe)₃** (1.72 g, 16.22 mmol, 1.1 equiv) in **MeOH** (15 mL) at 0 °C, was added **TsOH·H₂O** (28 mg, 0.15 mmol, 0.01 equiv). RM was stirred at the same temp for 1 h, and warmed up to rt. After the RM was stirred for 18 h, was carefully added a 15% aq solution of **NaOH** (0.2 mL), and passed through a pad of Celite® washing with **Et₂O** (10 mL). Solvents dried over anhyd. **MgSO₄**, concentrated *in vacuo*, and the residue was purified on silica gel flash chromatography (5% EtOAc/hexanes) to afford the title compound as a bright greenish yellow oil (1.65 g, 7.35 mmol, 50%).

**Rᶠ** = 0.50 (30% EtOAc/hexanes).

**¹H NMR** (400 MHz, CDCl₃) δ 5.53 (s, 1 H), 3.65 (s, 3 H), 2.88 – 2.94 (m, 2 H), 2.35 – 2.40 (m, 2 H), 1.71 – 1.79 (m, 2 H), 1.55 – 1.63 (m, 2 H), 1.36 – 1.45 (m, 2 H), 1.16 – 1.32 (m, 10 H).

**¹³C NMR** (101 MHz, CDCl₃) δ 201.8, 175.1, 100.9, 55.2, 45.5, 29.0, 28.0, 27.1, 26.5, 25.7, 25.5, 24.7, 24.6, 23.7.

**HRMS (m/z):** 224.1778 (Calcd for C₁₄H₂₄O₂, 224.1776).
To a suspension of LiAlH$_4$ (127 mg, 3.35 mmol, 1.0 equiv) in Et$_2$O (9 mL) at -78 °C was added a solution of 2-156 (750 mg, 3.34 mmol, 1.0 equiv) in Et$_2$O (4 mL) over a period of 30 min. After addition, RM stirred at the same temp for 1.5 h and carefully was added H$_2$O (0.5 mL), followed by 10% aq solution of NaOH (0.5 mL), and finally an additional H$_2$O (1 mL). RM then warmed up to rt and stirred until the RM turned into a white slurry. Salts filtered by passing through a pad of Celite® (2 cm) washing with Et$_2$O (10 mL). Et$_2$O dried over anhyd. MgSO$_4$ and concentrated in vacuo to afford the title compound as a pale yellow syrup which was carried forward to next step without further purification.$^{69}$

$R_f = 0.31$ (30% EtOAc/hexanes).

To a degassed solution of 2-157 (1.00 g, 4.42 mmol, 1.0 equiv) and CH$_2$I$_2$ (3.20 g, 11.93 mmol, 2.7 equiv) in toluene (10 mL) at -15 °C, was slowly added (over a period of 1 h) a solution of Et$_2$Zn (1.47 g, 11.93 mmol, 2.7 equiv) in toluene (10 mL). After addition, stirred the cloudy RM for 30 min, then warmed up to rt, and stirred for about 18 h. The RM was then cooled to -15 °C and carefully was added a half satd. aq solution of NH$_4$Cl (20 mL), warmed up to rt, and stirred for 5 min. Salts filtered by passing through a pad of
Celite® (3 cm) washing with ether (20 mL). Layers separated, and aq layer extracted with ether (2 x 15 mL). Combined organic extractions were dried over anhyd. MgSO₄ and concentrated in vacuo. The residue was purified on silica gel flash chromatography (0-20% EtOAc/hexanes, buffered with 1% Et₃N) to afford the title compound as an off white paste (350 mg, 1.46 mmol, 33% from crude 2-124).

\[ R_f = 0.43 \text{ (50\% EtOAc/hexanes).} \]

\[^1\text{H NMR}\text{ (600 MHz, CDCl}_3\text{)}\delta 3.22 \text{ (s, 3 H), 3.14 (td, } J = 9.7, 1.8 \text{ Hz, 1 H), 2.30 (ddd, } J = 15.0, 11.5, 5.5 \text{ Hz, 1 H), 1.77 – 1.85 (m, 1 H), 1.58 – 1.65 (m, 2 H), 1.38 – 1.57 (m, 6 H), 1.27 – 1.38 (m, 8 H), 1.17 – 1.27 (m, 3 H), 1.00 – 1.06 (m, 1 H), 0.90 (dd, } J = 10.3, 5.6 \text{ Hz, 1 H), 0.33 (dd, } J = 7.0, 5.3 \text{ Hz, 1 H).} \]

\[^{13}\text{C NMR}\text{ (101 MHz, CDCl}_3\text{)}\delta 72.2, 65.8, 53.0, 36.1, 33.1, 29.6, 27.0, 25.5, 25.2, 25.0, 24.4, 24.4, 23.5, 15.4.\]

\text{HRMS (m/z): 240.2082 (Calcd for C}_{15}\text{H}_{28}\text{O}_2, 240.2089).}

\[ \text{Compound 2-124} \]

Following literature protocol,\textsuperscript{70} to a solution of (COCl)\textsubscript{2} (158 mg, 1.25 mmol, 1.5 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (4 mL) at -78 °C was added dropwise, a solution of DMSO (162 mg, 2.07 mmol, 2.5 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (1 mL). The RM was stirred for 10 min, then a solution of 2-123 (200 mg, 0.83 mmol, 1.0 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (1 mL) was added dropwise (syringe pump addition, 0.05 mL/min). After addition, the RM was stirred for 30 min, then Et\textsubscript{3}N (420 mg, 4.15 mmol, 5.0 equiv) was slowly added. Stirring continued for an additional 15 min, warmed up to rt, and H\textsubscript{2}O (10 mL) was added. Layers separated, aq layer extracted
with CH$_2$Cl$_2$ (2 x 10 mL), combined organic extractions were dried over anhyd. MgSO$_4$, and concentrated \textit{in vacuo}. The residue was purified on silica gel flash chromatography (0-15\% EtOAc/hexanes, buffered with 1\% Et$_3$N) to afford the title compound as a pale yellow oil (52 mg, 0.23 mmol, 28\%).

R$_f$ = 0.78 (30\% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.17 (app ddt, $J$ = 15.1, 10.6, 1.3 Hz, 1 H), 5.33 (d, $J$ = 10.6 Hz, 1 H), 5.28 (dt, $J$ = 15.0, 7.2 Hz, 1 H), 3.55 (s, 3 H), 2.31 – 2.35 (m, 2 H), 2.16 (app dq, $J$ = 7.1, 1.2 Hz, 2 H), 1.54 - 1.60 (m, 2 H), 1.43 – 1.49 (m, 2 H), 1.34 – 1.39 (m, 2 H), 1.18 – 1.31 (m, 10 H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 157.8, 127.7, 126.3, 99.9, 54.2, 30.3, 27.4, 27.2, 26.5, 26.2, 26.0, 25.6, 25.1, 23.7, 23.1.

![Compound 2-125](image)

The title compound was isolated along with \textbf{2-124} as an off white paste (25 mg, 0.11 mmol, 13\%).

R$_f$ = 0.42 (30\% EtOAc/hexanes).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.71 (s, 4 H), 2.48 (t, $J$ = 6.3 Hz, 4 H), 1.66 (quin, $J$ = 6.3 Hz, 4 H), 1.31 - 1.22 (m, 8 H), 1.18 - 1.12 (m, 4 H).

$^1$H NMR spectrum was in agreement with previously reported data.$^{71}$
Compound 2-128

Following literature protocol, to a mixture of 2-126 (470 mg, 2.24 mmol, 1 equiv) and isopropenyl acetate (2-127, 1.57 g, 15.64 mmol, 7 equiv) at rt was added a few crystals of TsOH·H₂O. RM was then heated to reflux and maintained for 2 h. Cooled to rt, diluted with CH₂Cl₂ (15 mL), and washed with ice cold Satd. aq solution of NaHCO₃. Combined organic extractions were dried over anhyd. MgSO₄, and concentrated in vacuo. The resulting purple syrup was purified on silica gel flash chromatography (10% EtOAc/hexanes) to afford the title compound as a yellow syrup (254 mg, 1.07 mmol, 45%).

Rᶠ = 0.69 (20% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 6.09 (s, 1 H), 2.34 (s, br, 4 H), 2.26 (s, br, 3 H), 1.67 (s, br, 4 H), 1.34 (s, br, 12 H).

HRMS (m/z): 252.1721 (Calcd for C₁₅H₂₄O₃, 252.1725).

Compound 2-131

To a slurry of Me₃SOI (156 mg, 0.71 mmol, 1.2 equiv) in DMSO (1 mL) at rt was added NaH (60% w/w in mineral oil, 35 mg, 0.88 mmol, 1.5 equiv). Stirred the RM for 1 h, then a solution of 2-128 (140 mg, 0.59 mmol, 1 equiv) in DMSO (1 mL) was added dropwise.
The RM was stirred for an additional 18 h, then H₂O (10 mL) was slowly added. RM extracted into EtOAc (2 x 15 mL), dried over anhyd. MgSO₄, and concentrated in vacuo. The resulting yellow oil was purified on silica gel flash chromatography (50% EtOAc/hexanes) to afford the title compound as an off white fluffy material (99 mg, 0.37 mmol, 56%).

Rₓ = 0.22 (30% EtOAc/hexanes).

¹H NMR (600 MHz, CDCl₃) δ 5.63 (s, 1 H), 5.29 (s, 2 H), 3.45 (s, 3 H), 2.45 (t, J = 6.5 Hz, 4 H), 1.61 - 1.71 (m, 4 H), 1.12 - 1.30 (m, 10 H), 1.05 - 1.12 (m, 2 H).

¹³C NMR (101 MHz, CDCl₃) δ 147.6, 104.9, 83.4, 50.6, 36.7, 27.4, 26.8, 26.2, 25.3.

Following literature protocol,⁷³ to a mixture of 2-150 (11.00 g, 66.80 mmol, 1 equiv) and TEMPO (1.05 g, 6.72 mmol, 0.1 equiv) in CH₂Cl₂ (110 mL) at rt was added BIAB (25.00 g, 77.62 mmol, 1.2 equiv). Stirred the RM at rt until 2-150 was completely consumed (by TLC). The RM was washed with satd. aq solution of Na₂S₂O₃ (100 mL), layers separated, and aq layer again extracted with CH₂Cl₂ (2 x 100 mL). Combined organic extractions were washed with satd. aq NaHCO₃ (100 mL), dried over MgSO₄, and concentrated in vacuo. The residue was then purified on silica gel flash chromatography (0-5% EtOAc/hexanes) to afford the title compound as a yellow oil (10.32 g, 63.45 mmol, 95%).

Rₓ = 0.42 (20% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 9.77 (t, J = 1.8 Hz, 1 H), 3.53 (t, J = 6.6 Hz, 2 H), 2.43 (td, J = 7.3, 1.8 Hz, 2 H), 1.73 – 1.81 (m, 2 H), 1.59 – 1.68 (m, 2 H), 1.40 – 1.49 (m, 2
$^1$H NMR spectrum was in agreement with previously reported data.$^{73}$

![Compound 2-148](image)

**Compound 2-148**

Following literature protocol,$^{74}$ to a suspension of the salt **2-151** (6.32 g, 18.44 mmol, 1.2 equiv) in THF (45 mL) at -78 °C was added a solution of $t$BuOK (2.25 g, 20.05 mmol, 1.3 equiv) in THF (10 mL). RM was then slowly warmed up to rt, stirred for 1 h, and cooled back to -78 °C. To this cold RM was slowly added, a solution of **2-149** (2.50 g, 15.37 mmol, 1.0 equiv) in THF (10 mL). After addition, RM slowly warmed up to rt, and stirred for 14 h before concentrating *in vacuo*. The residue was dissolved in Et$_2$O (50 mL) and washed with H$_2$O (50 mL). The aq layer was extracted with Et$_2$O (2 x 50 mL), combined organic extractions were dried over MgSO$_4$, and concentrated *in vacuo*. The crude compound was then purified on silica gel flash chromatography (0-10% EtOAc/hexanes) to afford the title compound as an inseparable mixture of E and Z isomers (1.0:0.7; 2.67 g, 14.00 mmol, 91%).

$R_f = 0.56$ (15% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$)

Signals correspond to E-isomer: δ 6.26 (d, $J = 12.3$ Hz, 1 H), 4.70 (dt, $J = 12.6$, 7.2 Hz, 1 H), 3.51 (td, $J = 6.8$, 1.8, Hz, 2 H), 3.48 (s, 3 H), 1.90 (q, $J = 6.8$ Hz, 2 H), 1.72 – 1.78 (m, 2 H), 1.37 – 1.45 (m, 2 H), 1.27 – 1.35 (m, 6 H).

Signals correspond to Z-isomer: δ 5.84 – 5.86 (m, 1 H), 4.29 – 4.33 (m, 1 H), 3.56 (s, 3 H), 3.51 (td, $J = 6.8$, 1.8 Hz, 2 H), 2.01 – 2.07 (m, 2 H), 1.72 – 1.78 (m, 2 H), 1.37 – 1.45
(m, 2 H), 1.27 – 1.35 (m, 6 H).

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 147.0, 146.0, 106.8, 102.9, 55.8, 45.0, 32.6, 30.6, 29.0, 28.7, 27.6, 26.8.

HRMS ($m/z$): 181.1467 (Calcd for C$_{10}$H$_{19}$ClO, 181.1467).

![Compound 2-153](image)

Compound 2-153

Following literature protocol,$^{75}$ to a mixture of 2-148 (1.18 g, 6.19 mmol, 1 equiv) in MeCN (11 mL) at rt, was added NaCN (0.76 g, 15.47 mmol, 2.5 equiv). The RM was then heated to 120 °C in a microwave reactor for 16 h. Cooled to rt, filtered through a plug of cotton, washed with CH$_2$Cl$_2$ (10 mL), and concentrated in vacuo. The resulting residue dissolved in CH$_2$Cl$_2$ (25 mL), washed with H$_2$O (25 mL), and aq layer extracted with CH$_2$Cl$_2$ (2 x 25 mL). Combined organic extractions were dried over MgSO$_4$, and concentrated in vacuo. The crude compound was then purified on silica gel flash chromatography (0-15% EtOAc/hexanes) to afford the title compound as a pale yellow oil (0.77 g, 4.25 mmol, 69%).

$R_f = 0.42$ (20% EtOAc/hexanes).

$^1$H NMR (600 MHz, CDCl$_3$) E:Z; 1.0:0.7.

Signals correspond to E-isomer: δ 6.27 (d, $J = 12.3$ Hz, 1 H), 4.71 (dt, $J = 12.6, 7.5$ Hz, 1 H), 3.50 (s, 3 H), 2.33 (td, $J = 7.3, 2.9$ Hz, 2 H), 1.91 (q, $J = 6.5$ Hz, 2 H), 1.65 (quin, $J = 7.3$ Hz, 2 H), 1.41 – 1.49 (m, 2 H), 1.26 – 1.38 (m, 6 H).

Signals correspond to Z-isomer: δ 5.87 (app d, $J = 6.5$ Hz, 1 H), 4.32 (q, $J = 6.8$ Hz, 1 H),
3.57 (s, 3 H), 2.33 (td, $J = 7.3$, 2.9 Hz, 2 H), 2.02 – 2.07 (m, 2 H), 1.65 (quin, $J = 7.3$ Hz, 2 H), 1.41 – 1.49 (m, 2 H), 1.26 – 1.38 (m, 6 H).

**HRMS (m/z):** 181.1467 (Calcd for C$_{11}$H$_{19}$NO, 181.1467).
2.8 Notes and References


17. *In vitro* studies against human breast adenocarcinoma cell lines MCF-7 and MDA-MB231.


23. Authors observed low yields with often used dimethylformamide.


56. See experimental for details.


60. CCDC-1498472 contains the crystal data for compound 2-131. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


62. Pure diethyl zinc (Alfa Aesar 39564) was diluted in toluene under N$_2$ atmosphere (glovebox).


65. A uniform stirring is a must. In instances when the RM was stirred too slow, only starting material was isolated. When the RM was stirred too fast, a dialkylated product was observed.


69. Product was always impure with either starting material or by-product, (Z)-cyclotridec-2-en-1-one.


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Appendix IA. Royal Society of Chemistry:

“Synthesis and reactivity of alkoxy-activated cyclobutane-1,1-dicarboxylates.”

“The [4+2] cycloaddition of donor–acceptor cyclobutanes and nitrosoarenes”

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Appendix IB. John Wiley and Sons:

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Licensed Content Title: “Synthesis of Tetrahydro-1,2-oxazines and Pyrrolidines via Cycloadditions of Donor–Acceptor Cyclobutanes and Nitrosoarenes”
Licensed Content Author: Naresh Vemula, Brian L. Pagenkopf
Licensed Content Date: Jun 22, 2015
Appendix IC. American Chemical Society:

Title: “Cascade Reaction of Donor-Acceptor Cyclopropanes: Mechanistic Studies on Cycloadditions with Nitrosoarenes and cis-Diazenes”

Author: Tristan Chidley, Naresh Vemula, Cheryl A. Carson, Michael A. Kerr, Brian L. Pagenkopf.

Publication: Organic Letters

Publisher: American Chemical Society

Date: Jun 1, 2016

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Appendix II. NMR Spectral Data of New Compounds for Chapter 1
Compound 1-97a

$^1$H NMR

CDCl$_3$, 400 MHz
Compound 1-97a
$^{13}$C NMR
CDCl$_3$, 101 MHz

- 167.92
- 167.65
- 146.70
- 128.54
- 123.00
- 117.52
- 88.64
- 83.65
- 66.97
- 52.16
- 62.02
- 33.26
- 30.82
- 29.56
- 13.94
NMR correlations of 1-974
Compound 1-97c

$^1$H NMR
CDCl$_3$, 600 MHz
Chemical Shift (ppm)

- 167.7
- 167.5
- 145.4
- 128.1
- 128.5
- 118.9
- 88.7
- 83.6
- 77.3
- 77.0
- 76.7
- 67.1
- 62.2
- 62.1
- 33.4
- 30.5
- 29.4
- 14.0

Compound 1-97c
$^{13}$C NMR
CDCl$_3$, 101 MHz
NOE correlations of 1-97c
Compound 1-97d
$\text{\textsuperscript{13}C NMR}$
CDCl$_3$, 101 MHz
Compound 1-97e
$^{13}$C NMR
CDCl$_3$, 101 MHz
Chemical Shift (ppm)
Compound 1-97g
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 1-97j
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 1-97k
$^1$H NMR
CDCl$_3$, 600 MHz
NDE correlations of 1-97FK
Compound 1-98k
$^{13}$C NMR
CDCl$_3$, 101 MHz
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**Compound 1-97I**

$^1$H NMR

CDCl$_3$, 400 MHz
Compound 1-97
$^{13}$C NMR
CDCl$_3$, 101 MHz

Chemical Shift (ppm)

- 167.3
- 166.9
- 152.0
- 142.3
- 124.7
- 115.8
- 88.0
- 83.7
- 77.3
- 77.0
- 76.7
- 62.5
- 62.4
- 33.4
- 30.3
- 28.9
- 14.0
- 13.9
Compound 1-98k
$^{13}$C NMR
CDCl$_3$, 101 MHz
$^{1}H -^{15}N$ HMB Correlations of I-98n
Compound 1-101n
\(^{13}\)C NMR
CDCl\(_3\), 101 MHz
Compound 1-102n
$^{13}$C NMR
CDCl$_3$, 101 MHz
NOE Correlations of 1-1010
Compound 1-107k
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 1-198p
$^1$H NMR
CDCl$_3$, 600 MHz
Chemical Shift (ppm)

Normalized Intensity

Compound 1-198q

$^{13}$C NMR

CDCl$_3$, 101 MHz
oe Correlations of 1-198g
Chemical Shift (ppm)

Normalized Intensity

Compound 1-108aa

$^1$H NMR

CDCl$_3$, 600 MHz
Compound 1-110an

$^{13}$C NMR

CDCl$_3$, 101 MHz

Chemical Shift (ppm)

-171.1
-153.3
-137.8
-118.0
-113.8
-90.0
-74.0
-76.7
-63.9
-61.7
-55.5
-38.2
-35.1
-23.7
-20.7
-14.0
-13.9
NOE correlations of 1-110an
Compound 1-108ga

$^{13}$C NMR

CDCl$_3$, 101 MHz
Compound 1-108gc
$^1$H NMR
CDCl$_3$, 600 MHz
Compound 1-108gc

$^{13}$C NMR

CDCl$_3$, 101 MHz
Compound 1-108fa
$^1\text{H}$ NMR
CDCl$_3$, 600 MHz
Compound 1-108fa
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 1-109fn
$^1$H NMR
CDCl$_3$, 600 MHz

Chemical Shift (ppm)
$^{15}N$ HMBC Correlations of 1-1096m
Compound 1-111fn

$^1$H NMR

CDCl$_3$, 400 MHz

Chemical Shift (ppm)
Compound 1-111fn

$^{13}$C NMR

CDCl$_3$, 101 MHz
Compound 1-124bb

$^1$H NMR
CDCl$_3$, 400 MHz
Compound 1-124bb
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 1-167I
$^1$H NMR
CDCl$_3$, 400 MHz
Compound 1-167I
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 1-136b
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 1-145a
$^{13}$C NMR
CDCl$_3$, 101 MHz
Chemical Shift (ppm)

-1.27
1.23
1.25
1.95
1.97
2.42
2.43
2.44
2.45
2.61
2.63
3.38
3.40
3.42
4.06
4.07
4.09
4.17
4.18
4.19
4.20
4.21

Compound 1-149a

$^1$H NMR
CDCl$_3$, 400 MHz
Compound 1-149a

$^{13}$C NMR

CDCl$_3$, 101 MHz

Chemical Shift (ppm)

-169.3

-157.1

-90.3

77.3

77.0

-76.7

-70.5

-61.0

52.3

-28.8

24.8

-24.8

-14.0
Appendix III. NMR Spectral Data of New Compounds for Chapter 2
Compound 2-79
$^1$H NMR
CDCl$_3$, 400 MHz
Compound 2-79
$^{13}$C NMR
CDCl$_3$, 151 MHz
Compound 2-78

$^1$H NMR

CDCl$_3$, 600 MHz

Chemical Shift (ppm)
Compound 2-78
$^{13}$C NMR
CDCl$_3$, 151 MHz
Compound 2-77
$^1$H NMR
CDCl$_3$, 600 MHz
Compound 2-77
$^{13}$C NMR
CDCl$_3$, 151 MHz
Compound 2-113
\(^{13}\text{C} \) NMR
CDCl\(_3\), 101 MHz
Compound 2-76
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 2-117
$^1$H NMR
CDCl$_3$, 600 MHz
Compound 2-117
$^{13}$C NMR
CDCl$_3$, 101 MHz

-158.3
-101.0
77.3
77.0
76.7
-70.0
-54.4
-37.7
-32.1
27.2
27.0
23.5
24.8
Compound 2-118
$^1$H NMR
CDCl$_3$, 600 MHz
Compound 2-118
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 2-154

$^1$H NMR

CDCl$_3$, 600 MHz
Compound 2-155
$^1$H NMR
CDCl$_3$, 600 MHz
Chemical Shift (ppm)

Compound 2-156

$^1$H NMR
CDCl$_3$, 600 MHz
Compound 2-156
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 2-123
$^1$H NMR
CDCl$_3$, 600 MHz
Compound 2-124

$^1$H NMR

CDCl$_3$, 600 MHz

Chemical Shift (ppm)
Compound 2-124
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 2-125
$^1$H NMR
CDCl$_3$, 400 MHz
Compound 2-128

$^1$H NMR

CDCl$_3$, 400 MHz
Compound 2-131
$^{13}$C NMR
CDCl$_3$, 101 MHz
Compound 2-148
$^{13}$C NMR
CDCl$_3$, 151 MHz
Compound 2-153
$^1$H NMR
CDCl$_3$, 600 MHz
Curriculum Vitae

EDUCATION

August 2016  Ph.D. in Chemistry
The University of Western Ontario, London, ON Canada
Supervisor: Prof. Brian L. Pagenkopf

2007  M.Sc. Organic Chemistry
Kakatiya University, Warangal, TS India

2004  B.Sc. Chemistry, Botany, and Zoology
Osmania University, Hyderabad, TS India

EMPLOYEMENT HISTORY

Sep 2011 - Aug 2016  Graduate Research/Teaching Assistant
Department of Chemistry
The University of Western Ontario, London, ON Canada
Supervisor: Prof. Brian L. Pagenkopf

May 2010 - Jul 2011  Research Associate
Discovery Research, DuPont Crop Protection
E. I. DuPont India (P) Ltd, Hyderabad, TS India

July 2007 - April 2010  Senior Executive
Process R&D
Dr. Reddy’s Laboratories Ltd, Hyderabad, TS India

PATENTS


PUBLICATIONS


**SELECTED CONFERENCE PRESENTATIONS**


(3) **Vemula, N.;** Pagenkopf, B. L. “Divergent Synthesis of Tetrahydro-1,2-oxazines and Pyrrolidines via Cycloadditions of Donor-Acceptor Cyclobutanes and Nitrosoarenes”, *Oral Presentation*, 246th ACS National Meeting & Exposition, Indianapolis, IN, United States, September 8-12, 2013

(2) **Vemula, N.;** Pagenkopf, B. L. “Donor-Acceptor Cyclobutanes as Synthetic Building Blocks”, *Oral Presentation*, 23rd Quebec-Ontario Mini-Symposium on Bio-organic and Organic Chemistry (QOMSBOC) Conference, Windsor, ON, Canada, November 9-11, 2012

AWARDS & AFFILIATIONS

2015         CSC 2004 Conference Travel Award
Sep 2011 - Aug 2016 Western Graduate Research Scholarship
Sep 2011 - Aug 2016 Western International Student Scholarship
Sep 2012 - present Member of American Chemical Society
Sep 2011 - Aug 2016 Member of Western Society of Graduate Students