Investigations into the Ruthenium Catalyzed Ring Opening and Dimerization Reactions of Oxabicyclic Alkenes

by

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INVESTIGATIONS INTO THE RUTHENIUM CATALYZED RING OPENING AND DIMERIZATION REACTIONS OF OXABICYCLIC ALKENES

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Oxabicyclic alkenes have been the focus of many synthetic studies as they are versatile compounds which act as synthetic intermediates to produce a variety of useful heterocyclic, carbocyclic and acyclic products. The nucleophilic ring opening reaction of oxabenzonorbornadiene was studied. Methanol was the primary nucleophile used throughout the investigation, however various other alcohol nucleophiles were also tested for their efficacy. The effects of substitution were explored, providing ring opened products in yields of up to 81%.

The [2+2] cyclodimerization reaction of oxanorbornadienes was also examined providing the first examples of dimers of this kind. The scope was expanded to include other 2,3-diester oxanorbornadienes as well as various C¹ substitutions. Changing the ester moiety did not affect the reaction, however the addition of a C¹ alkyl substituent did result in lower yields. Moderate yields of up to 66% were obtained. Additionally, a new ruthenium complex was discovered in the process.
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<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>APT</td>
<td>Attached Proton Test</td>
</tr>
<tr>
<td>Ar</td>
<td>Any Aromatic Group</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>CO</td>
<td>Carbonyl</td>
</tr>
<tr>
<td>COD</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>Cp</td>
<td>Cyclopentadienyl</td>
</tr>
<tr>
<td>Cp*</td>
<td>Pentamethylcyclopentadienyl</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical Shift (NMR)</td>
</tr>
<tr>
<td>d</td>
<td>Doublet (NMR)</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>DMAD</td>
<td>Dimethyl Acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl Sulfoxide</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric Excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Impact Ionization</td>
</tr>
<tr>
<td>eq</td>
<td>Equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared Spectroscopy</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium Diisopropyl Amine</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet (NMR)</td>
</tr>
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</table>
M Any Metal
MCH Melatonin-Concentrating Hormone
Me Methyl
MS Mass Spectrometry
NBS n-Bromosuccinimide
n-Bu Butyl (Straight Chain)
NMR Nuclear Magnetic Resonance
NOE Nuclear Overhauser Effect
Nu Nucelophile
Ph Phenyl
PhH Benzene
ppm Parts per Million
q Quartet (NMR)
R Organic Group
RSE Ring Strain Energy
s Singlet (NMR)
t Triplet (NMR)
TC Thiophene-2-Carboxylate
TBS tert-Butyldimethylsilyl
Tf Triflate
TFE Trifluoroethanol
TMS Trimethyl Silyl
TPS tert-Butyldiphenylsilyl
X Any Halogen
Chapter 1: Introduction
1.1 Introduction to Bicyclic Alkenes

The synthesis of natural products presents a challenging goal to synthetic chemists due to their complex structure which often contains multiple ring systems.\textsuperscript{1} Bicyclic alkenes provide a useful starting structure for building the framework of such natural products (Scheme 1-1). Estrone 1-1 is an estrogenic hormone which was first synthesized by Cohen and coworkers in the 1930s.\textsuperscript{2} Since this time, Woodward\textsuperscript{3} and Li and coworkers\textsuperscript{4} have provided more efficient syntheses which start from an oxabicyclic alkene. The total synthesis of other hormones such as prostaglandins\textsuperscript{5-7} 1-2 as well as anticancer agents such as Epoxyquinol\textsuperscript{8} 1-3 and (±)-Pedicularine\textsuperscript{9} 1-4 has been demonstrated involving oxabicyclic alkenes as important intermediates.

\textbf{Scheme 1-1:} Natural Products Synthesized from Bicyclic Alkenes
Bicyclic alkenes make up a diverse class of organic compounds (Figure 1-1). The bicyclo[2.2.1]alkenes are comprised of norbornene 1-5 and norbornadiene 1-6 as well as a variety of heteroatom derivatives such as 2,3-diazo heterobicycles 1-7, 7-azaheterobicycles 1-8, 2-aza-3-oxa heterobicycles 1-9, and 7-oxaheterobicycles 1-10. Of particular interest to the Tam group is the 7-oxaheterobicycles which can be further divided into three main subclasses: 7-oxabenzonorbornadiene 1-11, 7-oxanorbornadienes 1-12, and 7-oxanorbornenes 1-13 (Figure 1-2).  

![Figure 1-1: Types of Bicyclic Alkenes](image1)

![Figure 1-2: Types of Oxabicyclic Alkenes](image2)

The synthetic interest and utility in bicyclic alkenes lies in their increased reactivity in comparison to monocyclic or linear alkenes. The unfavourable angle of the heteroatom bridge results in the high ring strain seen in this class of
molecules. The ring strain energies (RSE's) of oxanorbornadiene 1-12 and oxanorbornene 1-13 were calculated to be 36.1 kcal/mol and 22.1 kcal/mol respectively using the homodesmotic method. In comparison, cyclopropane was determined to have a RSE of 27.5 kcal/mol using the same method. This method however, was unable to be used to calculate the RSE for Oxabenzonorbornadiene 1-11. Alternatively, the relative RSE of oxabenzonorbornadiene was determined to be 8.4 kcal/mol when compared to oxanorbornane.\textsuperscript{12}

Bicyclo[2.2.1]alkenes contain two faces, one of which react preferentially depending on the conditions employed (Figure 1-3). The convex \textit{exo} face is less sterically hindered than the concave \textit{endo} face which is subject to homoconjugative effects.\textsuperscript{13} Homoconjugation is defined by IUPAC as “The orbital overlap of two \(\pi\)-systems separated by a non-conjugating group, such as CH\(_2\).”\textsuperscript{14} This orbital overlap is responsible for many of the reactive characteristics of bicyclic alkenes.\textsuperscript{15} Photoelectron spectroscopy of norbornadiene has revealed strong interaction between the two ethylene systems.\textsuperscript{16,17} Further studies revealed decreased bond lengths in bicyclic alkenes, providing additional evidence of homoconjugation being present in these systems.\textsuperscript{18}

\textbf{Figure 1-3:} Properties of Bicyclic Alkenes
Although numerous classes of bicyclic alkenes have been synthesized to date, only two are of interest to this thesis. The synthesis and reactions of oxabenzonorbornadiene 1-11 and the oxanorbornadiene 1-12 will be explored in order to provide the basis for the research to be presented in later chapters.

1.2 Synthesis of Oxabenzonorbornadiene

Oxabenzonorbornadiene is synthesized via a [4+2] Diels-Alder cycloaddition between furan and benzyne which is generated in situ (Scheme 1-2). It is possible to prepare oxabenzonorbornadienes containing a variety of substitution patterns (Figure 1-4). Differently substituted benzenes and furans are used to create these various oxabenzonorbornadienes.

\[
\text{1-14} + \text{1-15} \rightarrow \text{1-11}
\]

Scheme 1-2: Synthesis of Oxabenzonorbornadiene

Figure 1-4: Oxabenzonorbornadiene Substitution Patterns
In the Diels-Alder cycloaddition, benzyne is generated in situ due to its highly reactive nature. A variety of methods can be used to synthesize benzyne (Scheme 1-3). The thermal decomposition of anthranilic acid in the presence of isoamyl nitrite results in the emission of nitrogen and carbon dioxide gasses as a biproduct of the formation of benzyne.\textsuperscript{19} Fluoride can be used to promote the 1,2-elimination of TMS and triflate from 1-18.\textsuperscript{20} Various mono- and di-halogenated benzenes can also be used to generate benzyne. A metal-halide exchange involving lithium or magnesium followed by a halide elimination has been shown to successfully produce benzyne.\textsuperscript{21,22} Deprotonation ortho to a halogen substituent of a benzene system using a strong base such as \textsuperscript{t}BuLi results in elimination of the halogen to provide the desired benzyne.\textsuperscript{23}

\textbf{Scheme 1-3: Generation of Benzyne}
The method employed to generate benzyne is dependent on the substitution pattern of the desired oxabenzonorbornadiene. Anthranilic acid is most commonly used for the synthesis of unsubstituted oxabenzonorbornadienes as well as $C^1$ and $C^{1-4}$ substituted bicyclics. When substitutions on the benzo component of oxabenzonorbornadiene a method involving the elimination of a halogen are commonly employed on a poly substituted benzene to generate a substituted benzyne.

1.3 Reactions of Oxabenzonorbornadienes

The simplicity of synthesis of oxabenzonorbornadiene combined with this compounds potential to create valuable synthetic intermediates in the form of highly substituted ring systems has led to extensive exploration into its reactive capabilities. Of particular interest are those involving transition metal catalysts to prompt the reaction. Cycloaddition, cyclodimerization, deoxygenation, cyclization, cyclopropanation, isomerization and ring-opening reactions have all been previously investigated (Scheme 1-4).\textsuperscript{11}
A multitude of cycloaddition reactions involving oxabenzenorbornadienes have been demonstrated (Scheme 1-4). The [2+2] cycloaddition to provide 1-21 has been extensively explored using a Ru-catalyst to promote the reaction between oxabenzenorbornadiene and a variety of alkynes. Wender and coworkers provide the only examples of this reaction using an alkene as an alternative.\textsuperscript{24} Alkynes containing ester moieties provided generally moderate
yields of the cycloadduct.\textsuperscript{25,26} The use of alkynyl halides,\textsuperscript{27} alkynyl sulfides and sulfones,\textsuperscript{28} and alkynyl phosphonates\textsuperscript{29} in the [2+2] cycloaddition have all been explored with success by Tam and coworkers. Other attempts to expand the scope of this reaction by Tam and coworkers involved the use of propargylic alcohols. Although the cycloadduct was observed, a cyclopropanated side product was also seen.\textsuperscript{30} Co\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} proved to be a successful in catalyzing the [2+2] cycloaddition between a variety of alkynes and oxabenzonorbornadiene providing a range of yields from low to excellent depending on the alkynyl substituents and reaction conditions.\textsuperscript{31} Nickel catalysis of the same reactions provided generally similar yields as when cobalt was employed.\textsuperscript{32} Shao and coworkers provide the only enantioselective examples of this cycloaddition through the use of chiral iridium catalysts.\textsuperscript{33}

Although the [2+2] cycloaddition has been the most extensively investigated, Pauson-Khand [2+2+1] cycloadditions to give 1-22 have also been examined using a variety of catalysts. Traditionally, transition metals such as nickel, ruthenium, rhodium, and iridium have been used to promote this reaction. More recently, however, investigations by Aguilar and coworkers using W(CO)\textsubscript{5} to catalyze this reaction have been undertaken.\textsuperscript{34} Cheng and coworkers have done extensive research into the [2+2+2] cycloaddition reaction which provides 1-23. The use of a nickel catalyst with either two equivalents of alkyne or a diyne has been shown to produce this cycloadduct.\textsuperscript{35-37}
The isomerization of oxabenzonorbornadiene into 1-naphthols \textbf{1-24} is a well known reaction which is commonly observed as a side product of ring opening reactions of this compound. Villeneuve and Tam launched the first investigation into the formation of naphthalene oxides which can then be further isomerized to provide 1-naphthols with mild conditions (Scheme 1-5).\textsuperscript{38} The use of a Ru catalyst followed by purification in neutral alumina was needed to provide the naphthol oxide \textbf{1-32}. When silica gel was alternatively used for purification, only the naphthol was obtained. Further investigation into the Ru catalysed isomerization to synthesize naphthols resulted in high yields of a variety of highly substituted naphthols.\textsuperscript{39} Aluminum powder\textsuperscript{40} and Cu(OTf)\textsubscript{2}\textsuperscript{41} were also shown to be capable of promoting this isomerization.

\textbf{Scheme 1-5: Isomerization of Oxabenzonorbornadiene}

Cyclopropanation reactions of oxabenzonorbornadienes take a variety of forms giving the general product \textbf{1-25} (Scheme 1-4). Dimedone \textbf{1-33} in the presence of Mn and Cu was used by Balci and coworkers to prepare cyclopropane \textbf{1-34} among other products in a 35% yield (Scheme 1-6).\textsuperscript{42,43} Palladium and ruthenium can be used to catalyze a cyclopropanation reaction
between alkynes and oxabenzonorbornadiene. Terminal alkynes with Pd(OAc)$_2$ provided 1-38 in 56% yield (Scheme 1-7), whereas the ruthenium catalyzed variant of this reaction results in a variety of products depending on the conditions employed (Scheme 1-8). A reaction mixture containing the terminal acetylene acetate 1-39, oxabenzonorbornadiene, and dioxane in the presence of CpRuCl(PPh$_3$)$_2$ provided only the cyclopropanated product 1-40. The use of a disubstituted alkyne and various ruthenium catalysts resulted in a combination of cyclopropane 1-41 as well as the ring opened cyclopropanated system 1-42. Solvent was determined to play a critical role in the formation of the cyclopropane 1-44. The use of THF provided primarily the desired cyclopropane whereas the use of MeOH alternatively resulted in isochromene 1-29. The [2+2] cycloadduct also resulted as a minor bi-product in both cases.

Scheme 1-6: Cyclopropanation of Oxabenzonorbornadiene with Dimedone
Dimerization reactions of oxabenzonorbornadienes have followed two distinct routes. Rhodium has been shown to catalyze the asymmetric dimerization to provide 1-26 (Scheme 1-4). Cheng and coworkers utilized a nickel catalyst with zinc metal to promote the [2+2] dimerization of oxabenzonorbornadiene which resulted in 1-27.

Cyclization reactions of oxabenzonorbornadienes have produced two main classes of polycyclic compounds; benzocoumarins 1-28 and isochromenes.
1-29 (Scheme 1-4). Nickel in the presence of zinc was shown to catalyze the synthesis of benzocoumarins via a reaction with various propriolates.\textsuperscript{51,52} As previously described, isochromenes have been synthesized via the reaction between oxabenzonorbornadiene and a propargylic alcohol in the presence of Cp*Ru(COD)Cl. The isochromene was the preferentially formed product when the reaction was carried out in MeOH.\textsuperscript{47}

Deoxygenation of the epoxide is a convenient method to provide substituted naphthalene systems such as 1-30 (Scheme 1-4). Titanium is a popular deoxygenating reagent which has also shown utility for this system. TiCl\textsubscript{4} with \textsuperscript{1}Bu\textsubscript{2}Te was shown to be successful in synthesizing naphthalenes from oxabenzonorbornadiene.\textsuperscript{53} Other less traditional methods have also been used to promote this process. Coordination of the epoxide with Fe(CO)\textsubscript{9} followed by thermal extrusion has also provided naphthalene 1-30.\textsuperscript{54} Grignard reagents were shown by Gribble and coworkers to insert Mg into the C\textsuperscript{1}-O bond which allows for the elimination of MgO to give the desired product.\textsuperscript{55}

Ring opening reactions of oxabenzonorbornadienes to provide compounds such as 1-31 have been extensively studied (Scheme 1-4). Transition metals including Ni, Pd, and Rh have been paired with different nucleophiles to provide a variety of ring opening products. Examples of nucleophiles explored to date include hydrides, alkyl groups, and heteroatoms. In some cases, other compounds such as boronic acids have also been capable of promoting the ring opening of oxabenzonorbornadienes.\textsuperscript{56}
1.4 Synthetic Utility of Oxabenzonorbornadiene

[4+2] Diels-Alder cycloadditions to provide highly substituted oxabenzonorbornadienes which are then able to undergo further derivation have been crucial steps in the synthesis of a variety of natural products. As previously stated, the complex poly cyclic nature of many natural products makes the synthesis of oxabenzonorbornadienes as well as the exploration into reactions possible by this compound an area of interest to synthetic chemists. Discovering new transition metal catalyzed reactions provides the potential to create shorter synthetic routes to obtain natural products.

C-Aryl glycosides make up a class of natural products possessing biological activity such as antibiotic and anticancer properties. The substitution patterns of the rings have divided this molecular class into four categories. Kidamycin is a C-aryl glycoside whose biological activity is due to its ability to bind to DNA and cause single strand cleavage. Kidamycin is light and acid sensitive and is easily converted to the slightly more stable stereoisomer Isokidamycin 1-43. When O’Keefe and coworkers undertook the total synthesis of Isokidamycin (Scheme 1-9) an intramolecular Diels-Alder cycloaddition was a key step in the synthesis to provide 1-45. Acid catalyzed ring opening is then used to continue along the path towards the total synthesis of Isokidamycin.
Scheme 1-9: Retrosynthesis of Isokidamycin

5-Hydroxyaloin A 1-49 and Galtamycinone 1-50 (Figure 1-5) are two other C-aryl glycosides whose total synthesis have been completed. Both syntheses involve a [4+2] Diels-Alder cycloaddition followed by an acid catalyzed ring opening. Due to the similarities in structure between the C-aryl glycosides 5-Hydroxyaloin A and Galtamycinone both follow similar synthetic pathways to that of Isokidamycin which was shown previously.
C-Aryl glycosides are not the only class of natural products which have utilized oxabenzonorbornadiene as a part of their synthesis. Geovanie 1-51 is an azaanthracenone isolated from the trunk of *Annona ambotay*. Azaanthracenones have shown antimalarial activity against a drug resistant strain of *Plasmodium falciparum*. Other observed biological activity of such compounds includes cytotoxicity providing the possibility for azaanthracenones to be used as antitumor agents in humans. The total synthesis of Geovanie required nine steps (Scheme 1-10). As expected, the synthesis involves a Diels-Alder cycloaddition between quinolone and furan. Acid catalyzed ring opening is again seen as the step following cycloaddition. In this synthesis, bromination of 1-53 followed by treatment with LDA was used to generate benzyne.
1.5 Synthesis and Reactions of 2,3-Dicarboxylate Oxanorbornadienes

As with oxabenzonorbornadiene, the 2,3-dicarboxylate oxanorbornadiene 1-56 (formally named 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate and referred to as oxanorbornadiene from this point forward) is synthesized via a Diels-Alder cycloaddition (Scheme 1-11). Thermal promotion of furan 1-15 with dimethyl acetylenedicarboxylate (DMAD) 1-57 results in the desired oxanorbornadiene.\(^{62}\) Although other methods such as Lewis Acid catalysis\(^{63}\) and microwave conditions\(^{64}\) have also been used to aid in synthesizing this compound, the basic thermal reaction remains the most straightforward and highest yielding mode of synthesis.
As with oxabenzonorbornadiene, the ease of synthesis of oxanorbornadiene \textbf{1-56} makes investigation into the reactions it can participate in a viable option for synthetic chemists. The bicyclic nature of this compound provides a highly reactive framework which results in a variety of synthetically useful products (Scheme 1-12). Despite the similarity in properties between oxabenzonorbornadiene and this class of oxanorbornadienes, there has been much less exploration into reactions in which it can participate. Transition metal catalysts have been used to expand the reaction scope of this compound. The transition metal catalyzed reactions of oxanorbornadiene thus far explored include cycloaddition, cyclopropanation, deoxygenation, and ring opening reactions.
The cyclopropanation of oxanorbornadiene 1-56 was explored in an attempt to expand the scope of this cyclopropanation reaction of oxabenzonorbornadiene. Both Tenagila and coworkers and Tam and coworkers explored this scope expansion using different acetylenes (Scheme 1-13). Tenaglia’s investigation involved propargylic acetates which provided 1-58 through the use of CpRuCl(PPh$_3$)$_2$ as a catalyst.$^{45}$ Tam’s exploration into this reaction involved propargylic alcohols as the acetylene and Cp*Ru(COD)Cl as
the catalyst. The reaction elicited interesting results when applied to the oxabenzonorbornadiene system as [2+2] cycloadducts, cyclopropanation products, and isochromenes were all isolated. In the alternative case utilizing oxanorbornadiene as the alkene, only the cyclopropanated product was recovered.\(^{47}\)

![Scheme 1-13: Cyclopropanation of Oxanorbornadienes](image)

The asymmetric dimerization of oxabicyclic alkenes has resulted in various products depending on the alkene employed in the reaction. When oxanorbornadiene 1-56 is subjected to a Rh-catalyst and a chiral ligand in the presence of AgBF\(_4\) the cyclopropanated dimer 1-59 is formed as the primary product (Scheme 1-12). This compound differs in structure from that formed when these conditions are employed with oxabenzonorbornadiene however the reaction mechanism is proposed to be similar in both situations.\(^{48,49}\)

The deoxygenation of oxanorbornadiene has been demonstrated on multiple occasions. Titanium was the most popular reagent chosen to carry out
this process. Huang and coworkers utilized TiCl$_4$ with LiAlH$_4$ to promote this reaction.$^{65,66}$ Alternatively, Wong and coworkers used a different titanium system involving CpTiCl$_3$ with LiAlH$_4$ in THF to obtain the deoxygenated product 1-60 from oxanorbornadiene 1-56 (Scheme 1-12).$^{67}$ Chow and coworkers took a different approach, using a molybdenum carbonyl to promote the thermolysis of oxanorbornadiene. In this reaction, furan was recovered as a side product due to retrocyclization.$^{68}$

Cycloadditions are also a popular reaction with oxanorbornadiene 1-56 (Scheme 1-12). Only two cycloadditions have been explored with this compound, the [2+2] and the [2+2+1] Pauson-Khand. Ruthenium was shown by Tam and coworkers to catalyze [2+2] cycloadditions between oxanorbornadiene and acetylenes containing phosphate$^{29}$ and ester$^{26}$ moieties to give 1-61. The reaction was much more successful with the use of the ester acetylene as opposed to the phosphate acetylene. The [2+2+1] Pauson-Khand cycloaddition was carried out using Co$_2$(CO)$_8$. Terminal and dialkyl acetylenes underwent the cycloaddition to provide the exo-cycloadducts 1-62 in moderate yields. During the investigation, the reaction did not seem possible under thermal conditions but when NMO was used as a solvent it also served to promote the cycloaddition.$^{69}$

Various ring openings of 1-56 have been explored by synthetic chemists (Scheme 1-12). Sonoda and coworkers provided examples of ring openings to provide phthalic acids such as 1-63. IrCl$_3$ and FeCl$_3$ systems were both tested with FeCl$_3$ providing the product in quantitative yields. 2,3,4-Trisubstituted and
2,3,4,5-substituted oxanorbornadienes were also subjected to these conditions resulting in highly substituted phthalic acids.\textsuperscript{70} An alternative ring opening using palladacycles to catalyze the reactions was explored by Hou and coworkers. BnZnBr was used to open the ring with the aid of the palladacycle resulting in 1-64.\textsuperscript{71} In a final ring opening example, Alexakis and coworkers demonstrated a copper mediated asymmetric ring opening. Trialkylaluminums were used as the reagent of choice to undergo conjugate addition and ring open the oxanorbornadiene. Various chiral ligands and alkylaluminums were tested, successfully producing alkylated ring opened products such as 1-65.\textsuperscript{72}

1.6 Synthetic Utility of 2,3-Dicarboxylate Oxanorbornadienes

Oxanorbornadienes strained bicyclic framework provide its synthetic utility for natural product synthesis. The bicyclic and polycyclic structure of many natural products makes a Diels-Alder cycloaddition to provide an oxabicyclic alkene as an intermediate a viable option in their synthesis. The bicyclic framework visible in natural products synthesized via different methods provides the potential to develop more efficient routes based on starting from oxanorbornadiene.

Salvinorin A 1-67 was isolated from a mint species It has shown hallucinogenic properties and is used by Oaxaca natives for the treatment of headaches, rheumatism, and abdominal swelling. An investigation into the
necessity of the furan moiety for receptor binding was launched by Prisinzano and coworkers. As such, a Diels-Alder cycloaddition with DMAD was completed to provide 1-68 (Scheme 1-14). Further derivations of the oxanorbornadiene were also undertaken to further explore the biological activity of this compound.\textsuperscript{73}

![Scheme 1-14: Conversion of Salvinorin A](image)

Dynemicin A 1-69 was first isolated from the fermentation broth of a soil sample containing \textit{Micromonospora chersina} (Figure 1-6). It was the first antitumor agent with an enediyne structure. Dynemicin A also has antibiotic properties. Its biological activity is proposed to act via bioreductive activation. The total synthesis of Dynemicin A by Magnus and coworkers does not involve a Diels-Alder cycloaddition. The polycyclic structure containing an epoxide functionality provides the possibility for a future synthesis based starting from a bicyclic alkene. Magnus and coworkers did use a [4+2] cycloaddition to synthesize 1-70 (Scheme 1-15) which they intended to use to test the biological activity of Dynemicin A as it was thought that the anthraquinone portion of the molecule was responsible for the antitumor activity seen.\textsuperscript{74}
Furanoheliangolides are natural sesquiterpene lactones containing biological activity. These compounds cytotoxic and schistosomicidal properties as well and their macrocyclic bicyclic structure has made them both valuable and interesting synthetic targets for chemists.\textsuperscript{75} Synthesis of the core structure of furanoheliangolides \textbf{1-76} (Figure 1-7) was undertaken by the Constantino group and the McDougal group\textsuperscript{76} with both using a Diels-Alder cycloaddition as a key
step. Constantino and coworkers used a Diels-Alder cycloaddition with DMAD followed by multiple reductions and a Cope rearrangement to afford the core structure (Scheme 1-16).\(^7^7\)

**Figure 1-7:** Core Structure of Furanoheliangolides

**Scheme 1-16:** Synthesis of a Furanoheliagolide
Lactones isolated from *Podophyllum* have antimitotic properties and have been used historically as indigenous medicine by Himalayan peoples. Since this time, this structure has led to the development of two semisynthetic drugs used as chemotherapy agents. A Diels-Alder reaction between isobenzofuran 1-87 and DMAD was used to prepare the bicyclic alkene 1-88 (Scheme 1-17) from which Rodrigo and coworkers were able to derive eight diatereomeric lignans of *Podophyllum* in order to test the stereochemical requirements of the observed biological activity.\(^78\)

![Scheme 1-17: Synthesis of Podophyllum Lignans](image)

### 1.7 Scope of Thesis

The background information presented provides an overview of the extensive research carried out involving transition metal catalyzed reactions of oxabicyclic alkenes. These reactions have made the synthesis of natural
products a more accessible goal for synthetic chemists. The complex nature of many of these synthetic targets spurs the need for continued investigation into discovering new reactions of this kind.

Ring opening reactions of oxabicyclic alkenes have been thoroughly explored using many different types of nucleophiles and Pd, Ni, or Rh catalysts to promote the reaction. Thus far, however, there has been no exploration into the effectiveness and scope of using Ru to catalyze this reaction. As such, the first section of this thesis will cover the Ru catalyzed nucleophilic ring opening reaction of oxabenzonorbornadienes using MeOH as the nucleophile of choice.

With a shift in focus from oxabenzonorbornadiene to the 2,3-dicarboxylate oxanorbornadiene, the second section of this thesis will focus on the Ru catalyzed dimerization of these compounds. Although many investigations into the transition metal catalyzed dimerization of norbornadienes have been undertaken in the past, there are no examples using this bicyclic system or Ru as a catalyst available in the literature. The aim of this project is to optimize this Ru catalyzed dimerization reaction and determine the scope of the reaction by exploring the ability of various oxabicyclic alkenes able to participate.

1.8 References


(10) Tam, W.; Cockburn, N. *Synlett* **2010**, *1170*.


(47) Villeneuve, K.; Tam, W. Organometallics 2007, 26, 6082.


Chapter 2: Ruthenium Catalyzed Ring Opening Reactions of Oxabenzonorbornadienes
2.1 Background

Ring opening reactions of oxabenzonorbornadienes have been thoroughly investigated for the past 15 years. They have attracted much attention due to their ability to create and control many stereocenters with one reaction. Ring opening reactions are used to desymmetrize the oxanorbornadiene by adding in new functionalities. Transition metals, most popularly Pd and Rh, have been shown to be extremely effective in catalyzing these reactions with a wide variety of nucleophiles.

Metal catalyzed ring opening reactions can result in two possible stereoisomers, a syn isomer 2-1 and an anti isomer 2-2 (Scheme 2-1) depending on which face the nucleophilic attack occurs. There is consistency observed for each catalyst system in the stereochemical relationship between the nucleophile added and the hydroxyl group which results from the opening.

![Scheme 2-1: Stereochemical Configurations of Ring Opened Products](image)

2.1.1 Palladium Catalyzed Ring Opening Reactions

The investigations into the various ring opening reactions have revealed preferential pairings of ring opening reagents with certain transition metal
catalysts. Pd catalysts are traditionally paired with dialkyl zinc reagents resulting in an alkylated ring opened product (Scheme 2-2). In this case, the reaction proceeds to form the syn ring opened product. This ring opening example has also been carried out asymmetrically with a wide array of chiral ligands (Figure 2-1) able to successfully produce the asymmetric products with excellent ee.

Scheme 2-2: Pd Catalyzed Ring Opening with Dialkyl Zinc Reagents

Figure 2-1: Chiral Ligands for Pd Catalyzed Asymmetric Ring Opening

PdCl₂ was the most common palladium catalyst used to promote this reaction, however many other Pd(II) catalysts were also shown to be effective. The dialkyl zinc reagents explored were limited to dimethyl or diethyl zinc.
Instead, the scope of the reaction was expanded using benzo- substituted oxabenzonorbornadienes to determine the effects of substitution on the reaction. Many different chiral ligands were also examined in order to obtain as high of an ee value as possible.

Mechanistic investigations into the Pd catalyzed ring opening reaction were undertaken by Lautens and coworkers to determine if a carbopalladation pathway or an ionization and alkylation pathway is followed. Support for a carbopalladation pathway was revealed via trapping of the transmetallated carbozinc intermediate using both deuterium and iodide. Additionally it was found that the addition of Zn(OTf)$_2$ improved the yield of the reaction. The Pd catalyzed ring opening reactions using alkyl zinc reagents are initiated via transmetallation between the Pd catalyst and the alkyl zinc in order to produce an alkylated palladium 2-12. The reaction then proceeds though carbopalladation of the C$^2$-C$^3$ bond of oxabenzonorbornadiene. β-Oxygen elimination occurs quickly to opened the strained epoxide ring. A second transmetallation provides the organozinc 2-16 which, when quenched provides the cis ring opened product (Scheme 2-3).$^{2,9,12}$
Scheme 2-3: Mechanism of Pd Catalyzed Ring Opening Reaction

Having witnessed the success of dialkyl zinc reagents in promoting the Pd catalyzed ring opening of oxabenzonorbornadienes, Hou and coworkers decided to attempt to expand the scope of this reaction to include alkylzinc halides. The ready availability and versatility of these reagents make them an attractive alternative to dialkyl zinc reagents for this type of reaction. During their investigations into this reaction, the use of chiral ligands to promote the asymmetric ring opening was also explored with great success.\textsuperscript{13}

Although Pd catalyzed ring opening reactions have most commonly been carried out with alkyl zinc reagents as previously summarized, other nucleophiles
have also been explored using this catalyst system. Investigations using aryl boronic acids were first undertaken by Lautens and coworkers (Scheme 2-4). Once again, the ring opening occurs through a syn addition of the boronic acid to product a cis-1,2-dihydronaphthalene. Hou and coworkers successfully carried out this reaction asymmetrically, producing the ring opened product with up to 79% ee.

Scheme 2-4: Pd Catalyzed Ring Opening Reaction with Boronic Acids

During the synthesis of C-aryl glycosides, Martin and coworkers discovered and optimized the Pd-catalyzed ring opening reaction using aryl halides (Scheme 2-5). Aryl iodides proved to be the most effective in this reaction providing the ring opened product in yields of up to 97%.

Scheme 2-5: Pd Catalyzed Ring Opening with Aryl Halides

Organophenylstannane surprisingly opened oxabenzonorbornadiene in the presence of PdCl₂(PhCN)₂ and chloroacetate (Scheme 2-6). When other bicyclic alkenes were subjected to these conditions, it was the 2,3-addition product that resulted.
Scheme 2-6: Phenylation of Oxabenzonorbornadiene

The final example of a Pd catalyzed ring opening reaction of oxabenzonorbornadiene is a reductive opening using carboxylic acids (Scheme 2-7). Cheng and coworkers provided the first example of an asymmetric reductive ring opening using organic acids. Benzo, C\textsuperscript{1}, and C\textsuperscript{1}-C\textsuperscript{4} substituted oxabenzonorbornadienes were all successfully opened in this manner with high yields and good ee\textsuperscript{18}.

Scheme 2-7: Reductive Ring Opening of Oxabenzonorbornadiene

2.1.2 Rhodium Catalyzed Ring Opening Reactions

Unlike the Pd-catalyzed ring opening reaction where alkyl zinc reagents were the most common nucleophile used, heteroatom nucleophiles were found to be the most effective nucleophiles for use with a rhodium catalyst. Other nucleophiles such as carboxylates and boronic acids have also shown
proficiency in opening oxabenzonorbornadienes with the aid of a rhodium catalyst.

Where Pd-catalyzed ring opening always resulted in the *syn* ring opened product, the Rh-catalyzed process results in either the *syn* or the *anti* product depending on the type of nucleophile used in the process. Boronic acids resulted in the production of *syn* naphthols while any of the heteroatom nucleophiles provided an *anti* naphthol.

[Rh(COD)Cl]$_2$ was shown on multiple occasions to catalyze the *syn* addition of aryl boronic acids to oxabenzonorbornadienes (Scheme 2-8).$^{19}$ Murakami and coworkers explored the reaction using substituted aryl boronic acids, looking at substituents in the *o*-, *m*-, and *p* - positions as well as substituents with different electronic properties. They also chose to explore the effect of substitutions on the bicyclic alkene when phenyl boronic acid was used in the ring opening. Lautens and coworkers demonstrated the asymmetric ring opening using boronic acids with a Rh-catalyst. They found PPF-P$^t$Bu (Figure 2-2) to be an effective ligand for promoting the asymmetric ring opening.$^{20}$ Decreased temperature was found to improve the *ee* of the reaction; increasing from 67% to 93% with a change from reflux conditions to running the reaction at room temperature. It was also discovered that an excess of base increased the speed of the reaction significantly.
Rhodium catalyzed ring opening reactions with heteroatom nucleophiles have been carried out using many different heteroatoms including alcohols, carboxylates, amines, thiols, as well as malonates acting as soft carbon nucleophiles. The challenge to undertake these ring opening reactions in an asymmetric fashion was met with success using a variety of chiral phosphine ligands such as PPF-P$^\text{t}$Bu$_2$, 2-22. This provided a method to synthesize dihydronaphthalenes containing alternative stereochemistry to their Pd-catalyzed counterparts.

The initial heteroatom nucleophilic ring opening reaction was carried out by Lautens and coworkers in 2001. They adapted the Rh-catalyzed ring opening reaction of 2,3-dicarboxylate oxanorbornadiene as initially carried out by Hogeveen and Middelkoop to provide 70% of the ring opened product 2-23 (Scheme 2-9). MeOH was the initial alcohol used as a nucleophile in this
reaction, and was used as solvent in a 1:1 ratio with TFE. Other alcohols such as EtOH, iPrOH, and 2-TMS alcohol were also tested as nucleophiles providing yields from 52-61%. The asymmetric reaction was optimized using chiral phosphine ligands and the scope expanded to include many substituted phenols as nucleophiles. With a change in solvent from TFE to THF, the asymmetric reaction provided much higher yields of >90% with equally excellent ee values.22

\[
\text{Scheme 2-9: Rh-Catalyzed Ring Opening with Alcohols}
\]

Having successfully carried out the ring opening using alcohols as nucleophiles, Lautens and coworkers expanded the nucleophilic scope of the reaction. Many aliphatic and aromatic amines were tested and although not all were successful under the initial conditions, optimization of the reaction provided moderate to high yields of the ring opened products.23,28 Other primary amines were explored as nucleophiles on benzosubstituted oxabenzonorbornadienes by Yang and coworkers.26 Sulfur and carboxylate nucleophiles provided other examples of heteroatom additions.25,27 Dimethyl malonate was able to act as a soft carbon nucleophile and form at C-C bond in the ring opened product.28

Two different mechanisms are seen in the Rh-catalyzed reaction depending on the type of nucleophile involved. Boronic acid nucleophiles,
providing the \textit{anti} addition ring opened product follow one mechanism (Scheme 2-10) while heteroatom nucleophiles which provide the \textit{syn} ring opened product follows a different pathway (Scheme 2-11).

The Rh-catalyzed ring opening using aryl boronic acids follows a similar path as the Pd-catalyzed reaction (Scheme 2-10). Initially, the dimerized catalyst is dissociated to give the rhodium monomer 2-25. Transmetallation of the aryl boronic acid results in the formation of the aryl rhodium(I) species, 2-26. Coordination of the catalyst to the \textit{exo} face followed by carborhodatation of oxabenzonorbornadiene occurs to give 2-27 which can undergo \(\beta\)-oxygen elimination to give the initial ring opened product 2-28. Quenching with water results in the final \textit{syn} product, 2-17.\textsuperscript{20}
Scheme 2-10: Rh-Catalyzed Ring Opening Mechanism Using Aryl Boronic Acids

In the nucleophilic ring opening involving a heteroatom nucleophile dissociation of the dimerized catalyst is once again required (Scheme 2-11). Coordination of the Rh-catalyst to the exo face of the oxabenzonorbornadiene followed by oxidative insertion into the C-O bond gives 2-30. The Rh-alkoxide is protonated by the heteroatom nucleophile (alcohol, amine, thiol, etc.). Nucleophilic attack on the endo face at C^2 or C^3 promotes the ring opening to provide the anti product 2-32.\textsuperscript{24,26,28,30} The use of a chiral ligand in this reaction
promotes insertion of the Rh-catalyst into one side of the C-O bond preferentially followed by a selective attack of the nucleophile at either C² or C³.

Scheme 2-11: Heteroatom Nucleophilic Rh-Catalyzed Ring Opening Mechanism

2.1.3 Nickel Catalyzed Ring Opening Reactions

Nickel has catalyzed ring opening reactions of oxabenzonorbornadiene using hydrides,³¹ terminal acetylenes,³² and alkenylzirconiums³³ as nucleophiles (Scheme 2-12).
The addition of acetylenes and alkenyl zirconiums was determined to occur in a \textit{syn} fashion. No investigations into which face the hydride addition occurs from have yet been launched. Despite the differences in nucleophile, the mechanism of addition remains fairly consistent (Schemes 2-13 and 2-14). As an aside, in exploring the hydride ring opening, Lautens and coworkers found slow addition of DIBAL-H to be crucial to controlling the \textit{ee}.

\textbf{Scheme 2-12:} Nickel Catalyzed Ring Opening Reactions
Scheme 2-13: DIBAL-H Nickel Catalyzed Ring Opening Mechanism

Scheme 2-14: Acetylene or Alkenyl Nickel Catalyzed Ring Opening Mechanism
The hydride mechanism (Scheme 2-13) begins with dissociation of the COD ligand from the Ni catalyst. Association of the Ni with a chiral ligand follows. Coordination of the Ni with the bridgehead O and C²-C³ alkene results in the formation of the Π complex 2-37. Nucleophilic attack of the hydride can occur at C² or C³ which will result in the formation of two possible enantiomers (only one is shown in the mechanism). β-Oxygen elimination once again opens the ring, which when quenched with water gives the final product 2-32.³¹

The main difference between the hydride mechanism and the alkyne or alkene addition mechanism (Scheme 2-14) is in the transmetallation of these nucleophiles. The alkene or alkyne is transmetallated to create the Nickel complex 2-41 which goes on to complex with the exo face of oxabenzonornbornadiene giving 2-42. Insertion of the double bond into the Ni-R complex followed by β-oxygen elimination opens the ring, which when quenched yields the desired products.²₂,³³

2.1.4 Copper Catalyzed Ring Opening Reactions

The copper catalyzed ring opening of oxabenzonornbornadienes involves using organometals such as Grignard reagents,³⁴-³⁷ aluminum reagents,³⁷,³⁸ alkylzinc,³⁹ and organolithium⁴⁰ reagents as nucleophiles. Whereas previously, the addition reactions occurred purely as a syn or an anti addition, in the copper catalyzed reactions only a strong preference is observed for the anti addition in
all cases. These results are promising based on the rare existence of an anti selective alkylative ring opening reaction.

Copper salts were found to be essential for the Grignard addition to oxabenzenonorbornadiene (Scheme 2-15). Interestingly, Cu(I) and Cu(II) salts were both very effective in catalyzing this reaction. CuCl, CuTC, and Cu(OTf)₂ were the most popular copper reagents chosen to promote this reaction. The scope of Grignard reagents able to result in generally high yields of the ring opened product was expanded to include primary and secondary alkyl groups as well as aryl magnesium bromides. Further investigation found that substituted oxabenzenonorbornadienes also underwent ring opening effectively using these conditions.

![Scheme 2-15: Copper Catalyzed Ring Opening Using Grignard Reagents](image)

Mechanistic studies into this reaction revealed results consistent with an $S_N2'$ reaction (Scheme 2-16). The organocuprate is formed in situ and performs an *endo* attack on the alkene to open the ring. Reductive elimination removes the Copper moiety which can then be quenched to give the final product.
Alexakis and coworkers were able to demonstrate the copper catalyzed asymmetric ring opening reaction using Grignard reagents and aluminum reagents. Having tested a variety of ligands, the most efficient provided the ring opened products in ee of up to 94%.\textsuperscript{[37]}

In the ring opening reaction utilizing alkyl aluminum reagents, the copper counter ion once again played an important role in the reaction. Only aromatization products were obtained when the counter ion was changed from TC to OTf.\textsuperscript{[38]} The reaction required a trialkyl aluminum, CuTC as a catalyst and a chiral ligand in MTBE to provide the ring opened product 2-2.

The ring opening reactions using organozinc and organolithium reagents both proceeded smoothly and were able to be adapted to form asymmetric products. Substituted oxabenzonorbornadienes were also successfully opened to provide highly substituted dihydronaphthalenes.\textsuperscript{[39,40]}

\textbf{2.1.5 Other Transition Metal Catalyzed Ring Opening Reactions}

Other transition metals such as gold,\textsuperscript{[41]} iridium,\textsuperscript{[42]} and zirconium\textsuperscript{[43]} were also shown to catalyze ring opening reactions of oxabenzonorbornadienes.
(Scheme 2-17). The Au catalyzed ring opening utilized allylTMS or TMSCl in the presence of HAuCl₄ to form the aromatized product 2-47. Iridium catalyzed the asymmetric ring opening using analines as nucleophiles. This reaction followed a similar mechanism to those previously shown using other transition metals and involves complexation of the catalyst with oxabenzonorbornadiene, oxidative insertion, attack of the nucleophile and β-oxygen elimination to provide the final product. BuLi was used to remove the α-proton from amine 2-50 which was then able to add to oxabenzonorbornadiene using Zr mediation resulting in the ring opened product 2-51.

Scheme 2-17: Other Transition Metal Catalyzed Ring Opening Reactions
2.2 Synthesis of 2-Substituted Furans and C\textsuperscript{1}-Substituted Oxabenzonorbornadienes\textsuperscript{1}

Substituted oxabenzonorbornadienes play an important role in gaining insight into the mechanisms of transition metal catalyzed reactions. The steric and electronic effects of these substituents can sometimes present interesting results when examining the scope of a reaction. C\textsuperscript{1} substitutions in particular can provide valuable regiochemical information about reactions by removing the symmetry seen in unsubstituted oxabenzonorbornadiene. It was therefore surprising when a literature search revealed very few known C\textsuperscript{1} substituted compounds (Figure 2-3).\textsuperscript{44-47} An investigation was therefore launched in the Tam group to discover an efficient synthesis to create a larger variety of these compounds.

![Image of C\textsuperscript{1} Oxabenzonorbornadienes Previously Synthesized](image)

**Figure 2-3: C\textsuperscript{1} Oxabenzonorbornadienes Previously Synthesized**

The synthesis of C\textsuperscript{1}-substituted oxabenzonorbornadienes involved a Diels-Alder cycloaddition between 2-furan and benzyne (Scheme 2-18). In order to carry out the synthesis of C\textsuperscript{1} oxabenzonorbornadienes, 2-substituted furans were

\textsuperscript{1} Work completed during undergraduate work term
required. Very few are commercially available and previous work cited in the literature minimal (Scheme 2-19).\(^{48}\) It was therefore decided to carry out coupling reactions with 2-bromofuran in order to synthesis previously unavailable 2-furans.

**Scheme 2-18:** Synthesis of C\(^1\)-Substituted Oxanorbornadienes

**Scheme 2-19:** Previously Synthesized 2-Substituted Furans

2-Bromofuran 2-53h is synthesized from furan and NBS in DMF (Scheme 2-20). Steam distillation is used to purify the product with a 75% yield.\(^{49}\) From here Pd-catalyzed Suzuki coupling with boronic acids (Scheme 2-21) and Fe-catalyzed with Grignard reagents (Scheme 2-22) was used to synthesize a wide array of 2-substituted furans (Table 2-1).\(^{50}\)
Scheme 2-20: Synthesis of 2-Bromofuran

Scheme 2-21: Suzuki Coupling to Synthesize 2-Substituted Furans

Scheme 2-22: Fe Catalyzed Coupling to Synthesis 2-Substituted Furans

Table 2-1: Synthesis of 2-Bromofurans Through Coupling Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>X</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Conditions</th>
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<tr>
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<td>Br</td>
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<td>Cl</td>
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<td>X</td>
<td>Product</td>
<td>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Conditions</td>
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<tr>
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<td>Cyclohexyl</td>
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<td>2-53u</td>
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<td>69&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>A</td>
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<tr>
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<td>53&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>-</td>
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<td>-</td>
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<td>A</td>
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<td>74&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>A</td>
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<tr>
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<td>2-53ae</td>
<td>74&lt;sup&gt;b&lt;/sup&gt;</td>
<td>B</td>
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<tr>
<td>24</td>
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<td>-</td>
<td>2-53af</td>
<td>87&lt;sup&gt;b&lt;/sup&gt;</td>
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<sup>a</sup>Isolated yield after chromatography; <sup>b</sup>Reactions performed by Jamie Haner, Jaipal Nagireddy, or Mohammed Abdul Raheem
The investigations into the synthesis of 2-substituted furans 2-53a-af provided some interesting results. Of the two coupling reactions studied, each had their own strengths. The Fe-catalyzed coupling provided moderate yields when alkyl Grignard reagents were used. Primary and secondary alkyl groups were examined as the attempted reaction with tBuMgCl provided no coupling products. Within the exploration of small and medium rings (entries 1, 4-7), cyclohexyl MgCl provided the highest yield at 56% (entry 6). Cyclopropyl MgBr provided the lowest yield of this group with 35% while cyclobutyl, cyclopentyl, and cycloheptyl (entries 4, 5, and 7) ranged in between with yields of 51, 44, and 46% respectively. The linear secondary alkyl group sBuMgCl (entry 3) was also examined and provided a yield of 55% which is similar to the cyclohexyl variant. The primary alkyl groups showed similar yields of 39 and 40% despite a large increase in chain length from butyl to dodecyl.

Less success was seen in the Fe-catalyzed coupling using aryl Grignard reagents. Although coupling products were observed, their yields were extremely low. The unsubstituted PhMgBr (entry 10) gave only 5% yield. Substituted aromatic systems provided higher yields ranging from 22-26% when the substituents were at the m- or p- positions. The o-substitution once again provided low yields of 4-6%. The electronic nature of the substituent did not appear to have much of an effect as the tolyl systems (entries 11-13) and the methoxy systems (entries 14-16) were both explored. Surprisingly, the p-fluoro system gave only 4% of the desired coupling product. Other aromatic
substituents such as BnMgCl and 4-biphenyl MgBr provided low yields of 15 and 20% respectively.

The Pd-catalyzed Suzuki coupling showed much higher yields of synthesized 2-aryl furans. The unsubstituted phenyl boronic acid provided 71% of the coupling product (entry 10), which is a huge improvement over the 5% obtained with Fe-catalyzed coupling. In exploring the effects of substitution on the aryl group, similar trends as previously mentioned are seen. With the tolyl and methoxy systems, similar yields were observed for the m- and p-substitutions, with the o- showing up to a 20% decrease in yield. The three chloro substituted boronic acids used provided very consistent yields of the 2-furans, ranging from 77-80% (entries 17-19).

Two other p-substitued aromatic systems were examined. The p-Et substituent gave 84% yield (entry 22). Changing that group to a larger Ac substituent resulted in a decrease in yield to 74% (entry 23). The extended Π system contained within a naphthyl substituent provided 87% of the coupled product (entry 24) while 4-biphenyl gave a 74% yield which is once again a large increase when compared to the 20% produced in the Fe-coupling reaction.

With the 2-substituted furans in hand, we studied the synthesis of the corresponding C1-oxabenzonorbornadienes (Table 2-2). The primary alkyl furans underwent cycloaddition in good to moderate yields. An increase in the length of the alkyl chain resulted in a decrease in yield of the cycloadduct. In the case of 2-ethylfuran 2-53ag, the product was obtained in 80% yield (entry 21) whereas the
larger 2-octylfuran 2-53j and 2-dodecylfuran 2-53p provided yields of 55 and 58%, respectively (entries 5 and 11). When secondary linear alkyl groups were examined, the size of the substituent seemed to have a profound effect. 2-octylfuran 2-53k (entry 6) has a bulkier substituent which resulted in a much lower yield of the C1-norbornadiene than when 2-isopropylfuran 2-53ah (entry 22) was used in the cycloaddition having yields of 70 and 29% respectively. The tertiary alkyl group, 2-isobutylfuran 2-53ai (entry 23) was also explored with the expectation that the yield of its cycloadduct would be lower than the other systems previously explored. Surprisingly, it underwent cycloaddition in higher yield than 2-octylfuran 2-53k with a 66%.

The scope of secondary alkyl groups explored was expanded to include cycloalkyl substituents. 2-Cyclobutylfuran 2-53l (entry 7) provided the highest yield of the cycloadduct with 62%. This was significantly higher than any of the other cycloalkyl substituents. Low yields were observed for 2-cyclopropylfuran 2-53i, 2-cyclopentylfuran 2-53m, and 2-cycloheptylfuran 2-53o of 29, 33, and 32%, respectively (entries 4, 8, and 10). A slightly higher yield of 45% was obtained for 2-cyclohexylfuran 2-53n (entry 9).

The cycloaddition of a variety of 2-arylfurans 2-53r-af provided the corresponding 1-aryloxabenzonorbornadiene in moderate yields. The unsubstituted 2-Phenylfuran 2-53r underwent cycloaddition in 43% yield (entry 12). Comparison of other aryl substituents to this base resulted in an increase and decrease of yields depending on the substituent. For example, those
aryl furans containing an extended π-system, 2-(4-Biphenyl)furan 2-53ab and 2-(1-Naphthyl)furan 2-53af both provided much lower yields of 16 and 24% respectively (entries 19 and 20). Examination of the ortho-, meta-, and para-tolyl 2-53s-u (entries 13-15) and chloro 2-53y-aa (entries 16-18) systems provided insight into the effects of adding an electron donating or withdrawing substituent on the phenyl group. Both of these cases provided generally higher yields than the unsubstituted 2-phenylfuran. Of the tolyl systems, a range to yields from 31% for the para-tolyl to 53% for the meta resulted. This contrasts the chloro-substituted reactions where the para-system provided the highest yield of the group with 63%. The yields were higher overall for the chloro-substituted 1-aryloxabenzonorbornadienes which ranged from 51-63%

In our investigations, three other systems were explored resulting in a wide range of yields. 2-Trimethylsilylfuran 2-53f furnished the bicyclic alkene 2-52f in 75% yield (entry 21) which was higher than the 66% yield from the comparable system of 2-1-butylfuran 2-53ai. Due to the steric similarities of these two systems, we can liken the difference in yields to the stronger electron donating effect of the silicon of the TMS group as opposed to the carbon of the 1Bu substituent. 2-Bromofuran 2-53h provided the cycloadduct in only 36% yield (entry 22). Sterically we would expect the bromo substituent to result in a higher yield than this, therefore it is thought that the electronic effects of this substituent are responsible for this low yield. Slight decomposition was observed during the purification (column chromatography) of 2-52h. Finally, the tertiary alcohol-
containing furan 2-53g underwent cycloaddition in 47% yield (entry 23) which is much lower than its tertiary counterparts.

Table 2-2: Synthesis of C^1-Oxabenzonorbornadienes

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)^\text{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1^b</td>
<td>TMS</td>
<td>2-52f</td>
<td>75</td>
</tr>
<tr>
<td>2^b</td>
<td>C(CH_2)_2OH</td>
<td>2-52g</td>
<td>47</td>
</tr>
<tr>
<td>3^b</td>
<td>Br</td>
<td>2-52h</td>
<td>36</td>
</tr>
<tr>
<td>4^b</td>
<td>Cyclopropyl</td>
<td>2-52i</td>
<td>29</td>
</tr>
<tr>
<td>5^b</td>
<td>nBu</td>
<td>2-52j</td>
<td>55</td>
</tr>
<tr>
<td>6^b</td>
<td>sBu</td>
<td>2-52k</td>
<td>29</td>
</tr>
<tr>
<td>7^b</td>
<td>Cyclobutyl</td>
<td>2-52l</td>
<td>62</td>
</tr>
<tr>
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<td>Cyclopentyl</td>
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<td>2-52o</td>
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<td>51</td>
</tr>
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<td>4-Biphenyl</td>
<td>2-52ab</td>
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<tr>
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<td>1-Naphthyl</td>
<td>2-52af</td>
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<td>Entry</td>
<td>R</td>
<td>Product</td>
<td>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>2-52ai</td>
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</table>

<sup>a</sup>Isolated yield after chromatography;  
<sup>b</sup>Reactions performed by Jamie Haner, Jaipal Nagireddy, Mohammed Abdul Raheem, Michelle Menard, or Jennifer Howell

2.3 Results and Discussion

With a thorough investigation into transition metal catalyzed ring opening reactions, there is a notable hole. There are no literature examples of ruthenium catalyzing this reaction. It was during the investigation into the cyclopropanation of oxabenzenorbornadiene by Villeneuve and Tam (Scheme 2-23) that an additional product was isolated.<sup>51</sup> Further investigation into the reaction revealed that by eliminating the equivalency of propargylic alcohol added to the reaction flask the only observed product was that resulting from the nucleophilic ring opening.

![Scheme 2-23: Discovery of Ru-Catalyzed Nucleophilic Ring Opening](image-url)
To begin investigations into this ring opening the reaction conditions employed were optimized (Table 2-3). The optimization began by screening a variety of Ru-catalysts for their ability to promote this reaction. Cationic Ru species (entries 1 and 2) provided the ring opened product 2-61 in low yields of 7-12%. Small quantities of the aromatized naphthol, 2-62 were also formed due to the isomerization of 2-3. [Ru(COD)Cl]₂, [RuCl₂(CO)₃]₂, and CpRu(PPh₃)₂Cl (entries 3-5) all resulted in the recovery of starting material without the formation of any of the ring opened product. [RuCl₂(CO)₃]₂ did additionally produce 45% of the naphthol. Ru(PPh₃)₂Cl₂, as well as the series of CpRu(COD)X (X=Cl, Br, I) provided very low yields of both the ring opened and naphthol products. The yields started to increase when the series of Cp*Ru(COD)X catalysts (entries 10-12) were examined. Although Cp*Ru(COD)I produced only 10% of the ring opened product, Cp*Ru(COD)Br gave 57% yield. Cp*Ru(COD)Cl provided the highest yield observed at 66%. Unfortunately, all three of these catalysts also resulted in the formation of small amounts of the naphthol. Having determined the optimal catalyst for the reaction, the focus turned to determining the most effective temperature and solvent for the reaction. The reaction was run at 65, 40, and 25°C (entries 12-14). Although a slightly higher yield was obtained by running the reaction at 25°C, the increased reaction time made 65°C the preferred temperature for this reaction. Finally examining the use of a variety of co-solvents (entries 15-20) provided much lower yields than using MeOH as both solvent and nucleophile.
Table 2-3: Optimization of Ru-Catalyzed Ring Opening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ru catalyst</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>Yield(^a) (%)</th>
<th>Yield(^a) (%)</th>
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<tr>
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<td>[CpRu(CH(_3)CN)]PF(_6)</td>
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<td>MeOH</td>
<td>7(^c)</td>
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<tr>
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<td>[Cp*Ru(CH(_3)CN)]PF(_6)</td>
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<td>MeOH</td>
<td>12(^c)</td>
<td>5</td>
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<td>0(^c)</td>
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<tr>
<td>5</td>
<td>CpRu(PPh(_3))(_2)Cl</td>
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<td>MeOH</td>
<td>0(^c)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ru(PPh(_3))(_3)Cl(_2)</td>
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<td>MeOH</td>
<td>5(^c)</td>
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<td>MeOH</td>
<td>11(^c)</td>
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<td>MeOH</td>
<td>6(^c)</td>
<td>6</td>
</tr>
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<td>MeOH</td>
<td>8(^c)</td>
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<td>14</td>
<td>Cp*Ru(COD)Cl</td>
<td>25</td>
<td>MeOH</td>
<td>68(^e)</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>Cp*Ru(COD)Cl</td>
<td>65</td>
<td>THF(^b)</td>
<td>8(^c)</td>
<td>38</td>
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<tr>
<td>16</td>
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<td>65</td>
<td>DCE(^b)</td>
<td>5(^c)</td>
<td>47</td>
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<tr>
<td>17</td>
<td>Cp*Ru(COD)Cl</td>
<td>65</td>
<td>toluene(^b)</td>
<td>13(^c)</td>
<td>36</td>
</tr>
<tr>
<td>18</td>
<td>Cp*Ru(COD)Cl</td>
<td>65</td>
<td>acetone(^b)</td>
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<td>48</td>
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<tr>
<td>19</td>
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<td>65</td>
<td>dioxane(^b)</td>
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<td>42</td>
</tr>
<tr>
<td>20</td>
<td>Cp*Ru(COD)Cl</td>
<td>65</td>
<td>hexanes(^b)</td>
<td>0</td>
<td>44</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield after column chromatography; \(^b\)20 equivalent of MeOH was used; \(^c\)7-Oxabenzonorbornadiene 1a was recovered (22-91%); \(^d\)The reaction mixture was stirred for 4 h; \(^e\)The reaction mixture was stirred for 6 h; \(^f\)Optimization completed by Elisabeth Fatila.
Having determined the optimal conditions for this reaction, we then moved on to explore the scope of this reaction (Table 2-4). Many differently substituted oxabenzonorbornadienes were subjected to the reaction conditions. Substitution on the benzo component (entries 2-5) of the ring provided moderate yields of the ring opened product. The electron donating Me- and OMe- groups (entries 2 and 3) provided none of the napthol isomerization product. When the positioning and electronic nature of the benzo substituents was changed and the electron withdrawing Br- and F- (entries 4 and 5) were explored, a significant amount of the isomerization product was observed. The yield of the stronger electron withdrawing F- substituent was significantly higher than that of the Br-substituent. The highly substituted oxabenzonorbornadiene 2-3f required a reaction temperature of 80°C to promote the ring opened reaction. Even with the increase in temperature however, only a very low yield of 26% of the ring opened product was observed.

The unsymmetrical oxabenzonorbornadienes 2-3g and 2-3h (entries 7 and 8) provided a mixture of the two ring opened regioisomers in a 1:1 ratio. Low yields of 30% for the –OMe substitution and 42% for the –COOMe substitution were observed. Interestingly, when the –OMe substituent on the benzo ring was shifted from the W to the X position only decomposition was observed. Oxabenzonorbornadiene 2-3k also did not ring open when subjected to the optimized conditions, even with increases in temperature and reaction time.

Finally, C1 and C1-C4 substituted oxabenzonorbornadienes were explored. Decomposition of the starting material and trace product in the crude 1H NMR
was observed from reaction with the C\(^1\)-ester 2-3k. The C\(^1\)-Me oxabenzonorbornadiene resulted in 20% of the ring opened product when extended reaction times were used. 70% of the corresponding 1-napthol was also observed. The C\(^1\)-C\(^4\) dimethyl oxabenzonorbornadiene 2-3m did not provide any of the desired ring opened product, however 35% of the naphthol was isolated. This is presumed to be due to steric hindrance caused by the addition of the second methyl group preventing addition of the nucleophile to open the ring.

\textbf{Table 2-4: Ru-Catalyzed Nucleophilic Ring Opening Reactions of Oxabenzonorbornadienes}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxabenzonorbornadiene (2-3)</th>
<th>Nucleophilic Ring Opened Product (2-61)</th>
<th>Time (h)</th>
<th>Yield(^a) (%) of 2-61 (2-62)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\includegraphics[width=0.5\textwidth]{figure1}</td>
<td>\includegraphics[width=0.5\textwidth]{figure2}</td>
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<td>66 (5)(^b)</td>
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<td>2</td>
<td>\includegraphics[width=0.5\textwidth]{figure3}</td>
<td>\includegraphics[width=0.5\textwidth]{figure4}</td>
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<td>59</td>
</tr>
<tr>
<td>3</td>
<td>\includegraphics[width=0.5\textwidth]{figure5}</td>
<td>\includegraphics[width=0.5\textwidth]{figure6}</td>
<td>1</td>
<td>40(^c)</td>
</tr>
<tr>
<td>Entry</td>
<td>Oxabenzonorbornadiene (2-3)</td>
<td>Nucleophilic Ring Opened Product (2-61)</td>
<td>Time (h)</td>
<td>Yield(^a) (%) of 2-61 (2-62)(^b)</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
<td>----------------------------------------</td>
<td>---------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="2-3d" /></td>
<td><img src="image" alt="2-61d" /></td>
<td>1</td>
<td>56 (17)(^b)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="2-3e" /></td>
<td><img src="image" alt="2-61e" /></td>
<td>2</td>
<td>81 (19)(^b,f)</td>
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<tr>
<td>6</td>
<td><img src="image" alt="2-3f" /></td>
<td><img src="image" alt="2-61f" /></td>
<td>1(^d)</td>
<td>26(^c)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="2-3g" /></td>
<td><img src="image" alt="2-61g(_1)" /> + <img src="image" alt="2-61g(_2)" />((-1:1))</td>
<td>1</td>
<td>30(^c)</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="2-3h" /></td>
<td><img src="image" alt="2-61h(_1)" /> + <img src="image" alt="2-61h(_2)" />((-1:1))</td>
<td>2(^d)</td>
<td>42</td>
</tr>
<tr>
<td>Entry</td>
<td>Oxabenzonorbornadiene (2-3)</td>
<td>Nucleophilic Ring Opened Product (2-61)</td>
<td>Time (h)</td>
<td>Yield$^a$ (%) of 2-61 (2-62)$^b$</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
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<tr>
<td>9</td>
<td><img src="image" alt="2-3i" /></td>
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<td>48</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="2-3j" /></td>
<td>-</td>
<td>3</td>
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<td>-</td>
<td>72</td>
<td>0$^e$</td>
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<tr>
<td>10</td>
<td><img src="image" alt="2-3l" /> <img src="image" alt="2-61l" /></td>
<td>72</td>
<td>20 (70)$^b$</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="2-3m" /></td>
<td>-</td>
<td>48</td>
<td>0 (35)$^{b,f}$</td>
</tr>
</tbody>
</table>

$^a$Isolated yield after column chromatography; $^b$Yields in brackets are the amount of the corresponding naphthol; isomerization product isolated; $^c$Some starting material was recovered; $^d$The reaction was run at 80°C; $^e$Decomposition of 7-Oxabenzonorbornadiene 1i was observed; $^f$Reactions carried out by Colleen Hillis

In the unsymmetrical cases, NOESY NMR experiments were carried out to determine which regioisomer was formed. As NOESY experiments examine the through space interactions between protons, interaction between the substituent and the adjacent vinylic ($R_1$) or benzylic ($R_2$ or $R_5$) proton can be seen on the spectra.$^{52}$ Additionally, comparing the coupling constants between...
Hₐ and Hᵇ (Figure 2-4) to known literature values allowed for confirmation of the formation of the anti ring opened product.²²,⁵³

![Figure 2-4: Proton Assignment of Ring Opened Product]

Elisabeth Fatila attempted to expand the scope of the reaction in a different direction, other alcohols were explored for their nucleophilic ability (Scheme 2-24). Unfortunately the results obtained were not very promising, as only EtOH provided any of the ring opened product. Even though the ring opened product 2-61n was obtained, its yield was low at 25%. Using EtOH as a nucleophile, a 50% yield of the naphthol isomerization product was obtained. Increasing the size of the alkyl group on the alcohol resulted in only isomerization products with none of the ring opened product being observed.

![Scheme 2-24: Ru-Catalyzed Ring Opening Reactions Using Other Alcohols]
2.4 Proposed Mechanism

Due to the similarities between this reaction and the Rh-catalyzed nucleophilic ring opening, it is thought that the mechanism of this reaction will also bear resemblances (Scheme 2-25). Dissociation of the COD ligand initiates the mechanism to provide us with a Ru(II) species that will coordinated with the bridgehead O and the alkene. C-O insertion follows to provide the ruthenacycle 2-64. Nucleophilic attack to open the ring occurs from the endo face as the exo face is blocked by the catalyst. The ring opened product is then quenched to provide 2-61.

Scheme 2-25: Proposed Ring Opening Mechanism
2.5 Significance and Application

The dihydronaphthalenol core which is produced via ring opening of oxabenzonorbornadiene provides a convenient method of obtaining the tetrahydronaphthalene core which is common in a variety of natural products (Scheme 2-26). Compound 2-66 is a synthesized derivative of a glycogen phosphorylase which can act to inhibit glycogenolysis. Compounds with this biological property show potential for use in treating diabetes.\(^5^4\) Lasofoxifene 2-67 has been used in the treatment of Osteoporosis while Podophyllotoxin 2-68 has shown anti-mitotic activity giving it potential use as an anti-tumor agent.\(^5^5\) 2-69 is a nervous system agent with the ability to act as a melanin-concentrating hormone (MCH). MCH has important physiological functions relating to feeding and energy balance.\(^5^6\) Isoerianin 2-70 has shown promise as an anti-cancer agent, acting through the disruption of tubulin assembly/disassembly.\(^5^7\) Dihydrexidine 2-71 is a neurotransmitter, more specifically, a dopamine agonist.\(^5^8\),\(^5^9\) Sertaline 2-72 is another neurotransmitter which acts as a selective serotonin re-uptake inhibitor. It is marketed as an antidepressant under the brand name Zoloft.\(^6^0\)

Lautens and coworkers undertook the stereoselective synthesis of Sertraline in 9 steps (Scheme 2-27). Using an asymmetric Ni-catalyzed ring opening of oxabenzonorbornadiene 2-20 is synthesized. Bromination followed by Stille coupling adds the aromatic group to the core structure giving 2-75. Reduction and a Mitusnobu like inversion using dppa and DBU in THF provides
2-76. From here, reduction of the azide followed by treatment with \( \text{ClCO}_2\text{Et} \) and reduction with \( \text{LiAlH}(\text{OMe})_3 \) procided Sertraline in a 38% yield.\textsuperscript{61,62}
Scheme 2-27: Total Synthesis of Sertraline

2.6 References


Chapter 3: Dimerization of Oxanorbornadienes
3.1 Background

Atom economy has become an important consideration in organic synthesis. Highly efficient reactions are important in the synthesis of complex molecules as they result in less waste and higher yields of the desired products. Simple additions are among the best examples of atom economical reactions.\(^1\) Included in this category are the [2+2] dimerization reactions of bicyclic alkenes. It is this high atom efficiency that makes these dimerization reactions of such great interest to synthetic chemists.

Dimerization reactions of bicyclic alkenes have been investigated since the 1960’s. Wittig and coworkers provided one of the first examples of the dimerization of norbornadiene using phenyllithium (Scheme 3-1).\(^2\) Since this example, there has been further exploration into dimerization reactions using transition metals and light to catalyze the reaction. Due to the two different faces of bicyclic alkenes, there are six possible conformations, three \textit{cis} and three \textit{trans}, that can result from the dimerization of these compounds (Figure 3-1). The six conformers of dimerized norbornadienes all have at least one plane of symmetry. They can be distinguished from one another based on the splitting patterns and coupling constants of the \(^1\)H NMR spectra.\(^3\)
Whipple and coworkers were able to use Co$_2$(CO)$_6$(PPh$_3$)$_2$ to provide one of the first examples of the transition metal catalyzed dimerization of norbornadiene. When refluxed in benzene, a combination of 3-5a and 3-5c were produced in approximately a 10:1 ratio. Through a change in the catalyst system to Ni(CO)$_4$, the production of 3-5b was also seen.$^3$ Having successfully synthesized and characterized the three trans isomers, it became a desirable goal to produce the cis variants of the compounds in order to carry out their full characterization.
Further investigations into this reaction showed that a variety of other transition metals were able to catalyze the dimerization of norbornadiene (Scheme 3-2). However, despite the vastness of catalytic systems employed for this reaction, only the three trans isomers were able to be synthesized.

![Scheme 3-2: Transition Metal Catalyzed Dimerization of Norbornadiene](image)

Jennings and coworkers used Cr(CO)$_6$ to provide the first example of a catalytic system that produces all three trans dimers in a ratio of 1.8:1.4:1.0 for 3-5a:3-5b:3-5c in a 40% overall yield. Contrarily, Katz and coworkers have extensively explored the Rh-catalyzed dimerization and trimerization of norbornadiene. Initial investigations using rhodium on carbon to catalyze the reaction saw primarily the Diels-Alder adduct 3-6 being formed with 3-5a resulting as a side product (Scheme 3-3). A yield of 20-30% of the trimer 3-7 was also seen in this reaction.

![Scheme 3-3: Rh/C Catalyzed Dimerization and Trimerization of Norbornadiene](image)
Iron carbonyls were among the first catalyst systems used to promote the dimerization reaction. This catalyst provided the [2+2+1] cycloadduct when 7-tert-butoxynorbornadiene was subjected to the reaction conditions (Scheme 3-4). Wege and coworkers expanded the scope of this reaction to encompass the first examples of the dimerization of benzonorbornadienes and oxabenzenornorbornadienes (Scheme 3-5).

Scheme 3-4: [2+2+1] Cyclodimerization of Norbornadiene

Scheme 3-5: Fe-Catalyzed Dimerization of Oxabenzenornorbornadiene

Since the initial investigations into the dimerization of norbornadiene using Fe-catalysts, nickel has also become a common transition metal used to promote these reactions. Nickel catalysts such as Ni(CO)₄, NiCl₂(P"Bu₃)₂-NaBH₄, and Ni(CO)₂(PPh₃)₂ have been used for this reaction providing mixtures of the trans products. Cheng and coworkers explored alternative conditions and found that through the use of NiX₂ with zinc metal, the [2+2] dimerization proceeded to give only the exo-trans-exo product 3-5a. Cheng and coworkers
were able to expand the scope of this reaction to include the second example of the dimerization of oxabenzonorbornadienes obtaining a 96% yield of the product. They were also able to provide the first examples of the dimerization of substituted oxabenzonorbornadienes (Scheme 3-6).

Scheme 3-6: Ni-Catalyzed Dimerization of Substituted Oxabenzonorbornadienes

Cheng and coworkers proposed a mechanism for the nickel catalyzed [2+2] dimerization reaction based on their knowledge of nickel and organometallic chemistry principles (Scheme 3-7). The nickel halide, is reduced to a Ni\(^0\) species which is then able to coordinate to the two norbornadiene molecules. Coupling provides the metallacyclopentane intermediate 3-17. Reductive elimination provides the dimerized norbornadiene and regenerates the Ni\(^0\) species. The stereochemistry of the product is determined by the initial coordination of the norbornadienes to the Ni catalyst\(^{12}\).
Galoppini and coworkers used an alternative approach to synthesize the macrocyclic dimer 3-18 (Scheme 3-8). Reduction of the cyclopentadienone 3-19 followed by nucleophilic acyl substitution provides 3-18. The dimerized product was obtained from 3-20 using a copper mediated photocycloaddition. They found that the intramolecular [2+2] cycloaddition proceeded much faster than the corresponding intermolecular reactions with high regio- and stereoselectivity. Using a tethered system and carrying out the cycloaddition intramolecularly allows for the synthesis of isomers that are not observable through an intermolecular reaction.
3.2 Results and Discussion

As seen through the investigation into previously studied dimerization reactions, very little work has been done using oxanorbornadienes and there are no examples to date using ruthenium to catalyze the reaction. Therefore, when attempting to expand the scope of the ruthenium catalyzed isomerization of oxabenzonorbornadiene into naphthols (Scheme 3-9) it was surprising to discover a dimerized product when oxanorbornadiene 3-2 was subjected to the reaction conditions (Scheme 3-10).\textsuperscript{16}
The lack of previous work done with oxanorbornadienes and ruthenium as a catalyst for dimerization reactions led us to study the ruthenium catalyzed [2+2] dimerization of 7-oxabicyclo[2,2,1]hepta-2,5-diene-2,3-dicarboxylates 3-23. We initiated our investigation by optimizing the reaction conditions, looking into different catalyst systems, solvents and temperatures to see which provided the highest yields of the desired product. The optimization began by screening various Ru catalysts to determine their efficacy in this dimerization (Table 3-1). Initially, Cp*Ru(COD)Cl, a useful catalyst in many other reactions of bicyclic alkenes, was tested for its ability to dimerize 3-23, yielding 66% of the product 3-24. The CpRu(COD)X series (where X=Cl, Br, and I, entries 2-4) were also examined resulting in a lower yield in all three cases. Interestingly, the use of CpRu(COD)Br produced more product than its counterparts leading us to attempt the dimerization reaction catalyzed by Cp*Ru(COD)Br (entry 5). The use of the bromide ligand in this case also led to an increase in yield compared to the
chloride ligand, resulting in 70% conversion to the desired product. Two cationic Ru catalysts were additionally investigated (entries 6 and 7). Both gave good yields but were not as effective as either of the Cp*Ru(COD)X variants. Ru(COD)Cl₂ and (Ph₃P)₂CpRuCl provided no discernible products from reaction under these conditions. Despite Cp*Ru(COD)Br providing slightly higher yields, Cp*Ru(COD)Cl was chosen for all further investigations due to its commercial availability.

**Table 3-1: Catalyst Optimization for Dimerization of Oxanorbornadienes**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cp*Ru(COD)Cl</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>CpRu(COD)Cl</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>CpRu(COD)Br</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>CpRu(COD)I</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>Cp*Ru(COD)Br</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>[Cp*Ru(CH₃CN)₃]&lt;sup&gt;+&lt;/sup&gt;PF₆⁻</td>
<td>55</td>
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<tr>
<td>7</td>
<td>[CpRu(CH₃CN)₃]&lt;sup&gt;+&lt;/sup&gt;PF₆⁻</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>Ru(COD)Cl₂</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>(Ph₃P)₂CpRuCl</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated Yields

With our catalyst of choice, Cp*Ru(COD)Cl in hand, we went on to explore solvent and temperature effects on this dimerization (Table 3-2). All solvents tested provided moderate yields of the dimer, however some proved more
effective than others. DMSO provided the lowest yield of 39% (entry 1). Toluene
and DMF (entries 2 and 3) resulted in slightly higher yields at 44% and 45%
respectively. When the reaction ran in THF or hexanes (entries 4 and 5) an
increased yield was again seen providing 50% and 51% of the desired product
respectively. Utilizing DCE (entry 6) as a solvent resulted in a much higher yield
of 66% and was thus selected as our solvent of choice. Less variability was seen
when the effect of temperature on the dimerization was explored (entries 6-8).
Running the reaction at 60°C provided a slightly higher yield than at 45°C or
25°C.

Table 3-2: Optimization of Solvent and Temperature for Dimerization of
Oxanorbornadienes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>DMSO</td>
<td>60</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
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<td>60</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>Hexanes</td>
<td>60</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>DCE</td>
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<td>66</td>
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<td>7</td>
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<td>54</td>
</tr>
<tr>
<td>8</td>
<td>DCE</td>
<td>25</td>
<td>61</td>
</tr>
</tbody>
</table>

\(^a\)Isolated Yields
Having determined the optimal conditions for our desired reaction, we moved on to explore the scope (Table 3-3). We first examined the effect of changing the alkyl component of the ester. Increasing the size of the ester moiety did not affect the reaction (entries 1-3). Whether a Me, Et or tBu ester was present on C² and C³ of the starting oxabicyclic alkene 3-23a-c, the yield of the dimer 3-24a-c remained constant at 66%. This result negates any steric effect of the ester component of the bicyclic in the reaction mechanism. The [2+2] cycloaddition that occurs to produce the dimerized product occurs between C⁵ and C⁶ of both oxabicyclic alkenes so it follows that added steric bulk at C² and C³ would not have an effect on the outcome of the reaction. To determine which configuration the dimerized products were taking, x-ray analysis of 3-24c was completed showing that the dimer is exo-trans-exo (Figure 3-2). The addition of an alkyl substituent at the C¹ position did have an effect on the reaction. When a methyl group was introduced at this position (entry 4), a slight decrease in yield to 57% was observed. Substitution at this position does have a steric effect on the reaction as indicated by the sharp decrease in yield when the size of the substituent was increased from a methyl group to an ethyl or pentyl group which produced the corresponding dimer in a 24% and 23% yield respectively. X-ray crystallography was again utilized to aid in the determination of the configuration of the product as we were unsure if the C¹ substituent would end up on the same or opposite sides of the dimer. With the possibility of forming two different regioisomers, we were pleased to discover that the crystal structure of 3-24d (Figure 3-3) illustrated only one regioisomer where the substituents are on the
same side of the dimer. This knowledge gives insight into why such a decrease in yield is seen when the size of the C\(^1\) substituent is increased as steric clash is introduced into the system. With successful examples of primary alkyl groups, the dimerization of a C\(^1\) tBu oxabicyclic alkene 3-23g was undertaken (entry 7). To our surprise, starting material was recovered with no observable reaction under the initial conditions. In an attempt to try and promote the reaction to occur, the temperature was increased to 80°C and the reaction was allowed to stir for 48h instead of the usual 18h. The change in conditions did not produce the desired dimer but instead resulted in ring opened aromatized product 3-25g in a 68% yield. When the C\(^1\) TMS substituted oxabicyclic alkene 3-23h (entry 8) was subjected to our standard conditions we once again saw the production of a highly substituted phenol 3-25h, this time with only 24% conversion. The electronic effects of the TMS substituent compared to the tBu substituent could be partially responsible for this decrease in yield. Changing the electronic nature of the C\(^1\) substituent to the electron withdrawing methyl ester resulted in the dimerized oxanorbornadiene in 53% yield. X-ray crystallography of this structure was undertaken to determine if changing the electronic nature of the substituent resulted in a different exo/endo-cis/trans-exo/endo configuration of the product. The crystal structure of 3-24j determined its structure to also be exo-trans-exo (Figure 3-4). The effects of other substituents on the dimerization of oxabicyclic alkenes were unclear as the reactions of alkenes 3-23j-3-23l yielded complicated mixtures of products.
Table 3-3: Ruthenium Catalyzed Dimerization Reactions of Oxanorbornadienes

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td>3-23a</td>
<td>Me</td>
<td>H</td>
<td>3-24a</td>
<td>66</td>
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<tr>
<td>2</td>
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<td>Et</td>
<td>H</td>
<td>3-24b</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>3-23c</td>
<td>tBu</td>
<td>H</td>
<td>3-24c</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>3-23d</td>
<td>Me</td>
<td>Me</td>
<td>3-25d</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>3-23e</td>
<td>Me</td>
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<td>3-24e</td>
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<td>3-24f</td>
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<td>tBu</td>
<td>3-25g</td>
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<td>(47)&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>3-24i</td>
<td>55 [36]&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Me</td>
<td>Ph</td>
<td>-</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Me</td>
<td>CH₂OH</td>
<td>-</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolate yields, <sup>b</sup> Complicated mix of products recovered; <sup>c</sup> Yields in brackets indicate ring opened aromatized products; <sup>d</sup> Yields in square brackets indicate ruthenium complexed product
Figure 3-2: Crystal Structure of 3-24c

Figure 3-3: Crystal Structure of 3-24d
Figure 3-4: Crystal Structure of 3-24j

Other attempts were unsuccessfulessly made to prepare a wider variety of oxanorbornadienes to subject to the reaction conditions (Scheme 3-11). The oxidation of 3-hexyne-2,5-diol 3-26 using Jones reagent was unsuccessful. Multiple attempts were made using both an extreme excess of Jones reagent to oxidize both alcohols in one reaction and alternatively using only a slight excess to oxidize one alcohol at a time, neither producing the desired diketone 3-27.\textsuperscript{17,18} Attempts to synthesize the sulphonyl acetylene 3-28 also proved unsuccessful.

The conversion of trichloroethylene 3-29 into dichloroacetylene 3-30 proceeded smoothly, and it appeared that conversion to the thiol was also successful. However, oxidation of the bis(arythiol)acetylene with MCPBA did not provide the desired sulffphonl acetylene.\textsuperscript{19-22} Finally, saponification of 3-23 into the carboxylate 3-32 proceeded without issue, however attempts to saponify the second ester failed.\textsuperscript{23} An attempt to synthesize 3-34 was made using LiAlH\textsubscript{4} also proved unsuccessful.
Attempts to further expand the scope of this reaction were made using other bicyclic systems (Scheme 3-12). Due to the inability to synthesize the dicarboxylic acid 3-33, we decided to instead attempt the dimerization reaction using 3-32. Unfortunately, no reaction occurred and starting material was recovered. This trend continued with all other bicyclic alkenes subjected to the reaction conditions. Oxanorbornenes 3-35, varies from our original system only by the hydrogenation of one of the double bonds. This change however, was enough to prevent the reaction from occurring. Using the reduced bicyclic 3-36 also resulted in the recovery of starting material. The corresponding
norbornadiene 3-37 also failed to dimerize when subjected to the appropriate conditions, indicating the importance of the oxygen bridgehead to this reaction. Having recognized the need for an electronegative bridgehead atom, we attempted to dimerize two azabicyclic alkenes 3-38 and 3-39. To our surprise starting material was once again recovered in both cases. The heteroatom bicyclic 3-40 also provided none of the desired dimerized product.

* Reactions carried out by Melissa Ballantine

**Scheme 3-12**: Attempted Scope Expansion of Dimerization Reactions
Despite many unsuccessful attempts, an interesting result was observed during the dimerization of the C\textsuperscript{1}-COOMe oxanorbornadiene \textbf{3-23i} (Scheme 3-13). After initial purification by column chromatography, the \textsuperscript{1}H NMR indicated a clean mixture of two products. Crystallization was able to separate the two compounds. One was identified as the desired dimerization product, while the second was determined to be the ruthenium complex \textbf{3-41} through x-ray crystallography (Figure 3-5).

\textbf{Scheme 3-13: Formation of Ruthenium Complex 3-41}
There are literature examples of norbornadienes complexed in this fashion with transition metals such as Rh\textsuperscript{24} or Mo\textsuperscript{25} (Figure 3-6). However, there are presently no known examples of oxanorbornadiene complexed with transition metals in this way. This mode of coordination is responsible for reactions such as the homo-Diels-Alder (Scheme 3-14).\textsuperscript{26} The literature on this reaction involving bicyclic alkenes only provides examples of norbornadienes participating. With evidence of the endo coordination of Ru to oxanorbornadiene there is hope that this reaction could be optimized to provide the first examples of a homo-Diels-Alder involving oxanorbornadienes.
3.3 Proposed Mechanism

Synthesis of the dimerized product requires coordination of two oxanorbornadiene molecules with the ruthenium catalyst to initiate the mechanism (Scheme 3-15). Dissociation of the COD ligand from Cp*Ru(COD)Cl provides the Ru$^{2+}$ species that is able to coordinate with oxanorbornadiene 3-23. The coordination of the Ru to the exo face of both oxanorbornadienes as in 3-45 is responsible for the final exo-trans-exo configuration. The metallacyclopentane intermediate 3-46 is formed which is able to undergo reductive elimination to provide the dimerized product 3-24.
3.4 Significance and Application

Although there are no examples of natural products containing a dimerized structure as a core, macrobicycles are commonly seen among important natural products. Taxanes are a class of biologically important molecules comprised of a tricyclic diterpene framework. They have been shown to have potent antitumor and antileukemic properties.\textsuperscript{27,28} Among this class of compounds is the effective anticancer agent Taxol \textbf{3-47} which was originally isolated from the Pacific yew tree (Figure 3-7).\textsuperscript{29}
Nicolaou and coworkers provided the first total synthesis of Taxol in 1994 using a convergent synthetic strategy (Scheme 3-16). A Shapiro reaction and McMurry coupling combined 3-49 with 3-50 to prepare the tricyclic structure 3-52. The addition of the oxetane ring followed by oxygenation and esterification were used to synthesize the desired target.
Other syntheses of Taxol have been successfully undertaken since Nicolaou and coworkers originally provided a route to this compound. Many synthetic challenges were encountered along the way, the largest being how to accomplish coupling of 3-49 with 3-50. Today, Taxol is produced using a semisynthesis from baccatin III which is isolated from the needles of the Pacific yew tree.

Using our dimerized system, ring opening of the oxygen bridge followed by ring cleavage of the cyclobutene ring may provide an alternate route to bicyclo core systems such as the one seen in Taxol. The dimerized core could also help to provide natural products such as trichodiene 3-54 which is a mycotoxin that shows biological activity. Its synthesis (Scheme 3-17) is described from the photoadduct 3-55, a variant of which could possibly be synthesized from the deoxygenation of our dimer.

Scheme 3-17: Total Synthesis of Trichodiene
3.5 References


Chapter 4: Experimental
4.1 General Information

All reactions were carried out under an atmosphere of dry nitrogen or argon unless otherwise specified. All glassware was oven dried and purged with a flow of nitrogen or argon or flame dried under nitrogen. Flash chromatography was performed on 230-400 mesh silica gel. Analytical thin layer chromatography (TLC) was performed on Silicycle precoated silica gel 250 μm F-254 plates. Visualization was accomplished with UV light and/or anisaldehyde charring or KMnO₄.

Infrared spectra (IR) were obtained on a Nicolet 380-FTIR spectrophotometer and are reported as wavelength numbers (cm⁻¹). IR spectra were obtained as a thin film on a NaCl disk. ¹H and ¹³C NMR spectra were obtained on an Bruker Avance 400 or 600 MHz spectrometer. The ¹H and ¹³C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent, deuterated chloroform (δ=7.26 ppm) being used as an internal standard. High resolution mass spectrometry (MS) was performed at the Queen’s Mass Spectrometry and Proteomics Unit, Kingston, Ontario. The samples were ionized by electron impact ionization (EI), chemical ionization (CI) or electrospray ionization (ESI) as specified and detection of the ions was performed by time of flight or triple quadrupole. Single crystal x-ray diffraction was carried out by Dr. Alan J. Lough at the Univeristy of Toronto, Toronto, Ontario.

Reagents: Unless otherwise stated, commercial reagents and catalysts were using without further purification. Solvents were purified by distillation under
4.2 Synthesis of Ring Opened Products

General Procedure (A) for the synthesis of ring opened products (Table 2-4): Into an oven dried screw-cap vial equipped with a stir bar, 7-oxabenzonorbornadiene 2-3 (47.5 mg, 0.329 mmol) was weighed and purged with nitrogen. The vial was capped and brought into an inert atmosphere glovebox where Cp*Ru(COD)Cl (7.7 mg, 0.021 mmol) was added to a second vial and dissolved in degassed methanol (0.8 mL). The catalyst solution was transferred by pipette to the vial containing 7-oxabenzonorbornadiene. The reaction vial was capped and allowed to stir outside the glove box at 65°C for 1 h. The crude product was purified by flash chromatography in an ethyl acetate/hexanes mixture to yield the corresponding ring opened product.
Reaction of Oxabenzonorbornadiene 2-3a with Cp*Ru(COD)Cl in MeOH

Following the above procedure (A) with 7-oxabenzonorbornadiene 2-3a (1 eq, 47.5 mg, 0.329 mmol), Cp*Ru(COD)Cl (0.06 eq, 7.7 mg, 0.021 mmol), and 0.8 mL of MeOH. The crude product was purified by column chromatography (EtOAc:hexanes = 1:9) to give 2-61a (38.1 mg, 0.226 mmol, 66%) and 2-62a (0.016 mmol, 2.4 mg, 5%)

(1R*,2R*)-2-Methoxy-1,2-dihydronaphthalen-1-ol , 2-61a

White solid (m.p. 49-51°C). $R_f$ 0.22 (EtOAc:hexanes = 1:4); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.58 (d, 1H, $J = 6.8$ Hz), 7.24-7.27 (m, 2H), 7.08-7.10 (m, 1H), 6.48 (dd, 1H, $J = 9.9$, 2.0 Hz), 6.06 (dd, 1H, $J = 9.9$, 2.3 Hz), 4.91 (d, 1H, $J = 10.2$ Hz), 4.11 (app dt, 1H, $J = 10.3$, 2.2 Hz), 3.51 (s, 3H), 2.64 (br s, 1H); $^{13}$C NMR (APT, CDCl$_3$, 100 MHz) $\delta$ 135.8, 131.9, 128.3, 127.9, 127.8, 126.7, 126.3, 125.0, 82.2, 72.4, 56.8. IR (CH$_2$Cl$_2$) 3420, 3037, 2979, 2929, 2825, 1455 cm$^{-1}$; HRMS (EI) calcd for C$_{11}$H$_{12}$O$_2$ (M$^+$) 176.0837; found: 176.0840.
1-Naphthol, 2-62a

\[ \text{R} \text{f} \ 0.38 \text{ (EtOAc:hexanes=3:7); } ^1\text{H NMR (CDCl}_3, 300 \text{ MHz) } \delta \ 8.22-8.25 \text{ (m, 1H), 7.85-7.91 (m, 1H), 7.48-7.61 (m, 3H), 7.34 (apt t, 1H, J} \text{ = 7.4 Hz), 6.82 (d, 1H, } J = 7.4 \text{ Hz), 5.42 (br s, 1H); } ^{13}\text{C NMR (APT, CDCl}_3, 75 \text{ MHz) } \delta \ 151.2, 134.7, 127.6, 126.4, 125.8, 125.3, 124.3, 121.4, 120.7, 108.6. \text{ HRMS (Cl) calcd. for } \text{C}_{10}\text{H}_8\text{O } ((\text{M+H})^+) : 145.0653; \text{ found: 145.0666.} \]

(1R*,2R*)-2-Methoxy-5,8-dimethyl-1,2-dihydronaphtalen-1-ol, 2-61b

Following the above procedure (A) with 7-oxabenzonorbornadiene 2-3b (1 eq, 43.8 mg, 0.25 mmol), \text{Cp*Ru(COD)Cl} (0.06 eq, 5.9 mg, 0.016 mmol), and 0.6 mL of MeOH. The crude product was purified by column chromatography (EtOAc:hexanes = 1:4) to give 2-61b (30.7 mg, 0.150 mmol, 59%) as a yellow oil.

\[ \text{R} \text{f} \ 0.08 \text{ (EtOAc:hexanes = 1:4); } ^1\text{H NMR (CDCl}_3, 400 \text{ MHz) } \delta \ 7.03 \text{ (q, 2H, } J = 7.9, 10.9 \text{ Hz), 6.94 (d, 1H, } J = 9.9 \text{ Hz), 6.16 (ddd, 1H, } J = 1.1, 5.4, 9.9 \text{ Hz), 4.93 (d, 1H, } J = 6.7), 3.99 (dd, 1H, } J = 2.0, 5.4 \text{ Hz), 3.41 (s, 3H), 2.42 (s, 3H), 2.34 (s, 3H), 1.54 (d, 1H, } J = 7.0 \text{ Hz); } ^{13}\text{C NMR (APT, CDCl}_3, 100 \text{ MHz) } \delta \ 135.0, 132.8, 132.4, 130.6, 129.1, 127.8, 123.4, 75.9, 65.8, 56.5, 18.8, 18.1. \text{ IR } (\text{CH}_2\text{Cl}_2) \ 3376, 2725, 2359, 1260, 1084, 930, 808, 722 \text{ cm}^{-1}; \text{ HRMS (El) calcd. for } \text{C}_{13}\text{H}_{16}\text{O}_2 \text{ (M}^+) : 204.1150; \text{ found: 204.1152.} \]
(1R*,2R*)-2-Methoxy-5,8-dimethoxy-1,2-dihydronaphtalen-1-ol, 2-61c

Following the above procedure (A) with 7-oxabenzonorbornadiene 2-3c (1 eq, 55.6 mg, 0.27 mmol), Cp*Ru(COD)Cl (0.06 eq, 6.3 mg, 0.017 mmol), and 0.6 mL of MeOH. The crude product was purified by column chromatography (EtOAc:hexanes = 1:4) to give 2-61c (25 mg, 0.106 mmol, 40%) as a yellow oil. 

$R_f$ 0.04 (EtOAc:hexanes = 1:4); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.04 (d, 1H, $J = 10.0$ Hz), 6.79 (s, 2H), 6.09-6.13 (m, 1H) 5.17-5.18 (m, 1H), 4.06 (q, 1H, $J = 3.2$, 4.6 Hz), 3.85 (s, 3H), 3.79 (s, 3H), 3.45 (s, 3H), 2.47 (d, 1H, $J = 4.4$ Hz); $^{13}$C NMR (APT, CDCl$_3$, 100 MHz) $\delta$ 151.6, 150.0, 124.2, 124.0, 123.5, 121.4, 111.6, 111.1, 77.0, 65.1, 56.5, 56.2, 56.0. IR (CH$_2$Cl$_2$) 3422, 2936, 2836, 2359, 1596, 1484, 1395, 1260, 1192, 1086, 956, 804, 715 cm$^{-1}$; HRMS (El) calcd. for C$_{13}$H$_{16}$O$_4$ (M$^+$): 236.1049; found: 236.1046.

Reaction of 6,7-Dibromooxabenzonorbornadiene 2-3d with Cp*Ru(COD)Cl in MeOH

Following the above procedure (A) with 7-oxabenzonorbornadiene 2-3d (1 eq, 88.8 mg, 0.29 mmol), Cp*Ru(COD)Cl (0.06 eq, 6.7 mg, 0.018 mmol), and 0.7 mL of MeOH. The crude product was purified by column chromatography
(EtOAc:hexanes = 1:4) to give 2-61d (54.5 mg, 0.164 mmol, 56%) and 2-62d (14.7 mg, 0.049 mmol, 17%).

**1R*,2R*)-6,7-Dibromo-2-methoxy-1,2-dihydronaphtalen-1-ol, 2-61d**

![Structure of 2-61d](image)

White solid (m.p. 134-137°C). \( R_f \) 0.22 (EtOAc:hexanes = 1:4); \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta \) 7.83 (s, 1H), 7.31 (s, 1H), 6.35 (dd, 1H, \( J = 2.0, 10.0 \) Hz), 6.12 (dd, 1H, \( J = 2.0, 9.9 \) Hz), 4.82 (dd, 1H, \( J = 2.4, 10.9 \) Hz), 4.06 (td, 1H, \( J = 2.1, 10.9 \) Hz), 3.51 (s, 3H), 2.71 (bs, 1H); \(^{13}\)C NMR (APT, CDCl₃, 100 MHz) \( \delta \) 136.6, 132.7, 130.7, 130.3, 129.0, 126.2, 123.8, 123.7, 81.9, 71.8, 57.0. IR (CH₂Cl₂) 3167, 2726, 2671, 2359, 1304, 1169, 1049, 977, 889, 773, 722, 667 cm⁻¹; HRMS (EI) calcd. for C₁₁H₁₀Br₂O₂ (M⁺): 331.9049; found: 331.9051.

**6,7-Dibromo-1-naphthol, 2-62d**

\( R_f \) 0.28 (EtOAc:hexanes=1:9); \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta \) 8.50 (s, 1H), 8.10 (s, 1H), 7.35–7.30 (m, 2H), 6.82 (dd, 1H, \( J = 6.2 \) Hz, \( J = 2.2 \) Hz), 5.42 (s, 1H); \(^{13}\)C NMR (APT, CDCl₃, 100 MHz) \( \delta \) 150.5, 134.4, 131.9, 127.4, 127.0, 124.2, 123.0, 121.4, 119.6, 109.6. IR (NaCl) 3238, 2960, 2924, 2875, 2852, 1629, 1573, 1508, 1449, 1426, 1393, 1344, 1276, 1236, 1194, 1161, 1102, 1076, 1043 cm⁻¹; HRMS (EI) calcd. for C₁₀H₆Br₂O (M⁺): 299.8785; found: 299.8790.
(1R*,2R*)-Triphenylene-1,2-dihydronaphtalen-1-ol, 2-61f

Following the above procedure (A) with 7-oxabenzonorbornadiene 2-3f (1 eq, 54.4 mg, 0.22 mmol), Cp*Ru(COD)Cl (0.06 eq, 5.0 mg, 0.013 mmol), and 0.6 mL of MeOH. The reaction was stirred at 80°C. The crude product was purified by column chromatography (EtOAc:hexanes = 1:4) to give 2-61f (16 mg, 0.058 mmol, 26%) as a brown solid. Rf 0.08 (EtOAc:hexanes = 1:4); 1H NMR (CDCl3, 400 MHz) δ 8.71-8.75 (m, 2H), 8.36-8.38 (m, 1H), 8.30-8.32 (m, 1H), 7.62-7.71 (m, 5H), 6.48 (dd, 1H, J = 5.3, 9.9 Hz), 5.54 (d, 1H, J = 6.8 Hz), 4.23 (dd, 1H, J = 1.6, 5.4 Hz), 3.45 (s, 3H), 1.79 (d, 1H, J = 7.1 Hz); 13C NMR (APT, CDCl3, 100 MHz) δ 130.8, 130.8, 130.1, 128.7, 128.6, 127.4, 127.0, 126.9, 126.7, 126.2, 125.4, 125.2, 123.8, 123.7, 123.1, 123.1, 75.9, 65.8, 56.3. IR (CH2Cl2) 3337, 2726, 2359, 1303, 1027, 946, 769, 722 cm⁻¹; HRMS (El) calcd. for C19H16O2 (M⁺): 276.1150; found: 276.1153.

(1R*,2R*)-2,8-Dimethoxy-1,2-dihydronaphtalen-1-ol, 2-61g₁

Following the above procedure (A) with 7-oxabenzonorbornadiene 2-3g (1 eq, 45.9 mg, 0.26 mmol), Cp*Ru(COD)Cl (0.06 eq, 6.0 mg, 0.016 mmol), and 0.8 mL of MeOH. The crude product was purified by column chromatography (EtOAc:hexanes = 3:7) to give 2-61g₁ (9 mg, 0.043 mmol, 17%) as a brown solid. Rf 0.12 (EtOAc:hexanes = 3:7); 1H NMR (CDCl3, 400 MHz) δ 7.23-7.27 (m, 1H),
6.84 (d, 1H, J = 8.3 Hz), 6.80 (d, 1H, J = 7.6 Hz), 6.61 (d, 1H, J = 9.7 Hz), 6.12 (dd, 1H, J = 4.5, 9.6 Hz), 5.22 (t, 1H, J = 3.5 Hz), 4.08 (q, 1H, J = 3.5 Hz), 3.89 (s, 3H), 3.46 (s, 3H), 2.40 (d, 1H, J = 4.5 Hz); 13C NMR (APT, CDCl3, 100 MHz) δ 157.5, 132.4, 129.6, 129.5, 125.2, 122.7, 120.3, 110.8, 77.4, 64.8, 56.5, 55.6. IR (CH2Cl2) 3413, 2854, 2363, 2187, 1578, 1461, 1263, 1083, 745 cm⁻¹; HRMS (El) calcd. for C12H14O3 (M⁺): 206.0943; found: 206.0940.

(1R*,2R*)-2,5-Dimethoxy-1,2-dihydronaphtalen-1-ol, 2-61g2

Following the above procedure (A) with 7-oxabenzenorbornadiene 2-3g (1 eq, 45.9 mg, 0.26 mmol), Cp*Ru(COD)Cl (0.06 eq, 6.0 mg, 0.016 mmol), and 0.8 mL of MeOH. The crude product was purified by column chromatography (EtOAc:hexanes = 3:7) to give 2-61g2 (7 mg, 0.033 mmol, 12%) as a white solid. Rf 0.24 (EtOAc:hexanes = 3:7); 1H NMR (CDCl3, 400 MHz) δ 7.19-7.26 (m, 2H), 6.86 (dd, 1H, J = 1.9, 10.1 Hz), 6.80 (d, 1H, J = 7.8 Hz), 6.03 (dd, 1H, J = 2.3, 10.2 Hz), 4.84 (dd, 1H, J = 3.4, 10.4 Hz), 4.08 (td, 1H, J = 2.2, 10.5 Hz), 3.83 (s, 3H), 3.51 (s, 3H), 2.54 (d, 1H, J = 3.6 Hz); 13C NMR (APT, CDCl3, 100 MHz) δ 154.8, 137.3, 128.8, 125.4, 122.3, 120.6, 117.4, 110.2, 81.8, 72.5, 56.7, 55.6. IR (CH2Cl2) 3581, 3448, 3505, 2987, 2935, 2840, 2306, 1577, 1474, 1389, 1266, 1109, 1048, 748 cm⁻¹; C12H14O3 (M⁺): 206.0943; found: 206.0946.
(1R*,2R*)-2-Methoxy-7-methoxycarbonyl-1,2-dihydronaphtalen-1-ol, 2-62h₁ and (1R*,2R*)-2-Methoxy-6-methoxycarbonyl-1,2-dihydronaphtalen-1-ol, 2-62h₂ as an inseparable mixture

Following the above procedure (A) with 7-oxabenzonorbornadiene 2-3h (1 eq, 49.7 mg, 0.25 mmol), Cp*Ru(COD)Cl (0.06 eq, 7.0 mg, 0.018 mmol), and 0.6 mL of MeOH. The crude product was purified by column chromatography (EtOAc:hexanes = 2:3) to give 2-61h₁ and 2-61h₂ (18.5 mg, 0.079 mmol, 42%) as a white solid. R₇ 0.24 (EtOAc:hexanes = 2:3); ¹H NMR (CDCl₃, 400 MHz) δ 8.24 (s, 0.6H), 7.91-7.94 (m, 1H), 7.73 (d, 0.4H, J = 1.5 Hz), 7.67 (d, 0.4H, J = 7.9 Hz), 7.13 (d, 0.6H, J = 7.8 Hz), 6.49 (dt, 1H, J = 2.2, 9.9 Hz), 6.18 (dd, 0.6H, J = 2.2, 9.9 Hz), 6.11 (dd, 0.4H, J = 2.0, 10.0 Hz), 4.90-4.95 (m, 1H), 4.10-4.15 (m, 1H), 3.91 (s, 3H), 3.52 (s, 1.8H), 3.52 (s, 1.2H), 2.79 (d, 0.4H, J = 3.3 Hz), 2.72 (d, 0.6H, J = 3.6 Hz); ¹³C NMR (APT, CDCl₃, 100 MHz) δ 166.8, 166.8, 140.9, 136.2, 136.1, 132.2, 129.7, 129.6, 129.4, 129.4, 129.1, 127.9, 127.6, 127.5, 127.0, 126.2, 126.21, 124.9, 82.2, 82.1, 72.6, 56.9, 56.8, 52.1, 52.1. IR (CH₂Cl₂) 3587, 3448, 3054, 2987, 2953, 2829, 2306, 1717, 1611, 1439, 1266, 1204, 1104, 1050, 978, 743 cm⁻¹; HRMS (EI) calcd. for C₁₃H₁₄O₄ (M⁺): 234.0892; found: 234.0894.
Reaction of 1-Methyloxabenzonorbornadiene 2-3I with Cp*Ru(COD)Cl in MeOH

Following the above procedure (A) with 7-oxabenzonorbornadiene 2-3I (1 eq, 90 mg, 0.57 mmol), Cp*Ru(COD)Cl (0.1 eq, 21 mg, 0.055 mmol), and 1.5 mL of MeOH. The reaction was left to stir for 72h at 80°C. The crude product was purified by column chromatography (EtOAc:hexanes = 1:4) to give 2-61I (22 mg, 0.1169 mmol, 20%) and 2-62I (63 mg, 0.40 mmol, 70%)

(1R*,2R*)-2-Methoxy-4-methyl-1,2-dihydonaphtalen-1-ol, 2-61I

White solid. Rf 0.16 (EtOAc:hexanes = 1:4); 1H NMR (CDCl3, 400 MHz) δ 7.59-7.61 (m, 1H), 7.24-7.31 (m, 4H), 5.87 (s, 1H), 4.82 (d, 1H, J = 10.0 Hz), 4.02 (td, 1H, J = 2.0, 10.0 Hz), 3.50 (s, 3H), 2.55 (s, 1H), 2.09 (t, 1H, J = 1.6 Hz); 13C NMR (APT, CDCl3, 100 MHz) δ 136.1, 133.5, 133.4, 127.7, 127.6, 124.9, 123.4, 123.3, 81.9, 72.4, 56.7, 19.0. IR (CH2Cl2) 3429, 3054, 2934, 2827, 2306, 1734, 1646, 1453, 1379, 1319, 1266, 1224, 1097, 1026, 968, 910, 758, 704 cm⁻¹; HRMS (El) calcd. for C12H14O2 (M⁺): 190.0994; found: 190.0990.
4-Methyl-1-naphthol 2-62j

\[
\begin{align*}
\text{OH} & \quad R_f 0.40 \text{ (EtOAc:hexanes=1:9); } \\
\text{2-62j Me} & \quad ^1H \text{ NMR (CDCl}_3, 400MHz): \delta 8.28 \text{ (m, 1H), 7.99 (m, 1H), 7.58 (m, 2H), 7.16 (dd, 1H, } J = 7.6, 0.7 \text{ Hz), 6.72 (d, 1H, } J = 7.6 \text{ Hz), 5.37 (br. s, 1H), 2.65 (d, 3H, } J = 0.7 \text{ Hz); } \quad ^{13}C \\
\text{NMR (APT, CDCl}_3, 100MHz): \delta 149.7, 133.4, 126.7, 126.2, 126.1, 124.9, 124.5, \\
124.1, 122.0, 108.2, 18.8. \quad \text{HRMS (El) calcd. for } C_{11}H_{10}O (M^+): 158.0732; \text{ found: } 158.0738.
\end{align*}
\]

4.3 Synthesis of Dimerized Products

General Procedure (B) for the synthesis of dimerized oxanorbornadienes (Table 3-3): Oxanorbornadiene 3-23 (44 mg, 0.21 mmol) was weighed into an oven dried screw-cap vial equipped with a stir bar. The vial was purged with nitrogen and taken into the drybox where Cp*RuCl(COD) (8 mg, 0.02 mmol) and DCE (0.3 mL) were added and the vial was sealed. The reaction mixture was stirred outside the glove box at 60 °C for 16-20 hours. The crude product was purified by flash chromatography to yield the corresponding cycloadduct (ethyl acetate/hexanes mixture).
Dimer 3-24a

Following the above procedure (B) with oxanorbornadiene 3-23a (44 mg, 0.21 mmol), Cp*Ru(COD)Cl (8 mg, 0.02 mmol), and DCE (0.3 mL). The crude product was purified by column chromatography (EtOAc:hexanes 2:3) to give the dimer 3-24a (29.0 mg, 0.069 mmol, 66%) as a white solid (m.p. 180-182°C). $R_f$ 0.2 (EtOAc:hexanes 2:3); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 5.16 (s, 4H), 3.79 (s, 12H), 2.17 (s, 4H); $^{13}$C (APT, CDCl$_3$, 100 MHz) $\delta$ 162.61, 142.73, 82.62, 52.27, 39.69; IR (CH$_2$Cl$_2$) 3007, 2955, 2847, 1717, 1631, 1437, 1306, 1229, 1121, 917, 746 cm$^{-1}$; HRMS (ESI) calcd for C$_{20}$H$_{20}$O$_{10}$ (M$^+$): 420.1056; found: 420.1073.

Dimer 3-24b

Following the above procedure (B) with oxanorbornadiene 3-23b (161 mg, 0.68 mmol), Cp*Ru(COD)Cl (26 mg, 0.07 mmol), and DCE (1.0 mL). The crude product was purified by column chromatography (EtOAc:hexanes 3:7) to give the dimer 3-24b (106.2 mg, 0.22 mmol, 66%) as a white solid (m.p. 173-175°C); $R_f$ 0.31 (EtOAc:hexanes 3:7); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 5.14 (s, 4H), 4.20-4.26 (q, 8H, $J=7.12$ Hz), 2.16 (s, 4H), 1.27-1.30 (t, 12H, $J=6.7$ Hz); $^{13}$C NMR (APT, CDCl$_3$, 100 MHz) $\delta$ 162.38, 142.57, 82.63, 61.34,
Dimer 3-24c

Following the above procedure (B) with oxanorbornadiene 3-23c (45 mg, 0.15 mmol), Cp*Ru(COD)Cl (6 mg, 0.015 mmol), and DCE (0.5 mL). The crude product was purified by column chromatography (EtOAc:hexanes 1:9) to give dimer 3-24c (28.8 mg, 0.050 mmol, 66%) as a white solid (m.p. 120°C dec.); Rf 0.22 (EtOAc:hexanes 1:9); ¹H NMR (CDCl₃, 400 MHz) δ 5.07 (s, 4H), 2.14 (s, 4H), 1.49 (s, 36H); ¹³C NMR (APT, CDCl₃, 100 MHz) δ 161.71, 142.70, 82.79, 82.43, 40.04, 28.06; IR (CH₂Cl₂) 1725, 1655, 1422, 1370, 1164, 1123, 896 cm⁻¹; HRMS (ESI) calcd for C₃₂H₄₄O₁₀(M⁺Na⁺): 611.2832; found 611.2829.

Dimer 3-24d

Following the above procedure (B) with oxanorbornadiene 3-23d (45 mg, 0.20 mmol), Cp*Ru(COD)Cl (7.5 mg, 0.02 mmol), and DCE (0.3 mL). The crude product was purified by column chromatography (EtOAc:hexanes 2:3) to give dimer 3-24d (23.7 mg, 0.053 mmol, 57%) as a white solid (m.p. 129-131°C); Rf 0.29 (EtOAc:hexanes 2:3); ¹H NMR (CDCl₃, 400 MHz) 39.79, 14.03; IR (CH₂Cl₂) 2941, 1707, 1630, 1333, 1227, 1122, 1022, 918 cm⁻¹; HRMS (ESI) calcd for C₂₂H₂₈O₁₀(M⁺): 476.1682; found: 476.1665.
δ 5.07 (s, 2H), 3.82 (s, 6H), 3.76 (s, 6H), 2.16 (s, 4H), 1.63 (s, 6H); $^{13}$C NMR (APT, CDCl$_3$, 100 MHz) δ 164.41, 162.26, 146.89, 140.84, 89.42, 81.32, 52.32, 52.23, 41.38, 41.22, 12.44; IR (CH$_2$Cl$_2$) 2955, 2846, 1721, 1634, 1437, 1389, 1200, 1063, 1001, 832 cm$^{-1}$; HRMS (ESI) calcd for C$_{22}$H$_{24}$O$_{10}$ (M$^+$): 448.1369; found: 448.1355.

**Dimer 3-24e**

Following the above procedure (B) with oxanorbornadiene 3-23e (200 mg, 0.84 mmol), Cp*Ru(COD)Cl (25 mg, 0.06 mmol), and DCE (2 mL). The crude product was purified by column chromatography (EtOAc:hexanes 2:3) to give dimer 3-24e (48.4 mg, 0.086 mmol, 24%) as a white solid (m.p. 110-115°C); $R_f$ 0.44 (EtOAc:hexanes 2:3); $^1$H NMR (CDCl$_3$, 400 MHz) δ 5.10 (s, 2H), 3.83 (s, 6H), 3.76 (s, 6H), 2.14-2.20 (m, 4H), 1.96-2.10 (m, 4H), 0.99-1.03 (t, 6H, $J$=7.5 Hz); $^{13}$C NMR (APT, CDCl$_3$, 100 MHz) δ 164.92, 162.10, 146.51, 141.08, 94.05, 81.12, 52.31, 52.17, 41.60, 40.71, 19.74, 9.31; IR (CH$_2$Cl$_2$) 2955, 2884, 1720, 1631, 1437, 1330, 1226, 1074, 1014, 938, 896 cm$^{-1}$; HRMS (ESI) calcd for C$_{24}$H$_{28}$O$_{10}$ (M$^+$): 476.1682; found: 476.1702.
Dimer 3-24f

Following the above procedure (B) with oxanorbornadiene 3-23f (107 mg, 0.38 mmol), Cp*Ru(COD)Cl (15 mg, 0.038 mmol), and DCE (1 mL). The crude product was purified by column chromatography (EtOAc:hexanes 1:4) to give dimer 3-24f (24.5 mg, 0.044 mmol, 23%) as a white solid (m.p. 71-72°C); \( R_f \) 0.29 (EtOAc:hexanes 1:4); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.10 (s, 2H), 3.83 (s, 6H), 3.76 (s, 6H), 2.18-2.19 (d, 2H, \( J=5.80 \) Hz), 2.13-2.14 (d, 2H, \( J=5.80 \) Hz), 1.95-1.96 (m, 4H), 1.48-1.49 (m, 2H), 1.29-1.35 (m, 6H), 0.87-0.90 (t, 6H, \( J=6.68 \) Hz); \(^{13}\)C NMR (APT, CDCl\(_3\), 100 MHz) \( \delta \) 164.95, 162.17, 146.60, 141.02, 93.66, 81.22, 52.32, 52.21, 41.51, 41.04, 32.08, 26.57, 24.87, 22.34, 13.86; IR (CH\(_2\)Cl\(_2\)) 2955, 2872, 1720, 1630, 1437, 896 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{24}\)H\(_{28}\)O\(_{10}\) (M\(^+\)): 560.2621; found: 560.2636.

Dimer 3-24i

Following the above procedure (B), with oxanorbornadiene 3-23i (316 mg, 1.2 mmol), Cp*Ru(COD)Cl (45 mg, 0.12 mmol), and DCE (2 mL). The crude product was purified by column chromatography (EtOAc:hexanes 1:1) to give dimer 3-24i (165.5 mg, 0.617 mmol, 53%) as a white solid (m.p. 196-198°C); \( R_f \) 0.40 (EtOAc:hexanes 1:1); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 2.25 (s, 2H), 3.87 (s, 6H), 3.81 (s, 6H), 3.79 (s, 6H), 2.60-2.61 (d, 2H,
$J=5.4$ Hz), 2.35-2.37 (d, 2H, $J=5.4$ Hz); $^{13}$C NMR (APT, CDCl$_3$, 100 MHz) $\delta$
165.90, 162.49, 161.55, 143.82, 140.35, 90.47, 82.01, 52.96, 52.73, 52.55, 41.76, 40.99; IR (CH$_2$Cl$_2$) 2956, 2850, 1743, 1438, 1331, 1204, 1158, 1082, 1036, 896 cm$^{-1}$; HRMS (ESI) calcd for C$_{24}$H$_{24}$O$_{14}$ ($M^+$): 536.1166; found: 536.1166.

Phenol 3-25g

Following the above procedure (B) except running the reaction at 80°C for 2 days with oxanorbornadiene 3-23g (65 mg, 0.25mmol), Cp*Ru(COD)Cl (9mg, 0.02 mmol), and DCE (0.7 mL). The crude product was purified by column chromatography (EtOAc:hexanes 2:3) to give phenol 3-25g (45.3 mg, 0.169 mmol, 68%) as a brown oil; $R_f$ 0.18 (EtOAc:hexanes 2:3); $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 10.81 (s, 1H), 7.60-7.63 (d, 1H, $J=9.12$), 6.98-7.01 (d, 1H, $J=9.08$), 3.92 (s, 3H), 3.84 (s, 3H), 1.35 (s, 9H); $^{13}$C NMR (APT, CDCl$_3$, 100 MHz) $\delta$ 170.57, 169.72, 159.44, 138.32, 134.49, 133.03, 118.78, 110.23, 52.97, 52.05, 35.76, 31.53; IR (CH$_2$Cl$_2$) 3423, 2956, 1738, 1675, 1591, 1441, 1326, 1193, 1161, 1012 cm$^{-1}$; HRMS (EI) calcd for C$_{14}$H$_{18}$O$_{5}$ ($M^+$): 266.1154; found: 266.1162.
Phenol 3-25h

Following the above procedure (B) except running the reaction at 80°C for 2 days with oxanorbornadiene 3-23h (24 mg, 0.09 mmol), Cp*Ru(COD)Cl (3.5 mg, 0.01 mmol), and DCE (0.3 mL). The crude product was purified by column chromatography (EtOAc:hexanes 1:9) to give phenol 14g (10.9 mg, 0.042 mmol, 47%) as a yellow oil; \( R_f \) 0.32 (EtOAc:hexanes 1:9); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 10.84 (s, 1H), 7.61-7.63 (d, 1H, \( J=8.44 \) Hz), 7.03-7.05 (d, 1H, \( J=8.48 \) Hz), 3.92 (s, 3H), 3.86 (s, 3H), 0.254 (s, 9H); \(^{13}\)C NMR (APT, CDCl\(_3\), 100 MHz) \( \delta \) 170.14, 169.58, 161.71, 140.93, 140.87, 128.13, 118.39, 110.03, 52.90, 52.12, -0.46; IR (CH\(_2\)Cl\(_2\)) 3423, 2955, 1736, 1677, 1577, 1458, 1343, 1255, 1212, 1130, 1014, 895, 877, 802 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{13}\)H\(_{18}\)O\(_5\)Si (M\(^+\)) : 282.0924; found: 282.0935.

Ruthenium Complex 3-40

Following the above procedure (B) with oxanorbornadiene 3-23i (316 mg, 1.2 mmol), Cp*Ru(COD)Cl (45 mg, 0.12 mmol), and DCE (2 mL). The crude product was purified by column chromatography (EtOAc:hexanes 1:1) to give ruthenium complex 3-40 (23 mg, 0.043 mmol, 36% yield) as a red solid; \( R_f \) 0.40 (EtOAc:hexanes 1:1); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 5.94 (d, 1H, \( J=2.4 \) Hz), 4.49-4.50 (m, 1H), 4.33-4.35 (d, 1H, \( J=4.8 \) Hz), 3.86 (s, 3H), 3.70 (s, 3H), 3.68 (s, 3H), 1.64 (s, 15H); \(^{13}\)C NMR (APT, CDCl\(_3\), 100 MHz) \( \delta \) 168.65, 168.01, 166.66,
102.67, 93.90, 90.11, 75.71, 69.91, 61.72, 55.36, 52.64, 51.97, 51.86, 9.21; IR (CH₂Cl₂) 3054, 2987, 2686, 2306, 1751, 1705, 1442, 1265, 896, 747, 705 cm⁻¹.