Transition Metal Catalyzed Ring-Opening Reactions of Unsymmetrical Oxabicyclic Alkenes

by

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ABSTRACT

Transition Metal Catalyzed Ring-Opening Reactions of
Unsymmetrical Oxabicyclic Alkenes

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This report is an investigation of regioselectivity in transition metal catalyzed ring-opening reactions involving unsymmetrical oxabicycles, specifically with a substituent at the C1 position. This report also provides the details of the work conducted towards the preparation of various oxanorbornadienes and their precursors.

A large number of reactions have been developed using various transition metal catalysts on oxabicyclic alkenes to form functionalized organic scaffolds. However, most of the literature is limited to symmetrical substrates. Introduction of a substituent at the bridgehead carbon of the bicyclic ring makes the molecule unsymmetrical. The implications of loss of the plane of symmetry in C1 substituted oxabicyclic ring are manifested in interesting ways during various metal catalyzed reactions. The fundamental basis for the current work is to study the consequences of transition metal catalyzed ring opening reactions of unsymmetrical bicyclic alkenes.

The reactivity of a wide range of C1 substituted benzoanorbornadienes and oxanorbornadienes in palladium and nickel-catalyzed ring opening reactions was explored. The palladium catalyzed ring opening reaction of both electron rich and electron deficient C1 substituted benzoanorbornadienes are optimized. The ring opening reactions with electron withdrawing C1 substituent resulted in formation of substituted naphthalene-1-carboxylic acid methyl ester derivatives in up to 85% yield. Electron
donating substituents on the C$^1$ position of benzoxanorbornadiene led to the formation of substituted cis-1,2-dihydronaphthol rings in excellent yields. Palladium catalyzed ring opening reactions were also explored with a wide range of aryl iodides and halobenzenes. The electronic and steric effects of the substituent at the C$^1$ position of oxabicycles were also investigated.

The nickel catalyzed ring opening reactions resulted in formation of inseparable regioisomeric mixtures of products. However, it was found that the nickel catalyzed ring opening of 1-methoxycarbonyl-7-oxabenzonorbornadiene occurred regioselectively affording a single product.

A scalable procedure for preparation of large quantities of 2-bromofuran was developed. 2-Aryl furans were prepared using Suzuki cross coupling protocols of 2-bromofuran with aryl boronic acids whereas 2-alkyl furans were prepared by iron catalyzed cross coupling reaction of 2-bromofuran with various alkyl and cycloalkyl Grignard reagents. The 2-substituted furans were used for the preparation of novel C$^1$ substituted benzoxanorbornadiene and oxanorbornadienes.
Dedicated in loving memory of my father

Mohammed Abdul Qadeer
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# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetone</td>
</tr>
<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
</tr>
<tr>
<td>app</td>
<td>apparent</td>
</tr>
<tr>
<td>ARO</td>
<td>asymmetric ring opening</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>BHT</td>
<td>butylated hydroxytoluene</td>
</tr>
<tr>
<td>br s</td>
<td>broad singlet ($^1$H NMR) or broad strong (IR)</td>
</tr>
<tr>
<td>BINAP</td>
<td>$2,2'$-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>$n$-butyllithium</td>
</tr>
<tr>
<td>C-C</td>
<td>carbon-carbon</td>
</tr>
<tr>
<td>COD</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>Cp*</td>
<td>1,2,3,4,5-pentamethylcyclopentadienide</td>
</tr>
<tr>
<td>d</td>
<td>doublet ($^1$H NMR) or day</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DMA</td>
<td>dimethylacetamide</td>
</tr>
<tr>
<td>DMAD</td>
<td>dimethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DMPU</td>
<td>1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone</td>
</tr>
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<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1'-bis(diphenylphosphino)ferrocene</td>
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<tr>
<td>dppm</td>
<td>1,1-bis(diphenylphosphino)methane</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalents</td>
</tr>
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<td>EtOAc</td>
<td>ethyl acetate</td>
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<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectroscopy</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>m</td>
<td>multiplet ({$^1$H NMR}) or medium (IR)</td>
</tr>
<tr>
<td>NBD</td>
<td>norbornadiene</td>
</tr>
<tr>
<td>NBN</td>
<td>norbornene</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NMP</td>
<td>N-Methylpyrrolidone</td>
</tr>
<tr>
<td>PMP</td>
<td>1,2,2,6,6-pentamethylpiperidine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>RBF</td>
<td>round-bottomed flask</td>
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</table>
rt  room temperature
s  singlet ($^1$H NMR) or strong (IR)
sat'd  saturated
$S_{\text{N}2}$  Substitution nucleophilic bimolecular
t  triplet
TBAF  tetrabutylammonium fluoride
$^{1}$Bu  $\text{tert}$-butyl
TBS  $\text{tert}$-butyldimethylsilyl
TBSCl  $\text{tert}$-butyldimethylsilyl chloride
TEA  triethylamine
THF  tetrahydrofuran
TLC  thin-layer chromatography
TMEDA  N,N,N,N-$\text{tetramethylethylenediamine}$
TMS  trimethylsilyl
TMSCl  trimethylsilyl chloride
Ts  tosyl
$ee$  enantiomeric excess
w  weak (IR)
## Appendix List

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<tr>
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<td>$^{13}$C NMR of <em>cis</em>-1,2-Dihydro-4-ethyl-2-(4-methoxyphenyl)-1-naphthol</td>
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<td>4-44</td>
<td>$^1$H NMR of <em>cis</em>-1,2-Dihydro-4-methyl-2-(4-methoxyphenyl)-1-naphthol</td>
<td>254</td>
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<td>4-44</td>
<td>$^{13}$C NMR of <em>cis</em>-1,2-Dihydro-4-methyl-2-(4-methoxyphenyl)-1-naphthol</td>
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<tr>
<td>4-44</td>
<td>Molecular Structure of <em>cis</em>-1,2-Dihydro-4-methyl-2-(4-methoxyphenyl)-1-naphthol</td>
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<td>$^1$H NMR of <em>cis</em>-1,2-Dihydro-4-cyclobutyl-2-(4-methoxyphenyl)-1-naphthol</td>
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<td>4-48a</td>
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<tr>
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<td>4-83</td>
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<tr>
<td>5-37ab</td>
<td>$^1$H NMR of <em>cis</em>-1,2-Dihydro-4-ethyl-2-(4-methoxyphenyl)-1-naphthol and <em>cis</em>-1,2-Dihydro-1-ethyl-2-(4-methoxyphenyl)-1-naphthol</td>
<td>271</td>
</tr>
<tr>
<td>5-37ab</td>
<td>$^{13}$C NMR <em>cis</em>-1,2-Dihydro-4-ethyl-2-(4-methoxyphenyl)-1-naphthol and <em>cis</em>-1,2-Dihydro-1-ethyl-2-(4-methoxyphenyl)-1-naphthol</td>
<td>272</td>
</tr>
<tr>
<td>4-101</td>
<td>$^1$H NMR of 3-(4-Methoxy-phenyl)-naphthalene-1-methylketone</td>
<td>273</td>
</tr>
<tr>
<td>4-101</td>
<td>$^{13}$C NMR of 3-(4-Methoxy-phenyl)-naphthalene-1-methylketone</td>
<td>274</td>
</tr>
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</table>
5-36ab  $^1$H NMR of *cis*-1,2-Dihydro-4-ethyl-2-(phenyl)-1-naphthol (a) and *cis*-1,2-Dihydro-1-ethyl-2-(phenyl)-1-naphthol

5-36ab  $^{13}$C NMR of *cis*-1,2-Dihydro-4-ethyl-2-(phenyl)-1-naphthol (a) and *cis*-1,2-Dihydro-1-ethyl-2-(phenyl)-1-naphthol
Chapter 1

Introduction and Background
1. Introduction

Transition metal catalyzed reactions have been used exhaustively on oxabicyclic compounds to prepare a huge variety of synthetically important, highly functionalized organic templates. These molecules are extremely useful in the synthesis of synthetically challenging natural products, biologically useful active pharmaceutical ingredients (API’s) and complex polymer components. Oxabicyclic alkenes are also ideal substrates for the generation of heterocyclic, carbocyclic and acyclic structures in both excellent yield and stereoselectivity. A notable advantage in using these compounds is that many stereocenters can be efficiently generated in a single step by performing reactions with excellent control of relative and absolute stereochemistry of the products.

Figure 1.1 Most commonly used 2.2.1 bicyclic alkenes.

Bicyclic molecules (Figure 1.1) have been used as the cores to which functional groups are systematically appended. Over the past several years, the Tam group has also been exploring the chemistry of this interesting class of alkenes with exciting
developments in the synthesis of substituted norbornenes, norbornadiene derivatives, intramolecular 1,3-dipolar cycloadditions of nitrile oxides and nitrones, expansion of ruthenium catalyzed [2+2] cycloadditions with alkenes etc. A few recent developments on Tam group research related to metal catalyzed reactions on oxabicyclic alkenes are highlighted in section 1.5 of this chapter.

The unique geometry of fused bicyclo[2.2.1]alkenes in combination with the intrinsic angle strain on the carbon-carbon double bond and unsymmetrical bicyclic structure allow for easy activation by transition metal catalysts in a face-selective manner. The ring strain originates in these congested molecules as a result of unfavorable bond angles and eclipsing interactions. The ring strain in these molecules is alleviated via ring opening reactions to form several stereocenters in a single step. Introduction of a heteroatom either in the carbon framework or about the [2.2.1] bicycle greatly influences the reactivity of these molecules.

Recently Tam and Goddard examined the ring strain of various heterobicyclic alkenes using computational chemistry.\(^7\) The ring strain energies of norbornadiene \(1-2\) and norbornene \(1-1\) were calculated as 27.6 and 18.8 kcal/mol, respectively whereas the 7-heteroatom substituted analogues of norbornadiene containing oxygen or nitrogen were shown to have increased ring strain energy relative to the parent carbocyclic system of 35.8 and 33.0 kcal/mol respectively. This increased ring strain results from the electronegative nature of these atoms. Less ideal bond angles occur from decreased bond length of the carbon-heteroatom bond compared to the carbocyclic analogue. Furthermore, a decreased bond length of the alkene C=C bond was observed in [2.2.1] bicyclic ring systems. These trends indicate that factors such as the electronegativities of
heteroatom substituents and degree of saturation of the molecule are important factors in determining the ring strain of bicyclic alkenes. The calculated ring strain energies can be used to explain the high reactivity of bicyclic alkenes compared to unstrained or acyclic alkenes. Reaction with the double bond of bicyclic alkenes either to form saturated rings or ring-opened products would result in a release of ring strain and is thus a driving force for the unique reactivity of these compounds.

In addition to ring strain, the chemistry of this bicyclic system is also influenced by its unique geometry, a trait which is responsible for its exclusive facial selectivity and a distinct reactivity as a diene. The two faces of the cup-shaped [2.2.1] bicycle include a convex exo face and a concave endo face. Steric considerations in an unsubstituted molecule dictate that the exo face is more accessible to reactants. Norbornadiene derivatives show homoconjugation of their otherwise isolated double bonds as observed in their photoelectron spectrum. Homoconjugation, the phenomenon of interactions of the π-orbitals through space, occurs in this type of system due to the proximity of the alkene functionalities. This through space interaction creates opportunities to undergo reactions of both alkenes such as [2+2+2] homo-Diels-Alder cycloaddition with alkene and alkyne reaction partners and photochemical isomerisation into the corresponding quadricyclanes.

7-Oxabenzonorbornadiene 1-3, a derivative of norbornadiene 1-2, represents the basic skeleton of all the molecules studied in this thesis. It is a derivative of norbornadiene (bicyclo[2.2.1]hepta-2,5-diene). The [2.2.1] refers to the number of carbons in each of the three bridges attached to the bridgehead carbons 1 and 4. As stated previously, molecules of this type have an endo and exo face (Figure 1.2); however, the
oxygen at the 7-position in oxabenzonorbornadiene acts to increase electron density of the \textit{exo} face thus promoting a higher degree of face selective complexation when using metal catalysts.\cite{4}

C\(^1\) substituted 7-oxabenzonorbornadiene 1-9 contains an oxygen at the 7-position, a benzo-substituent at carbons 5 and 6, a double bond between carbons 2 and 3, and a substituent at carbon 1 (Figure 1.2). The implications of losing symmetry via introduction of a substituent to one of the bridgehead positions of 7-oxabenzonorbornadiene are manifested in many interesting ways during the ring opening reactions. These fascinating effects arising from loss of symmetry form the fundamental basis for our current work. The details of the regiochemistry of reactions on unsymmetrical substrates will be elaborated in section 1.4.

![Figure 1.2 Structure of Norbornadiene and C\(^1\) Substituted Oxabenzonorbornadiene.](image)

In terms of general mechanism, the ring opening reactions of oxabicyclic alkenes involves the addition of a nucleophile to the olefin followed by ring opening through cleavage of the C-O bond, whereby oxygen acts as a leaving group. When the leaving group is at the allylic position two possible modes of bimolecular nucleophilic substitution may operate. The incoming nucleophile may attack at the carbon atom bearing leaving group, without change in the position of double bond. These types of
reactions are classified as S\textsubscript{N}2 type reactions and gives products with 1,4-substitution patterns (Scheme 1.1).

Scheme 1.1 Nucleophilic addition reactions on 1-3.

Alternatively, when the nucleophile attacks the alkene carbon atom distal to the leaving group, causing concomitant shifting of the double bond to displace the leaving group, the reaction is said to proceed via an S\textsubscript{N}2\textsuperscript{r} pathway, providing the product with a 1,2-substitution pattern. When the leaving group form the part of a cyclic structure, an S\textsubscript{N}2 or S\textsubscript{N}2\textsuperscript{r} displacement of the leaving group results in the opening of the ring. In this scenario, the leaving group remains tethered to the molecule, thus providing another functional group which is available for further transformations.

There are a huge number of reactions that follow the S\textsubscript{N}2\textsuperscript{r} ring opening, for example the opening of vinylic epoxides 1-14 with organocuprates,\textsuperscript{11} opening of vinylic oxetanes\textsuperscript{12} 1-16, and chiral allylic cyclic acetals\textsuperscript{13} 1-12 to name a few (Scheme 1.2). The majority of ring opening reactions on oxabicyclic alkenes follow this S\textsubscript{N}2\textsuperscript{r} pathway though products formed through S\textsubscript{N}2 pathway are also reported.\textsuperscript{15}
Scheme 1.2 Examples of S$_{N}2'$ ring opening reactions.

The stereochemical outcome of ring opening reactions of oxabicycloalkenes is another important factor to be considered due to the possible formation of cis 1-18 and trans 1-19 isomers (Scheme 1.3). Although endo attack has been observed in some cases, the majority of S$_{N}2'$ reactions show a high propensity toward the exo face. This preference for the syn face have been rationalized through stereoelectronic effects.$^{14}$

Scheme 1.3 Exo and endo attack and cis/trans products.

The presence of a substituent at a bridgehead carbon makes the alkene unsymmetrical. The attack of nucleophile close to C$^1$ substituent leads to the formation of
tertiary alcohol product (1-23) while attack on the distal position generates the regiosiomer secondary alcohol derivative, 1-22 (Scheme 1.4). Some interesting examples are reported in literature where the issues of stereoselectivity and regioselectivity in bicyclic systems are discussed.\(^\text{15}\) The focus of the present investigation is on understanding the effect of various substituents on the C\(^1\) carbon. The literature background on the regioselectivity of oxabicyclic alkenes will be elaborated in section 1.4.

![Scheme 1.4 Regioselectivity in C\(^1\) substituted oxabicyclic alkenes.](image)

The first example of ring opening of oxabicyclic systems was reported by Caple and co-workers (Scheme 1.5). It was reported that treatment of 7-oxabenzonorbornadiene 1-3 with butyllithium or tert-butyllithium resulted in ring opening from the \textit{exo} face to form \textit{cis}-alcohols 1-24.\(^\text{16}\)

![Scheme 1.5 Ring opening with alkyllithium reagents.](image)
Brown’s group reported reductive ring opening of compound 1-3, this time using borane-dimethyl sulfide complex or 9-BBN (Scheme 1.6). The reaction was believed to proceed through hydroboration of the double bond to provide 1-25 followed by syn elimination to generate 1-26. When bulkier hydroborating agents were used the ring opened products were not formed. The greater steric demand of the bulkier alkyl groups was believed to interfere with the coordination of the boron atom with bridging oxygen atom thereby limiting the elimination step.

![Scheme 1.6 Reductive ring opening with boranes.](image)

Hydroarylation of oxabenzenonorbornadiene 1-3 was achieved for the first time by Cuny and Buchwald using zirconocene-3-methoxybenzene 1-28 prepared in situ from Cp₂Zr(Me)Cl (Scheme 1.7). The obtained product was found to be 2:1 mixture of both trans and cis isomers 1-29.

![Scheme 1.7 Hydroarylation of 1-3 with zirconium catalysts.](image)

Lautens’ group reported the alkylative ring opening with organocuprates. It was discovered that cuprates generated from secondary and tertiary organolithium reagents induced ring opening, whereas methyl and n-alkylcuprates were completely unsuccessful.
1.1 Transition Metal-Catalyzed Reactions on Oxabicyclic Alkenes

The chemistry of oxabicyclic olefins showed significant growth from early 90’s as result of the increase in application of transition metal catalyzed reactions. Several interesting metal-catalyzed reactions involving oxabicyclic compounds have been developed including ring-openings,\textsuperscript{20} cyclodimerizations,\textsuperscript{21} cycloadditions,\textsuperscript{23} isomerizations,\textsuperscript{82} and cyclizations\textsuperscript{2}. These reactions primarily make use of nickel, palladium, ruthenium and rhodium catalytic systems (Scheme 1.8). In this section an overview of reactions on [2.2.1] alkenes with transition metals will be provided. The reactions involving ring opening will be covered in more detail in a section 1.2.

Scheme 1.8 Various ring opening reactions of oxabenzonorbornadiene 1-3.
Cheng et al. reported that the reaction of 7-oxabenzonorbornadiene derivatives 1-40 with trichlorosilane in the presence of a palladium complex and zinc powder in toluene at ambient temperature led to the formation of corresponding biaryl products 1-41 in good to excellent yield (Scheme 1.9). This process appears to occur via a novel palladium-catalyzed hydrosilylative dimerization of 1,4-epoxy-1,4-dihydroarenes and subsequent elimination of HOSiCl₃ and H₂O.

Scheme 1.9 Palladium catalyzed deoxygenative dimerization of 1-40.

A cationic rhodium complex coordinated with BINAP was found to be highly effective in catalyzing the asymmetric cyclodimerization of 1-42, producing high yields of polycyclic tetrahydrofuran derivatives with high enantioselectivities (Scheme 1.10). Oxabenzonorbornadienes bearing substituents on the benzene ring also gave the corresponding cyclodimerization products in high yields with excellent enantioselectivities (96-99% ee).

Scheme 1.10 Rhodium catalyzed dimerization of 1-42.
Cheng et al. developed [2+2] cycloadditions between heterobicyclic alkenes 1-44 and substituted alkynes 1-45 in the presence of NiCl₂(PPh₃)₂ to give exo-cyclobutene derivatives 1-33 in high yields (Scheme 1.1).²³ These cyclobutene derivatives undergo novel ring expansion, converting the fused four- or six-membered rings into an eight-membered cyclooctadiene moiety in high yields.

Scheme 1.11 Ni and Co catalyzed [2+2] cycloaddition of 1-44 with alkynes.

The cycloaddition reactions did not work with dialkyl acetylenes under Ni catalysis. However CoI₂(PPh₃)₂/Zn system was found to be effective with a variety of alkynes to form cycloadducts.²⁴ Thus, the two metals were complementary; the nickel catalyst was effective with alkynes containing an electron-withdrawing group and the cobalt catalyst was more reactive, tolerating sterically more demanding alkyl-substituted alkynes. Both catalysts, however, required additional phosphine ligands and zinc powder to complete the catalytic cycles and produced exo cycloadducts exclusively.

Oxabicyclic alkenes 1-46 underwent cyclization with alkyl propiolates 1-47 in the presence of bidentate phosphine nickel complexes to give benzocoumarin derivatives 1-48 in high yields (Scheme 1.12).²⁵ Other bidentate phosphines, dppf, dppm, and dppp, were less effective, and monodentate phosphines either exhibited no activity or gave different products. The choice of solvent was also vital to the catalytic reaction with acetonitrile producing the best results.
Scheme 1.12 Ni catalyzed [2+2] cycloadditions with alkyl propiolates.

Similar to alkyl propiolates, o-iodobenzoate and β-iodo-(Z)-propenoates 1-50 underwent cyclization with oxabicyclic alkenes 1-49 to give structurally diverse benzocoumarin derivatives 1-51 (Scheme 1.13). This methodology was applied towards the synthesis of arnottin I 1-52, a natural product isolated from Xanthoxylum arnottianum. Arnottin I was obtained in 21% overall yield after six steps starting from catechol.

Scheme 1.13 Ni catalyzed cyclization of 1-49 with β-Iodo-(Z)-propenoates.

1.2 Transition Metal-Catalyzed Ring-Opening Reactions

Numerous metal-catalyzed nucleophilic ring-opening reactions have been developed using oxabenzenonorbornadiene 1-3 as the substrate. By varying the metal catalyst and nucleophile used, several possibilities exist for creating optionally-
substituted ring systems (Scheme 1.14)\(^1\) and through the use of chiral ligands, these asymmetric reactions have also displayed a high degree of enantioselectivity. Control of relative stereoselectivity can also be achieved by varying the transition metal. In general, Pd and Rh catalyzed reactions provide exclusively the \textit{syn} diastereomer whereas copper phosphoramidite catalyzed reactions give \textit{anti} diastereomers with carbon nucleophiles.

![Scheme 1.14 Metal-catalyzed nucleophilic ring-opening reactions of 1-3.](image)

**1.2.1 Palladium Catalyzed Ring Opening Reactions**

Among the many transition metals used in organic synthesis palladium is the most effective and versatile in catalyzing a wide range of reactions, particularly those involving carbon-carbon bond forming reactions.\(^{28}\) The importance of C-C bond formation in organic synthesis needs no explanation. The popular Pd catalyzed reactions that fall in this category include Negishi coupling,\(^{29}\) Suzuki coupling,\(^{30}\) Stille coupling,\(^{31}\) Heck reaction etc.\(^{32}\)
Cheng’s group reported the first stereoselective palladium-catalyzed reactions of 7-oxanorbornadiene derivatives with organic halides to give highly substituted aryl products (Scheme 1.15). This catalytic reaction provided a novel method for the preparation of cis-1,2-dihydro-l-naphthyl derivatives 1-56 which are otherwise very difficult to prepare. The dihydronaphthalene skeleton is found in naturally occurring compounds that exhibit diverse biological activities.

Scheme 1.15 Palladium catalyzed addition of organic iodides on 1-3.

From a mechanistic point of view, this transformation closely resembles a Heck type coupling which involves three elemental reactions: (1) oxidative addition of organic halide to form organo palladium species, (2) insertion of an alkene into a palladium-carbon bond (carbopalladation) and (3) syn elimination of a β-hydrogen to give aryl alkene or conjugated diene.

The stereochemical features of the Heck reaction for cyclic and acyclic alkenes are different. For example, the syn addition of Ar-Pd-X 1-57 to an acyclic alkene 1-58 is followed by syn elimination of a β-hydrogen via intermediate 1-59 to give trans alkene 1-61 after free rotation of intermediate 1-60 (Scheme 1.16). On the other hand, no such free rotation of intermediate 1-64 is possible in cases of simple cyclic substrates like 1-63; therefore elimination of neighboring β-hydrogen occurs to give the allylic compound 1-65 rather than substituted alkene.
Scheme 1.16 β-Hydride elimination in acyclic and cyclic alkenes.

In [2.2.1] bicyclic alkenes such as 1-3, the situation gets a little more complicated. For example the exo or endo addition of a palladium-carbon species 1-57 to 1-3 would produce intermediates 1-67 in which free rotation is not possible due to the cyclic structure. Thus, the formation of product 1-69 is unlikely (Scheme 1.17).

Scheme 1.17 β-Hydride elimination vs. β-oxygen elimination.

The β-hydrogen at the bridgehead cannot undergo elimination to give a cyclic olefin 1-68, due to the great angle strain of the resulting organic product. Furthermore, Bredt’s rule states that a double bond on a bridgehead carbon is too unstable because the rigid cage structure of the bicycle does not allow the planarity of the double bond. Therefore, in this scenario, instead of β-hydride elimination, a β-oxygen elimination
takes place by cleavage of C-O bond resulting in ring opening to afford cis-1,2-dihydro-1-naphthyl derivatives. These type examples of β-oxygen elimination appear very rarely in the literature.\textsuperscript{36}

In general, the palladium-catalyzed ring opening reactions were carried out in THF at 60 °C in the presence of Zn, ZnCl\textsubscript{2}, and Et\textsubscript{3}N. The inclusion of ZnCl\textsubscript{2} resulted in not only quicker reaction rates and improved yields but also reactions, could be done at a lower temperature with lower catalyst loading. The major disadvantage in having a ZnCl\textsubscript{2} presence is the reaction mixture is isomerisation of 1-3 under the reaction conditions to give 1-naphthol; however, the addition of Et\textsubscript{3}N appears to suppress the Lewis acidity of ZnCl\textsubscript{2} and inhibit formation of 1-naphthol.

A wide variety of aromatic iodides possessing both electron-withdrawing and electron donating substituents were reacted with benzoanorbornadiene 1-3 to give cis-1,2-dihydro-1-naphthol derivatives 1-56 in good to excellent yields. However, yields were generally low with aryl iodides containing electron withdrawing groups. β-Iodoenone, benzyl bromide and methyl iodide also reacted with 1-3 to form corresponding naphthol derivative. All the dihydronaphthalenol derivatives obtained from the ring opening reactions were found to exhibit cis stereochemistry.

On the other hand, only one example was reported where 7-oxanorbornadiene 1-7 reacted with p-iodotoluene 1-72 in the presence of a palladium catalyst (Scheme 1.18).

\begin{center}
\textbf{Scheme 1.18 Pd catalyzed ring opening of 1-7 with p-iodotoluene.}
\end{center}
Stoichiometrically, this product may be considered to result from addition of an aryl group to the unsubstituted double bond of 1-7 followed by dehydration to give unsymmetrical biaryl derivative 1-73. It was reported that due to the tendency of oxanorbornadienes derivatives to undergo retro-Diels-Alder reactions under the reaction conditions, the yield was low (37%).

The first example of asymmetric ring opening of benzoanorbornadiene was reported by Moinet and Fiaud, where the treatment of 1-3 with a palladium(0) BINAP complex, phenyl triflate, and sodium formate in dimethylformamide (DMF) at 55 °C for 166 h led to the formation of two products (Scheme 1.19).

![Scheme 1.19 Pd catalyzed asymmetric ring opening of 1-3 with phenyl triflate.](image)

The ring opened product 1-54 was minor, with only 13% yield but 96% ee, while the major product 1-75, arising from carbopalladation without ring-opening, was isolated in 71% yield and 64% ee. It was also found that changing the aryl component from phenyl triflate to phenyl iodide reversed the product distribution, giving 1-54 preferentially. However, when phenyl iodide was used, the products obtained were in recemic form.

Lautens’ group reported palladium catalyzed enantioselective alkylative ring opening reaction of oxabenzonorbornadiene 1-3 with a variety of diorganozincs in the presence of PdCl$_2$(CH$_3$CN)$_2$ and bis(diphenylphosphino) ferrocene (dppf) in
dichloromethane to afford exclusively the syn diastereomers 1-76 in good yields with high ee (Scheme 1.20).

Scheme 1.20 Pd catalyzed asymmetric ring opening of 1-3 with R₂Zn.

Among the chiral phosphines, it was found that 2-(2-((diphenylphosphino)-phenyl)-4-tert-butyl-1,3-oxazoline (t-Bu-POX 1-79) gave the best results for addition of dimethylzinc, and that 2,2ʹ-bis(di-4-tolyphosphino)-1,1ʹ-binaphthyl (Tol-BINAP 1-80) gave the best results for larger nucleophiles such as diethylzinc and bis(trimethylsilylmethyl)zinc. Oxabenzonorbornadienes with a variety of substituents on the aromatic ring, including both electron rich and electron-deficient substrates 1-77, gave good results (Scheme 1.21).

Scheme 1.21 Asymmetric ring opening of 1-77 using R₂Zn.
For ring opening of oxanorbornenes 1-82 the reaction conditions were modified by changing the solvent to dichloroethane and increasing the temperature to reflux and changing the chiral ligand to 2-(diphenylphosphino)-1-((4-tert-butyl-1,3-oxazolin-2-yl)ferrocene 1-81 (t-Bu-DIPOF) (Scheme 1.22). For example, substrate 1-82 gave product 1-83 in 87% yield and 91% ee.39

Scheme 1.22 Asymmetric ring opening of norbornenes 1-82 using Me₂Zn.

Carretero et al. developed Fesulphos ligands 1-86 having P,S-coordination mode and exclusive planar chirality for enantioselective alkylative ring opening of oxa- and azabicyclic alkenes with dialkylzinc reagents (Scheme 1.23).

Scheme 1.23 Asymmetric ring opening of 1-3 in the presence of Fesulphos ligands.
Inamato et al. prepared novel air stable P-chiral phosphine ligands 1-90 and applied them for enantioselective ring opening using PdCl$_2$(cod) to get ring opened products 1-89 in high yields with excellent ee of up to 97.6% (Scheme 1.24).\(^{41}\)

Scheme 1.24 Asymmetric ring opening of 1-88 using P-chiral phosphine ligands.

Hou et al. developed a Pd-catalyzed nucleophilic ring-opening reaction of oxabicyclic alkenes with readily available organozinc halides, in the presence of (S)-iPr-PHOX 1-94 to prepare corresponding 1,2-dihyronaphth-1-ols 1-93 in good yields and high enantioselectivity (Scheme 1.25).\(^{42}\)

Scheme 1.25 Asymmetric ring opening of 1-91 using organozinc halides.
Later Hou’s group reported the use of a palladacycle with as low as 0.05 mol% catalyst loading for the ring opening reactions of benzoxanorbonadines with in situ prepared organozinc halides.\textsuperscript{43}

Cheng et al. reported palladium catalyzed reductive ring opening of oxabenzonorbonadines 1-95 with acetic acid in the presence of zinc and 5 mol % Pd(R-binap)Cl\textsubscript{2} as the catalyst in toluene at room temperature to afford (S)-1,2-dihydronaphthalen-1-ol 1-96 with an enantiomeric excess (ee) of 71-90% (Scheme 1.26).\textsuperscript{44} The reaction was optimized by varying the organic acid to improve the enantioselectivity and yield.

\begin{equation}
\begin{array}{c}
\text{R}^1 \text-O \\
\text{1-95} \\
\text{R}^1 = \text{H or Me}
\end{array}
\begin{array}{c}
\text{RCOOH} \\
\text{Pd(binap)Cl}_2 \\
\text{or Ni(binap)I}_2 \\
\text{Zn, toluene, 25 ºC}
\end{array}
\begin{array}{c}
\text{R}^1 \text{OH} \\
\text{1-96} \\
\text{Yield = 86-89%, ee = 71-90%}
\end{array}
\end{equation}

**Scheme 1.26 Asymmetric reductive ring opening of 1-95 using organic acids.**

This type of asymmetric reductive ring opening reaction on oxabicyclic alkenes offers a convenient and mild method for constructing enantiomerically enriched 1,2-dihydronaphthalenols in one pot from easily accessible starting material. Optically pure 1,2-dihydronaphth-1-ols is an important precursor for the synthesis of sertraline, an antidepressant agent.\textsuperscript{45}

Lautens’ group reported palladium catalyzed ring opening of heterobicyclic alkenes with organoboronic acids 1-96 (Scheme 1.27).\textsuperscript{46} The addition of a variety of aryl groups proceeds in excellent yield and includes heteroaryl groups which can be problematic with other catalyst systems.
Scheme 1.27 Pd catalyzed ring opening of 1-3 with aryl boronic acids.

The chiral phosphine-containing palladacycle 1-101 was shown to have high catalytic activity as well as asymmetric induction ability in ring-opening reaction of oxabicyclic alkenes with arylboronic acids. Hou et al. demonstrated the substrate scope of the oxabicyclic alkenes and aryl boronic acids (Scheme 1.28). Most of the aryl boronic acids with electron-donating groups and electron-withdrawing groups reacted with substituted oxabicyclic alkenes smoothly to provide corresponding ring-opened products in good to excellent yields.

Scheme 1.28 Pd catalyzed ring opening of 1-99 with aryl boronic acids.

Substituents on the oxabicyclic alkene showed some effect on the enantioselectivity. For example, the ee value of the product increased to 83% when an electron-withdrawing group Br was present in 1-99 while the presence of electron-donating -CH₃ and -OCH₃ groups in 1-99 lowered the ee value of the products.
Martin’s group optimized the ring opening reaction of 7-oxabenzonorbornadienes 1-102 using a combination of Pd(OAc)$_2$, PPh$_3$, Zn, and PMP (1,2,2,6,6-pentamethylpiperidine) in dry DMF with aryl and vinyl halides 1-103 to afford the corresponding cis-2-substituted 1,2-dihydronaphthols 1-104 in good to excellent yields (Scheme 1.29).$^{48}$

![Scheme 1.29 Pd catalyzed ring opening approach to prepare C-aryl glycosides 1-105](image)

The intermediate 1,2-dihydro-1-naphthols was oxidized using IBX to produce the corresponding 2-substituted 1-naphthols in excellent yields. Using this protocol, Martin’s group reported an improved route to C-aryl glycosides such as 1-105 using ring opening with a glycal iodide as the key step followed by oxidation.

**1.2.2 Nickel Catalyzed Ring Opening Reactions**

Nickel catalyzed reactions occupy an important place in organometallic chemistry. The most prominent reactions that fall under this category are Suzuki coupling,$^{30}$ Corriu-Kumada-Tamao coupling,$^{49}$ Nigishi coupling,$^{29}$ etc. The Lautens group reported that nickel-phosphine complexes catalyze the regioselective and
enantioselective reductive ring opening of oxabicyclic alkenes.\textsuperscript{50} For example, the reaction of 1-20 with a DIBAL-H and Ni(COD)\textsubscript{2}/BINAP system gave the substituted cyclohexenol 1-106 in 95\% yield and 97\% \textit{ee} (\textbf{Scheme 1.30}). Using this strategy, expedient total synthesis of Sertraline 1-107, a clinically important antidepressant agent was achieved.\textsuperscript{45}

\textbf{Scheme 1.30} Ni catalyzed reductive ring opening of oxanorbornene 1-20.

Addition of Grignard reagents to oxabicyclic compounds was reported in the presence of a catalytic amount of (PPh\textsubscript{3})\textsubscript{2}NiCl\textsubscript{2}.\textsuperscript{51,52} When compound 1-20 was treated with 5.0 equiv of MeMgBr in THF the ring-opened addition products 1-108 were obtained in 70\% yield as a single isomer (\textbf{Scheme 1.29}). The reactions were found to be highly regioselective, forming a product as result of clean \textit{S_N}2' attack whereby the nucleophile attacks stereoselectively on the same side of the ring as the bridging oxygen.

\textbf{Scheme 1.31} Ni catalyzed addition of Grignard Reagents on oxanorbornene 1-20.
Cheng’s group reported nickel-catalyzed ring-opening reactions of 7-heteroatom norbornadienes and norbornenes with various organic halides to give products with multiple stereocenters.\(^{53}\) It was found that treatment of 7-oxabenzonorbornadiene 1-3 with aryl iodides (ArI) in the presence of NiCl\(_2\)(PPh\(_3\))\(_2\) and Zn powder gave the corresponding ring-opened addition products \(\text{cis}-1,2\)-dihydro-2-aryl-1-naphthol 1-109 with complete stereoselectivity in 50-83% yields (Scheme 1.32).

\[
\begin{align*}
\text{1-3} + \text{ArI} & \xrightarrow{\text{Ni}(\text{PPh}_3)_2\text{Cl}_2, \text{Zn}} \text{1-109} \\
\text{R} = \text{ArI, PhCH}_2\text{Br, PhCHCHBr, and PhCBrCH}_2
\end{align*}
\]

**Scheme 1.32 Ni catalyzed ring opening with organic halides on 1-3**

The nickel system was also found to catalyze the reaction of highly substituted non-aromatic oxabicyclic [2.2.1] compounds 1-20 with organic halides (PhI, PhCH\(_2\)Br, PhCHCHBr, and PhCBrCH\(_2\)) to give the corresponding ring-opened products 1-109 containing four fixed stereocenters (Scheme 1.33). The nickel catalyst was found to be more active than the palladium analogue as the ring opening of non-aromatic oxabicyclic ring systems were unsuccessful under palladium catalysis.

\[
\begin{align*}
\text{1-20} + \text{R-X} & \xrightarrow{(\text{PPh}_3)_2\text{NiCl}_2, \text{Zn, CH}_3\text{CN, 70 °C}} \text{1-110} \\
\text{R} = \text{ArI, PhCH}_2\text{Br, PhCH=CHBr, and PhCBr=CH}_2
\end{align*}
\]

**Scheme 1.33 Ni catalyzed ring opening with organic halides on norbornenes.**
Aliphatic and aromatic terminal acetylenes 1-112 can be added to bicyclic alkenes by using a nickel(II) complex and zinc as the catalyst, with catalytic amount of ZnCl₂ to form ring opened products 1-113 with high stereoselectivity (Scheme 1.34).\(^5\)\(^4\)  

![Scheme 1.34 Ni catalyzed ring opening with terminal acetylenes 1-112.](image)  

7-Oxabenzonorbornadiene 1-114 also underwent reductive coupling in the presence of Ni(dppe)Br₂ and zinc powder in acetonitrile at room temperature with various propynoates \((R^2=C\equiv CCO_2R^3)\) 1-115 to give the corresponding cis-1,2-dihydrophtalene derivatives 1-116 in good to excellent yields (Scheme 1.35).\(^5\)\(^5\)  

![Scheme 1.35 Ni catalyzed ring opening with propiolates 1-115.](image)  

The reaction of 7-oxabenzonorbornadiene 1-117 with alkenylzirconium reagents 1-118 in the presence of NiCl₂(PPh₃)₂ and zinc powder (10.0 mol %) in THF led to the stereoselective formation of ring opened addition products 1-119 in 70-89% isolated yield (Scheme 1.36).\(^5\)\(^6\) The reaction provides a convenient and general route to cis-2-alkenyl-1,2-dihydronaphthalene derivatives in good to excellent yields and with high
stereoselectivity from easily accessible starting materials. Internal alkenyl zirconium reagents also produced the corresponding ring opening products in good yields.

\[
\begin{align*}
\text{1-117} & \quad + \quad \text{Zr(Cp)}_2\text{Cl} \quad \xrightarrow{\text{NiCl}_2(\text{PPh}_3)_2, \text{Zn}} \quad \text{1-119} \\
\text{R}^1 &= \text{H, Et, n-Propyl} \\
\text{R}^2 &= \text{Et, n-Propyl, t-Bu, TMS} \\
\text{R} &= \text{H, Me}
\end{align*}
\]

**Scheme 1.36 Ni catalyzed ring opening with internal alkenyl zirconium reagents.**

However, the addition of alkyl zirconium reagents 1-120 to bicyclic alkenes using NiCl₂(PPh₃)₂ as a catalyst under the standard conditions for alkenyl addition did not afford any desired product. But when the catalyst system was changed to bidentate phosphine complexes such as NiBr₂(dppe), the addition proceeded effectively to give highly regio- and stereoselective cis-2-alkyl-1,2-dihydronaphthalene derivatives 1-121.⁵⁷

It is known that metal-catalyzed Csp³-sp³ bond formation reactions are limited due to: (a) slow oxidative addition, (b) transmetalation of the alkyl reagents to a metal center, and (c) rapid β-hydride elimination of the resulting alkylmetal complex (Scheme 1.37).

\[
\begin{align*}
\text{1-3} & \quad + \quad \text{Zr(Cp)}_2\text{Cl} \quad \xrightarrow{\text{NiBr}_2(\text{dppe}), \text{Zn}} \quad \text{1-121} \\
\text{R}^1 &= \text{t-Bu, n-Pentyl, TMS, (CH}_2\text{CH}_3\text{Br etc}} \\
\text{R}^1 &= \text{H, Me}
\end{align*}
\]

**Scheme 1.37 Ni catalyzed ring opening with alkyl zirconium reagents.**

The requirement of bidentate phosphine is likely associated with the inhibition of β-hydride elimination of the resulting alkyl-nickel complex, although the exact reason is
not clear. A range of alkylzirconium reagents underwent ring opening reactions with 1-3 to afford the corresponding ring opened products with high yields. This reaction is applicable to various longer and bulkier alkylzirconium reagents. In addition, this ring opening reaction is successfully extended into various allylzirconium reagents 1-122 (Scheme 1.38).

Scheme 1.38 Ni catalyzed ring opening with allyl zirconium reagents.

1.2.3 Rhodium Catalyzed Ring-Opening Reactions

The Lautens group described the first rhodium-catalyzed asymmetric ring opening (ARO) reaction of oxabenzonorbornadienes using alcohol and amine nucleophiles. This reaction generates a new carbon-oxygen or carbon-nitrogen bond via a net intermolecular allylic displacement of the bridgehead oxygen to produce trans-2-alkoxy-1,2-dihydronaphthalenols 1-124 in good yields and excellent ee’s.58

Scheme 1.39 Rh catalyzed ring opening with alcohols.

The regio, diastereo and enantioselectivities of these reactions were found to be excellent (Scheme 1.39). The most interesting aspect of these ring opening reactions was
the unusual stereochemical outcome due to the formation of trans product compared to previous literature on ring openings which resulted in exclusively cis products. Phenols also acted as good nucleophiles for this transformation, adding in typically >80% yield and >95% ee.59

Murakami and Igawa reported facile addition reaction of boronic acids 1-126 to oxabenzenonorbornadienes using a catalytic amount of a rhodium complex, Rh[(cod)Cl]₂ having P(OEt)₃ ligands, to form cis-2-aryl-1,2-dihydro-1-naphthol 1-127 stereoselectively and in good yields (Scheme 1.40).60

Scheme 1.40 Rh catalyzed ring opening with aryl boronic acids.

Almost at the same time, Lautens’ group reported a novel asymmetric ring opening reaction of oxabicyclic alkenes 1-20 with addition of alkenyl or aryl boronic acids (Scheme 1.41).61 The reactions proceeded in high yield under very mild conditions with a variety of boronic acids in excellent enantio- and diastereoselectivities using the [Rh(COD)Cl]₂/PPF-P₃Bu₂ catalyst system.

Scheme 1.41 Rh catalyzed ring opening of norbornenes with aryl boronic acids.
The scope of rhodium catalyzed ring opening reaction was extended by modifying catalysts and other additives to include aromatic amines, malonate and carboxylate nucleophiles \((\text{Scheme 1.42})\). The catalyst poisoning effect of aliphatic amines was reversed by employing halide and protic additives to afford high yield of ring opened products 1-129 with good ee. By changing the halide ligands on the rhodium catalyst from chloride to iodide, the reactivity and enantioselectivity of reactions employing an aromatic amine, malonate or carboxylate nucleophile was dramatically improved.

Scheme 1.42 Rh catalyzed ring opening with carboxylate and amine nucleophiles.

The desymmetrization of oxabenzonorbonadienes was further extended to sulfur nucleophiles by using halide and protic additives in the presence of radical inhibitors like BHT, BHA etc.\(^\text{63}\)

\textbf{1.2.4 Miscellaneous Metal Catalyzed Ring-Opening Reactions}

Organocuprates are known to be effective in ring opening of oxabicyclic compounds.\(^\text{64}\) Feringa et al. developed a copper-catalyzed nucleophilic ring-opening of oxabicyclic compounds 1-131 using dialkylzinc reagents.\(^\text{65}\) The reaction showed an unprecedented high level of \textit{anti}-stereoselectivity (up to 99:1 \textit{anti}/\textit{syn}). The stereoselectivity in copper phosphoramidite 1-133, 1-134 catalyzed reaction with dialkylzinc reagents is complementary to the Pd(0)- catalyzed \textit{syn}-selective ring-opening reactions, thus, providing a new access for the preparation of \textit{anti}-dihydronaphthols with high enantioselectivity upto 99\% ee (\text{Scheme 1.43}).
Scheme 1.43 Cu catalyzed ring opening with dialkylzinc reagents.

Carretero’s group demonstrated that Grignard reagents in combination with catalytic amounts of copper (I) salts are highly effective for alkylative and arylative ring opening reactions of oxabicyclic alkenes on a wide variety of substrates. In the presence of catalytic amounts of CuCl/Ph3P the reaction occurs with high anti selectivity in all cases (Scheme 1.44).

Scheme 1.44 Cu catalyzed ring opening with Grignard reagents.

Interestingly, primary, secondary and benzyl alkylmagnesium bromides and chlorides afforded the corresponding dihydronaphthalenols 1-135a in good chemical yield and very high anti selectivity. In addition to oxabenzonorbornadienes, the less reactive aza- analogues and non-aromatic [2.2.1] oxabicycles 1-20 also participated in the ring opening process under these reaction conditions (Scheme 1.45).
Scheme 1.45 Cu catalyzed ring opening of oxanorbornenes with Grignard reagents.

The asymmetric version of ring opening with Grignard reagents in the presence of copper salts was accomplished using spiro phosphoramidite ligands in excellent trans-stereoselectivity and good enantioselectivity. However, the reactions were found to be sensitive to the type of Grignard reagent used.

Scheme 1.46 Cu catalyzed ring opening of 1-3 with Grignard reagents.

The size of the alkyl group in the Grignard reagent influenced the enantioselectivity of the reaction. For instance, in the reaction of 1-3 with MeMgBr, which has a smaller alkyl group, the alkylated ring-opening product was obtained in 99:1 antil/syn selectivity with good enantioselectivity (79% ee), although the yield of desired product was low, while in the reaction of 1-3 with n-BuMgBr, which has a larger alkyl group, the enantioselectivity decreased to 33% ee (Scheme 1.46). When the Grignard reagent was changed to a more sterically hindered i-BuMgBr, the ring-opening product...
became racemic. There was no reaction when the aromatic Grignard reagent, PhMgBr was used.

Alexakis et al. demonstrated that SimplePhos ligands 1-140 are also efficient in the desymmetrization of oxabenzonorbornadiene with Grignard reagents. However, this reaction was found to be substrate limited as modification of the aromatic ring or the use of nonbenzylic substrate was very detrimental to the reaction.

Scheme 1.47 Cu catalyzed ring opening of 1-138 with aluminum reagents.

Alexakis et al. also reported the first copper catalyzed asymmetric ring opening of oxabenzonorbornadienes 1-138 using aluminum reagents in the presence of SimplePhos ligands 1-140 (Scheme 1.47).  

Scheme 1.48 Fe catalyzed ring opening of 1-20 with Grignard reagents.
An iron catalyst prepared \textit{in situ} by the reaction of iron (III) chloride and a Grignard reagent in the presence of TMEDA was shown to be effective for the arylative, alkenylative, and reductive ring opening of a [2.2.1] or [3.2.1] oxabicyclic alkene (Scheme 1.48). The reactions were found to take place with high regio- and stereoselectivity. Through the use of this procedure, the addition of PhMgBr to oxanorbornene 1-20 was achieved in the presence of FeCl$_3$ in THF to form \textit{cis} product 1-141.

1.3 The General Mechanisms of Ring Opening Reactions

The basic mechanism of these transition metal catalyzed reactions involves three fundamental processes: oxidative addition, insertion into alkene or transmetallation-insertion, and \textit{syn} elimination of the \textit{β}-oxygen. The catalytic cycle then restarts by reductive elimination of ligands from the H-Pd-X species to generate Pd(0) and HX.

The oxidative addition is the addition of a molecule R-X to Pd(0) with cleavage of its covalent bond, thus forming two new bonds. In this transformation, the Pd increases its formal oxidation state by two, i.e. Pd(0) is oxidized to Pd(II). A number of different covalent bonds are capable of undergoing oxidative additions to transition metals.

The oxidative addition takes place with coordinatively unsaturated Pd(0) complexes. The saturated (four-coordinate, 18 electrons) Pd(0) complex Pd(Ph$_3$P)$_4$, undergoes reversible dissociation \textit{in situ} to give the unsaturated 14-electron species Pd(Ph$_3$P)$_2$ which is capable of undergoing the oxidative addition.

The second step involves \textit{α}, \textit{β}-insertion of R-Pd-X species into the olefin of the bicycle to form a saturated species. The insertion is usually stereospecific, occurring as either a \textit{syn} or \textit{cis} process exclusively. Alternatively, the Ar-Pd-X species reacts with
organic compounds M-R and hydrides M-H, where M is main group metals such as Mg, Zn, B, Al, Sn and Si, to undergo transmetallation. In this transformation an organic group, R, or hydride is transferred to Pd by exchange with X. The driving force for this process is the difference in the electronegativities of the two metals.

The final step in this mechanistic cycle normally involves syn elimination of the β-hydrogen to release the Pd species. Since syn β-hydrogen elimination is not possible in carbopalladium species of oxabicyclic system β-oxygen elimination occurs instead resulting in ring opening.

1.3.1 Mechanism of Ring Opening with Carbon Nucleophiles

The arylative ring opening of oxabicyclic alkenes can be accomplished with either the Pd or Ni catalyzed reaction with aryl iodides or the Pd or Rh catalyzed reaction with aryl boronic acids to form cis-1,2-dihydro-2-aryl-1-naphthol derivatives. For trans-derivatives, Cu catalyzed ring opening involving reaction oxabicyclic alkenes with aryl Grignard reagents was developed. For alkylative ring opening, palladium catalyzed ring opening with alkylzinc reagents was found to be very efficient in synthesizing cis derivatives (Scheme 1.49).
The mechanism proposed by Cheng for palladium catalyzed hydrophenylation of oxanorbornadienes in the presence of Zn powder and ZnCl₂ involves initial reduction of Pd (II) to Pd (0) by zinc metal, followed by oxidative addition of aryl halide.³³ It was found that inclusion of ZnCl₂ enhances the activity of the catalyst system. Based on the mechanism two possible roles of ZnCl₂ are proposed.

One possibility is that ZnCl₂ acts as a Lewis acid associated with the bridging oxygen, facilitating β-heteroatom elimination. The other possible role is attachment of ZnCl₂ to the coordinated iodide of Pd(Ph₃P)₂ArI 1-142 thereby assisting the removal of this ligand and enhancing coordination of 1-143 to the palladium center and insertion of 1-143 into the R-Pd bond. Since the observed rate determining step of these catalytic reactions is insertion of 1-143 into the R-Pd bond, the role of ZnCl₂ is more likely to enhance the rate of insertion via removal of iodide from the Pd(Ph₃P)₂ArI complex.

Lautens⁷⁰ and Cheng proposed a similar mechanism for palladium catalyzed alkylative ring opening reactions with alkyl zinc reagents and Ni catalyzed ring opening
with ArI in the presence of Zn powder. The rate limiting step in the Ni catalyzed reaction was shown to be dissociation of PPh$_3$ from Ni(PPh$_3$)$_2$ArI to create a vacant coordination site so as to accommodate the incoming substrate 7-heteroatom norbornadiene 1-143. It was found that the rate of reaction is retarded considerably by use of excess Ph$_3$P. Further evidence for the importance of dissociation of PPh$_3$ from Ni(PPh$_3$)$_2$ArI arises from the observation that replacement of Ni(PPh$_3$)$_2$Cl$_2$ by Ni(dppe)Cl$_2$ as the catalyst for addition of iodobenzene with 1-143 sharply decreased the yield of 1-146. The bidentate dppe ligand is expected to be much less favored for dissociation.

For arylative ring opening using aryl boronic acids 1-149 the mechanism, as proposed by Lautens, starts with transmetalation of the arylboronic acid to a rhodium(I) chloride or hydroxide 1-148$_{61}$ or palladium catalyst to form 1-150$_{46}$. This species will then undergo an exo selective asymmetric carboration or carbopalladation at the oxabicycle olefin to generate intermediate 1-151 (Scheme 1.50).

![Scheme 1.50 Mechanism of Rh catalyzed ring opening reaction.](image-url)
Chelation of the olefin and the oxygen atom of the oxabicycle may help to contribute to the high exo selectivity with 1-3. β-Elimination of oxygen give ring-opened intermediate 1-152, followed by hydrolysis to liberate the ring-opened product and rhodium(I) hydroxide.

The copper catalyzed ring opening of oxabicyclic alkenes with Grignard reagents afforded trans derivatives. The mechanism proposed to explain this phenomenon by Carretero and Arrayas' involves the participation of π-allyl copper intermediate 1-155 in the reaction pathway. Similar to copper catalyzed S_N2’ reactions, the in situ formed organocuprate would react with the alkene, anti with respect to leaving group (endo attack), the resulting σ-allylic copper complex would then undergo reductive elimination to give the observed ring opened product 1-158.

Scheme 1.51 Mechanism of Cu catalyzed ring opening reaction.

The presence of highly electrophilic magnesium salts in the reaction medium would enhance the leaving group ability of the heteroatom functionality of the bicyclic system through the coordination with oxygen (Scheme 1.51).
1.3.2 Mechanism of Ring Opening Reactions with Heteroatom Nucleophiles

As mentioned in the previous section, several heteroatom nucleophiles like amines, carboxylates, alkoxides, phenoxides etc. have been used in Rh catalyzed ring opening reactions of oxabicyclic alkenes to form trans naphthols. Though detailed mechanistic information is available for Pd catalyzed reactions, direct evidence for ring opening reactions using Rh catalysts and heteroatom is not readily available.\(^{71}\) To explain the formation of trans products Lautens suggested a mechanism where the heteroatom nucleophile does not complex with the metal catalyst (Scheme 1.52) but instead complexes with the oxabicyclic alkene to form the π complex 1-163.

\[ \text{Scheme 1.52 Mechanism of ring opening with heteroatom nucleophile.} \]

The nucleophile then adds to the endo face of the oxabicyclic alkene because the metal catalyst complex is blocking the exo face. β-Oxygen elimination of 1-163 leads to
intermediate 1-165. Upon quenching with water, trans product 1-166 is formed. The other likely scenario is exo coordination of the rhodium followed by C-O insertion to form 1-164 and subsequent displacement of allyl rhodium species via endo nucleophilic attack. 58

The Pd and Rh-catalyzed reactions with alkyl and aryl nucleophiles produce cis products while the Rh-catalyzed ring-opening with heteroatom nucleophiles afford trans products. These two mechanisms are compared in Scheme 1.53.1b,70,61 In the first case, with the alkyl or aryl nucleophiles, transmetallation occurs between RM’ and the catalyst ML*-Xn to provide R-ML*, shown as complex 1-167 (X refers to a halide; L* refers to a chiral ligand). R-ML* then selectively complexes to the more electron-rich exo face of the oxabicyclic alkene, to form the π complex 1-168. A syn carbo-metallation of R-ML* across the double-bond of the oxabicyclic alkene leads to the formation of 1-169. β-oxygen elimination of 1-169 provides intermediate 1-170. Upon quenching with water, cis product 1-171 is formed.70
Scheme 1.53 Mechanism of ring-opening with internal Nu vs. external Nu.

In the second case, with the heteroatom nucleophile, the heteroatom nucleophile does not complex with the metal catalyst, instead, the metal catalyst complexes with the oxabicyclic alkene to form π complex 1-172. The nucleophile then adds to the \textit{endo} face of the oxabicyclic alkene as the \textit{exo} face is now sterically hindered by the metal catalyst complex. β-oxygen elimination of 1-173 then leads to intermediate 1-174. Upon quenching with water, \textit{trans} product 1-175 is formed.\textsuperscript{61}
1.4 Regioselectivity in Reactions of Unsymmetrical Oxabicyclic Alkenes.

As stated previously, introduction of a single substituent on either in the aromatic ring or on C₁ position of benzoxanorbornadiene or oxanorbornene results in a loss of symmetry. In such unsymmetrical oxabicyclo systems the two olefinic carbons at which $S_N2'$ attack may occur are no longer related by a plane of symmetry. As a result, attack at one alkene carbon produces products that are different from those derived from reaction at the other alkene carbon atom. This situation may lead to the formation of regioisomeric mixtures of the products.

The amount of regio control observed may vary depending on numerous reaction parameters like type of substitution on the substrate, catalyst, ligands, bases, additives, solvent, temperature, rate of addition of reagents etc.

The ring opening reactions of oxabicycles bear close resemblance to a Heck reaction. Regioselectivities are often an issue when utilizing Heck reactions in organic synthesis. The regioselectivities of several classes of olefins usually reported in the literature are shown in Figure 1.3 & 1.4. Even though huge varieties of reactions are developed on oxabicyclic substrates little is known of the regiochemical outcome when said oxabicycles are unsymmetrical.
Figure 1.3 Regioselectivity during Heck reaction using neutral Pd complexes.

![Diagram](image1)

Figure 1.4 Regioselectivity during Heck Reaction using cationic Pd complexes.

![Diagram](image2)

1.4.1 Non-C¹ Substituted Unsymmetrical Oxabicyclic Alkenes

The substitutions on the aromatic ring may result in loss of symmetry in oxabicyclic alkenes. The development of a regioselective ring opening reaction in which a remote substituent controls which C-O bond is broken is a challenging task. The alkylation ring opening reaction of unsymmetrical compound 1-184 with mixed
organocuprate provided 60:40 mixtures of products 1-185a and 1-185b with overall yield of around 90% (Scheme 1.54).  

![Organocuprate Reaction](image)

When $R^1 = CH_2OTBDMS$ $R^2 = H$, a+b 95%
When $R^1 = H$, $R^2 = CH_2OTBDMS$, a+b 88%

**Scheme 1.54 Ring opening of unsymmetrical oxabicyclic alkenes with organocuprates.**

In some cases, the regiochemical outcome can be controlled by introducing some structural features in the substrate. For example, Arjona et al. found that compound 1-186, possessing a free hydroxyl group, underwent highly regioselective ring opening when treated with primary, secondary, and tertiary organolithium reagents to produce 1-187a as single regioisomer (Scheme 1.55). The attack of an organolithium reagent occurred exclusively from the exo face and at C-5 to give product in high yields. The unprotected hydroxyl group at C-2 was found to be essential for the high regioselectivity.

![Organolithium Reaction](image)

$R^1 = H, Me, n-Bu$ etc
$R^2 = H, Bn$
$R^3 = Me, n-Bu, s-Bu$ etc

When $R^2 = H$, $85\%$ 1-187a
When $R^2 = Bn$, $90\%$ 1:2 a & b

**Scheme 1.55 Ring opening of unsymmetrical alkene with organolithium reagents.**
However, when the hydroxyl group is protected as a benzyl ether the regioselectivity in alkylative ring opening was lost, forming a 1:2 mixture of 1-187a & 1-187b in 90% yield.\textsuperscript{73}

The presence of an electron withdrawing group in the oxabicyclic system was found to be effective in controlling the regioselectivity dramatically by directing the nucleophilic attack in a Michael fashion. For example, by introduction of a phenylsulfonyl group regioselective S\textsubscript{N}2' ring opening was achieved with a number of different organolithium reagents (Scheme 1.56).\textsuperscript{74}

\begin{equation*}
\begin{array}{c}
\text{PhO}_2\text{S} \quad R^1 \quad R^2 \\
\text{1-188} \\
\text{R}^1 = \text{Me}, \text{R}^2 = \text{OBn} \\
\text{R}^1 = \text{H}, \text{R}^2 = \text{CH}_2\text{OBn} \\
\text{R}^1 = \text{R}^2 = \text{OCH}_2\text{CH}_2\text{O} \\
\rightarrow \\
\text{R}^3 \text{Li (3 eq.)} \\
-78 \degree \text{C} \\
\text{1-189} \\
\text{R}^1 = \text{Me}, \text{R}^2 = \text{OBn} \\
\text{R}^1 = \text{H}, \text{R}^2 = \text{CH}_2\text{OBn} \\
\text{R}^1 = \text{R}^2 = \text{OCH}_2\text{CH}_2\text{O} \\
64-95\%
\end{array}
\end{equation*}

Scheme 1.56 Regioselective ring opening of unsymmetrical oxabicyclic alkenes with organolithium reagents.

This type of directive effect by electron withdrawing group has been proposed by Miradeghi and Rickborn to explain the formation of diphenyl sulfone 1-193 by treatment of 1-190 with potassium tert-butoxide and sodium borohydride in DMF (Scheme 1.57).\textsuperscript{75}

\begin{equation*}
\begin{array}{c}
\text{SO}_2\text{Ph} \\
\text{SO}_2\text{Ph} \\
\text{1-190} \\
\text{t-BuOK} \\
\text{NaBH}_4 \\
\text{DMF, 59\%} \\
\rightarrow \\
\begin{array}{c}
\text{SO}_2\text{Ph} \\
\text{1-191} \\
\text{[H]} \\
\text{1-192} \\
\text{-H}_2\text{O} \\
\text{1-193}
\end{array}
\end{array}
\end{equation*}

Scheme 1.57 Regioselective reductive ring opening of unsymmetrical oxabicyclic alkenes with NaBH\textsubscript{4}. 
An introduction of an ortho-substituent on the aromatic ring of oxabenzonorbornadiene also renders the molecule unsymmetrical. When compound 1-194 was subjected to palladium catalyzed ring opening conditions with 4-iodoanisole 1-195, two regioisomeric products were formed in 52% and 46% yield (Scheme 1.58).\textsuperscript{33b} It was found that the steric bulk of MeO group was not significant in directing the addition of the incoming aryl group away from it.

Scheme 1.58 Regioselectivity in ring opening of unsymmetrical 1-194 with aryl iodides.

The regioselectivity of rhodium-catalyzed nucleophilic ring opening of unsymmetrical arene substituted oxabenzonorbornadienes 1-197 was investigated thoroughly by the Lautens group using a large variety of nucleophiles.\textsuperscript{71} It was found that good to excellent regioselectivities were obtained using strongly π-donating substituents containing either oxygen or nitrogen donor atoms (eg -OMe, or -N(CH\textsubscript{3})Ph). The ratio of major to minor products ranged from 3.5:1 to as high as 25:1 (Scheme 1.59).

Scheme 1.59 Regioselectivity in ring opening using methanol as nucleophile.
However the σ-donating substituents (e.g., methyl group) and π-withdrawing functionalities (e.g., acetyl group) showed little effect on the regiochemical outcome of the products. The ratio of major to minor regioisomer (1.05:1) was almost equal, thus showing no distinct preference. It was also found that the substitution in aromatic ring close to the reaction site generally afforded higher regioselectivity when compared to an equivalent proximal substitution (steric effect). In most of the cases, the regioselectivity was largely substrate-controlled, whereas the yield depended on the leaving-group properties of NuH. The nature of the nucleophile was found to have very limited influence on the regiochemical outcome.

![Scheme 1.60](image)

**Scheme 1.60** Regioselectivity in ring opening using amine as nucleophile.

As further extension of this methodology the Lautens group demonstrated catalyst-controlled asymmetric ring opening of a racemic oxabicyclic alkene **1-194** leading to formation of two regioisomeric products (**Scheme 1.60**). The obtained regioisomers were separated by chromatography to form optically pure products with excellent ee.\(^{76}\) A cationic Rh catalyst with NH\(_4\)BF\(_4\) to modulate reactivity was used to obtain synthetically useful yields. The utility of each substituted aminotetralin product
was demonstrated by their conversion to different biologically relevant molecules (1-201 & 1-204) in a highly efficient and practical manner.

1.4.2 C1 Substituted Unsymmetrical Oxabicyclic Alkenes

The introduction of a substituent on the bridgehead carbon removes the plane of symmetry in the oxabicyclic systems. Very few examples are reported in literature where C1 carbon substituted oxabicycles are used in ring opening reactions.

The organolithium/magnesium bromide reagents have been used for reductive ring opening of unsymmetrical 7-oxabicyclo [2.2.1] substrates 1-205.64a For example, a bridgehead methyl substituted substrate underwent nonselective opening via attack of hydride when t-BuLi was used, but the selectivity improved to 4.5:1 in favor of attack at the more hindered position when i-BuMgCl was used.64b

Table 1.1 Regioselectivity in C1 substituted oxanorbornenes with alkyl lithiats.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ratio of a:b in presence of different reagents</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t-BuLi</td>
<td>n-BuLi</td>
</tr>
<tr>
<td>X</td>
<td>1 : 2.4</td>
<td>1 : 1</td>
</tr>
<tr>
<td>Y</td>
<td>1.2 : 1</td>
<td>1 : 2.4</td>
</tr>
<tr>
<td>Z</td>
<td>3.6 : 1</td>
<td>2 : 1</td>
</tr>
</tbody>
</table>
Reaction with \(n\)-BuLi was of intermediate selectivity. Similarly substrate 1-205, possessing a sterically demanding substituent (OTBDMS) followed a similar tendency. However, the ring opening of substrate with \(-\text{CH}_2\text{OMe}\) substituents showed the opposite trend. In this case, the selectivity toward attack at the carbon distal to the substituent increases with increasing substitution at the \(\beta\)-carbon of the hydride source. This change was attributed to the simultaneous chelation of magnesium to the bridging oxygen and the methoxymethyl group, thereby directing the hydride to the distal carbon. Thus, the level of selectivity was found to vary as a function of the source of hydride and the substituent at the bridgehead position.

Lautens and Chiu reported that bridgehead methyl substituted [2.2.1] oxanorbornene 1-208 underwent a highly regioselective ring opening with organolithium reagents followed by elimination to give 1-209 (Scheme 1.61). The attack of the nucleophile occurred exclusively on the \(\text{exo}\) face and at the carbon atom furthest removed from the substituent. The high regioselectivity of the products was attributed to the reaction taking place at the less sterically hindered site.

![Scheme 1.61 Regioselectivity in ring opening using organolithium reagents.](image)

Several attempts to find suitable conditions to open unsymmetrical substrates with a methyl nucleophile failed. MeLi in TMEDA, MeLi in DME, MeLi/Me\textsubscript{3}Al, and MeLi/12-crown-4 either gave no reaction or led to the formation of many side products.
However, when the substrate 1-210 was treated with 5.0 equiv of MeMgBr in Et₂O at reflux in the presence of catalytic amount of Ni(COD)₂ a 74% yield of a single isomer 1-211 was obtained.¹⁵,⁵².

Scheme 1.62 Ni catalyzed ring opening using methyl magnesium bromide.

The regioselectivity of palladium catalyzed hydrostannylation of C¹ substituted oxabicycloheptene was studied by Lautens and Klute by varying ligand-metal ratio (Scheme 1.63).⁷⁸ It was found that when alkene 1-210 was treated with tributyltin hydride a 90:10 mixture of 1-213 and 1-215 were formed after 16 h. The major isomer was thought to arise from addition of the tributyltin moiety onto the less sterically hindered carbon.

Scheme 1.63 Regioselectivity during palladium catalyzed hydrostannylation.

The reaction rate increased in the presence of a catalytic amount of [Pd₂(dba)₃] (<2 h) unfortunately the regiomic ratio remained same. Addition of a phosphine ligand was able to remedy this however, improving both the regioselectivity (98.5/1.5) and chemical yield of the hydrostannylated product. Increasing the ligand-to-metal ratio from
2.25: 1 to 11.75: 1 led to further improvement, providing access to ratios as high as 99.4:0.6.

Cheng et al. used benzoanorbornene 1-216 which has a methyl group attached to one of the bridgehead carbons in a ring opening reaction. It was shown that the palladium catalyzed reaction of compound 1-216 with RI was highly regioselective, forming exclusively compound 1-217a with cis geometry.\textsuperscript{33b} The other regioisomer 1-217b, originating from the attack of nucleophile close to methyl substituent, was not detected in the crude product (Scheme 1.64).

![Scheme 1.64](image)

**Scheme 1.64 Regioselectivity in palladium catalyzed reaction on C1 methyl oxabenzonorbornadiene.**

The presence of a methyl group on a bridgehead carbon appears to block addition of an organic group to the nearby double-bond carbon. Of the three RI tested, all the organic groups added to the olefin carbon distal to the methyl group give the corresponding product 1-217a.

Similarly, the nickel catalyzed cyclization of 1-218, with alkyl propiolates 1-219 were found to be regioselective in forming benzocoumarins 1-220 in 62-71% yield (Scheme 1.65).\textsuperscript{25} Again in this case, the reaction occurred on the less hindered carbon of the olefin.
The nickel catalyzed ring opening reaction of unsymmetrical 7-oxanorbornene 1-210, with phenyl iodide in acetonitrile gave a mixture of two regioisomers 1-221a and 1-221b in a 2:1 ratio in 72% total yield. The major product 1-221a arose from *exo* addition of the phenyl group to the olefin carbon distal to the bridgehead methyl group (Scheme 1.66).53 No explanation was provided to account for the formation of mixture of products under Ni catalysis.

Interestingly, in the ring opening reaction of compound 1-218 with dimethylzinc in the presence of Pd(dppf)Cl₂ the product obtained was exclusively the tertiary alcohol derivative 1-223a (Scheme 1.67).70 The formation of 1-223a was due to addition of the methyl group to the olefin carbon close to the bridgehead methyl group.
Scheme 1.67 Regioselectivity in Pd-catalyzed ring opening with dimethylzinc.

To explain the formation of 1-223a Lautens proposed a carbopalladation mechanism (pathway A). According to this pathway, the more sterically encumbered palladium would migrate to the less hindered carbon while the smaller alkyl group would be transferred to the carbon next to the substituted bridgehead. If a Lewis acid promoted reaction was taking place, ionization at the tertiary center would be expected to predominate (pathway B).

Murakami and Igawa reported the formation of cis-4-methyl-2-phenyl-1,2-dihydronaphthalen-1-ol 1-224 by rhodium-catalyzed nucleophilic addition of phenylboronic acid to compound 1-218 with an excellent yield (Scheme 1.68).  

Scheme 1.68 Rh-catalyzed phenylboronic addition on 1-218.

The rhodium catalyzed ring-opening of the unsymmetrical azabenzenorbornadiene 1-225 with N-methylaniline produced the anti isomer of 1-226 in 45% yield along with aminonaphthalene 1-227 in 30% yield. The regioisomer 1-226...
was found to be the sole product, arising from selective carbon-nitrogen bond cleavage at the more substituted position of 1-228 (Scheme 1.69).

![Scheme 1.69 Rh-catalyzed addition of N-Methyl aniline addition on 1-225](image)

Scheme 1.69 Rh-catalyzed addition of N-Methyl aniline addition on 1-225

The regioselective ring-opening of 1-228 suggests that ionization of the carbon-nitrogen bond was a key step in the catalytic cycle. If oxidative insertion were occurring, then ionization of the tertiary carbon-nitrogen bond should be preferred from an electronic point of view since the tertiary carbocation 1-229 will be more stabilized.

Similarly, ring opening of bicyclic alkene 1-218 by addition of methanol in the presence of Rh halide complex [Rh(CO)₂Cl]₂ exclusively produced the anti isomer 1-230a in 66% yield; no other regioisomers were observed. However, when the catalyst was changed to [Rh(cod)Cl]₂ in the presence of the (R, S)-PPF-P'Bu₂, the yield dropped to only 12% (ee 99%), with formation of 28% by-product. Interestingly, the reaction in the presence of cationic Rh(I) triflate catalysts and (R,S)-PPF-P'Bu₂ Josiphos ligand produced the other regiosomer 1-230b in 42% yield (94% ee). Thus, in racemic bridgehead substituted oxabicycles, the enantiomers were found to give regioisomeric products implying strong catalyst control.
Table 1.2 Rhodium catalyzed regiodivergent resolution.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>1-230a</th>
<th>1-230b</th>
<th>1-231</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Rh(cod)Cl]₂(2.5mol%), TFE-MeOH (1:1), 60 °C</td>
<td>66% (+/-)</td>
<td>0% 0%</td>
<td></td>
</tr>
<tr>
<td>Rh(cod)₂OTf(5mol%), (R,S)-PPF-P'Bu₂ (6%) THF, 80 °C</td>
<td>0% 42% 94% ee</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>[Rh(cod)Cl]₂(2.5mol%), (R,S)-PPF-P'Bu₂ (6%), THF, 80 °C</td>
<td>12%, 99% ee</td>
<td>0% 28%</td>
<td></td>
</tr>
</tbody>
</table>

Lautens states that a matched/mismatched effect during the oxidative insertion of the Rh ligand complex into the C-O bridgehead bond was operative and responsible for the observed stereoselectivity. It was also reported that the degree of enantioselectivity results primarily from the identity of bridgehead substituent. From this study, Lautens et al. demonstrated an unusual mode of reagent control using cationic Rh(I) complexes to resolve racemic bridgehead substituted oxabicyclic alkenes into pairs of regiosiomeronic products with high enantioselectivity.

Copper phosphoramidite catalyzed enantioselective alkylative ring-opening reaction of 1-218 with Et₂Zn afforded *anti*-dihydronaphthol 1-233 (86% ee). The exclusive formation of compound 1-233 is regioisomeric to the tertiary alcohol derivative 1-223 obtained by the Pd-catalyzed protocol. In addition, when the reaction was performed in presence of chiral ligand with 0.75 equivalent of Et₂Zn, kinetic resolution of recemic 1-218 afforded unreacted 1-218 in 92% ee at 56% conversion along with *anti*-dihydronaphthol 1-233.
The formation of 1-233 was attributed to selective ionization at the tertiary center of 1-233 via a π-allyl pathway involving activation of the carbon-oxygen bond and anti-attack of the alkylcopper to form the allylcopper intermediate 1-232 (Scheme 1.70).

![Scheme 1.70 Cu catalyzed alkylative ring-opening with diethyl zinc.](image)

Subsequently, the intermediate 1-232 undergoes a reductive elimination, with retention of configuration at the less hindered secondary terminus. Thus, this reaction is complementary to the Pd(0)-catalyzed syn-selective ring-opening reported by Lautens in respect to both regio- and stereoselectivity.

Similarly, Carretero and Arrayas reported clean ring opening reaction with complete regioselectivity by attack of the ethyl Grignard reagent to the olefinic terminus distal to the methyl group, producing alcohol 1-233 in 70% yield exclusively (Scheme 1.71).\(^{66c}\)

![Scheme 1.71 Cu catalyzed alkylative ring-opening with Grignard reagent](image)
1.5 Tam’s Group Research on Metal Catalyzed Reactions of Oxabicyclic Alkenes

The Tam research group has been actively involved in transition metal catalyzed reactions involving C1-substituted oxabicycles. The reactions studied include [2+2] cycloaddition,\(^1\) isomerization \(^2\) and cyclodimerization (Scheme 1.72).\(^3\)

![Scheme 1.72 Overview on Tam group’s research using oxabicyclic alkenes.]

1.5.1 Ruthenium Catalyzed [2+2] Cycloadditions

The ruthenium-catalyzed [2+2] cycloaddition of a variety of bicyclic alkenes with unsymmetrical alkynes was investigated.\(^8\) It was found that the rate of reaction was significantly increased when the bicyclic alkene contained oxygen at the bridgehead, this was expected as the oxygen at the bridgehead makes the \textit{exo} face of the bicycle more electron rich, thus promoting the complexation of the metal catalyst to the \textit{exo} face. For
ruthenium [2+2] cycloadditions of bicycles the *exo* product is always formed due to the complexation of the Ru catalyst to the more electron-rich *exo* face of the bicyclic structure (Scheme 1.73).

![Scheme 1.73](image)

**Scheme 1.73 [2+2] Cycloadditions of C1-substituted oxabenzonorbornadienes.**

The regioselectivity of the Ru-catalyzed [2+2] cycloaddition of C1-substituted oxabenzonorbornenes 1-244 with unsymmetrical alkynes 1-245 produced cycloadducts 1-246a and 1-246b in moderate to good yields. A methyl ester in the C1 position of the oxabenzonorbornene provided the best regioselectivity of the alkenes studied. On the other hand a methyl group at C1 did not affect the electronics or steric of the alkene in any appreciable way, thus inducing no selectivity in the reaction. Of the alkynes employed in the study, the sulfone provided both the greatest yield and regioselectivity, forming 1-246a in a 110:1 ratio over 1-246b.

The relative rate of cycloaddition with various C1 substituted oxabicyclic alkenes 1-244 was studied. In general, oxabenzonorbornadienes with C1 substituents showed a decreased rate of cycloaddition. This is likely due to steric hindrance of the double bond which needs to complex with the Ru catalyst in order for the reaction to take place. It was found that electron-withdrawing C1 substituents increased the reactivity of the compound compared to electron-donating substituents (Table 1-3). Increasing the electron-withdrawing power of the C1 substituent of the oxabenzonorbornadiene
increases the reactivity of the alkene component in the Ru-catalyzed [2+2] cycloadditions, thus the reactivity of C(O)Me > COOMe > Me.

Table 1.3 Rate of reaction of C\textsuperscript{1}Substituted Oxabenzonorbornadienes

<table>
<thead>
<tr>
<th>1-244</th>
<th>C\textsuperscript{1} Substituent</th>
<th>Yield (%)</th>
<th>Relative Rate</th>
<th>Ratio (a:b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R= H</td>
<td>71</td>
<td>83</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>R= C(O)Me</td>
<td>82</td>
<td>48</td>
<td>66:1</td>
</tr>
<tr>
<td>3</td>
<td>R= COOMe</td>
<td>85</td>
<td>17</td>
<td>76:1</td>
</tr>
<tr>
<td>4</td>
<td>R= Me</td>
<td>75</td>
<td>5</td>
<td>1:1</td>
</tr>
<tr>
<td>5</td>
<td>R= CH\textsubscript{2}OH</td>
<td>36</td>
<td>1</td>
<td>8:1</td>
</tr>
</tbody>
</table>

The exceptionally low reactivity of 1-hydroxymethyl-7-oxa-benzonorbornadiene (entry 5) could be due to the fact that the bridgehead oxygen, the C\textsuperscript{1}-primary alcohol, and the double bond of the bicyclic alkene could coordinate to the Ru at the same time. This would prevent coordination of the alkyne to the Ru which is required for the cycloaddition to occur.

1.5.2 Ruthenium Catalyzed Cyclizations

While investigating the diastereoselective ruthenium-catalyzed [2+2] cycloaddition of propargylic alcohols 1-247 with oxabenzonorbornene 1-3, the Tam group unexpectedly found the formation of *meso* cyclopropane 1-248 as the major product. The formation of this product was found to be highly stereoselective, producing a single *exo* cyclopropane adduct (Scheme 1.65).\textsuperscript{84} In expanding the scope of the cyclopropane-forming reaction a series of reactions of alkynes with alkene 1-3 were performed. It was found that the primary and tertiary alcohols of alkyne produced the
[2+2] cyclobutene adduct. Similarly, attempts with a homopropargyl alcohol also yielded the cyclobutene derivatives 1-249.

Scheme 1.74 Ruthenium-catalyzed [2+2] cycloaddition of propargylic alcohols

The electron withdrawing group in the acetylenic position was also found to be important as replacement of this with a phenyl group resulted in no reaction. A number of bicyclic alkenes with both electron withdrawing and donating substituents on the aromatic ring were found to be compatible with the reaction conditions.

The effect of reaction solvent on the formation of the cyclopropane rings was also investigated. Slight variations in product distribution were observed with aprotic solvents of different polarity. However, when methanol was employed as the solvent in the reaction of oxabenzonorbornene 1-250 with a secondary propargylic alcohol 1-251, the formation of a new isochromene product 1-252 (Scheme 1.75) was observed.85

Isochromene skeletons have been known to exhibit diverse biological activities.86
The steric effect of the alkyne was investigated by employing alkynes with varying steric encumbrance in the propargyl position. It was shown that increasing the steric demand substantially decreased the yield of 1-252, favoring the formation of the [2+2] cyclobutene adduct 1-249. Interestingly, installing a t-Bu group in the homopropargyl position, as opposed to the propargyl position, enhanced the formation of the isochromene.

Unsymmetrically substituted oxabenzonorbornenes were also used and demonstrated similar reactivities to 1-3. The presence of an electron-withdrawing group on the bridge-head position favored the formation of the isochromene over the other possible products. Considering the above reactions, there are three possible products when a secondary propargylic alcohol is reacted with oxabenzonorbornene: a [2+2] cyclobutene adduct, a cyclopropane or an isochromene. By varying the reaction conditions one of these three species could be produced preferentially.

### 1.5.3 Ruthenium Catalyzed Isomerizations

The ruthenium-catalyzed isomerization of C\textsuperscript{1}-oxabicyclic alkenes into 1,2-naphthalene oxides was also studied. In particular, the effects of an electron-withdrawing ester substituent at the C\textsuperscript{1} position as well as an electron-donating methyl group were investigated. It was found that the electron-withdrawing ester in 1-253 increased the stability of the epoxide product 1-254, while the electron-donating methyl in 1-218 formed the naphthol product 1-260 \textit{in situ}. The latter occurred because the naphthalene oxide intermediate 1-255 was too unstable to isolate under the reaction conditions and aromatization to the naphthol occurred spontaneously.\(^8\) It is also important to note that alkenes 1-253 and 1-218, bearing respectively an electron-withdrawing and an electron-
donating group at the ring junction, gave a single isomer with opposite regioselectivity (Scheme 1.76).

Scheme 1.76 Ru-catalyzed isomerization reactions of C^1 substituted alkenes.

The proposed mechanisms for the mode of reaction involve chelation of ruthenium catalyst to the double bond as well as the bridging oxygen 1-261 (Scheme 1.77). The oxidative insertion of the Ru species into C-O bond occurs to relieve ring strain to form 1-262. Reductive elimination then closes the epoxide ring, thus regenerating the active catalyst. The opening of epoxide then leads to the formation of the corresponding naphthol.
Scheme 1.77 Mechanism of addition of Ru to the more electron-rich C-O bond.

In the case of the oxabicyclic alkene with the electron-donating methyl substituent at C¹, the Ru metal adds to the C-O bond closest to the methyl substituent, but in the case of the electron-withdrawing ester, the metal inserts in the C-O bond farthest from the electron-withdrawing group. The formation of the different isomers suggests that the ruthenium species oxidatively inserts preferentially into the more electron rich C-O bond.

When unsymmetrical alkenes possessing an ester substituent on aromatic ring 1-267 were subjected to the reaction conditions a regioisomeric mixture of two products 1-268a and 1-268b were formed (Scheme 1.78). Thus, the regioselectivity in ruthenium catalyzed isomerisation was significantly affected by the position and the nature of the functional group. Interestingly, oxanorbornene 1-6 or oxanorbornadiene 1-5 derivatives did not undergo isomerisation reaction in the presence of ruthenium catalysts under
similar conditions. This finding suggests that the added strain present in the oxabenzonorbornadienes might be a necessary feature for the isomerizations to occur.\textsuperscript{88}

Scheme 1.78 Regioselectivity in Ru-catalyzed isomerization to epoxide.

Ru-catalyzed isomerization of oxabenzonorbornadienes into naphthols was further investigated using both symmetrical and unsymmetrical derivatives with a wide variety of ruthenium catalysts.\textsuperscript{89}

Scheme 1.79 Regioselectivity in Ru-catalyzed isomerization to naphthols.

The rate of reaction was found to be faster for 7-oxabenzonorbornadienes substituted with electron donating groups like methoxy on the aromatic ring (Scheme 1.79). Most interestingly, the regioselectivity appears to depend on the position of attachment of methoxy group to aromatic ring. For example, compound 1-102 with 1,4-
methoxy substitution gave a mixture of regioisomers 1-269a and 1-269b whereas the compound 1-270 with 2,3-methoxy substitution gave single isomer 1-270.

1.5.4 Rhodium Catalyzed Cyclodimerization

The Tam group serendipitously discovered cyclodimerisation of oxabenzonorbornadienes 1-272 upon treatment with RhCl(cod)$_2$ to form naphtha[1,2-b]furan ring system 1-273 (Scheme 1.70).$^{90}$ Concurrently, a similar transformation was also reported independently by the Hayashi group using rhodium catalyst.$^{22}$

![Scheme 1.80 Rh catalyzed asymmetric cyclodimerization.](image)

A number of different rhodium catalysts, silver salts, solvents and phosphine ligands were investigated. RhCl(cod)$_2$ in the presence of AgBF$_4$ and BINAP in DCE provided the best conditions for this transformation. The reactions were found to be enantioselective in the presence of chiral BINAP ligands with ee as high as 98%. Various substituents on the aromatic ring such as Me, OMe, Br, F etc were compatible with the reaction, producing good to excellent enatioselectivities. Furthermore, the cycloadduct 1-274 can be isomerized in the presence of a mild acid to generate the oxabenzonorbornenol derivative 1-275 with no loss in chiral purity (Scheme 1.81).
Scheme 1.8 Acid catalyzed isomerisation of 1-274 to oxabenzonorbornenol.

Interestingly, C\textsuperscript{1} substituted oxabicycles did not undergo cyclodimerization under similar conditions; the starting materials were either isomerized to the corresponding naphthol 1-277 (entry 3) or remained mostly inert (Table 1.4).

Table 1.4 Results of cyclodimerization of C\textsuperscript{1} substituted oxabenzonorbornadienes.

<table>
<thead>
<tr>
<th></th>
<th>1-276</th>
<th>Time (h)</th>
<th>1-277 (% Yield)</th>
<th>1-276 (% Recovered)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R= C(O)Me</td>
<td>26</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>R= COO Me</td>
<td>26</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>R= Me</td>
<td>1.5</td>
<td>70</td>
<td>0</td>
</tr>
</tbody>
</table>

1.6 Research Goals

A multitude of metal-catalyzed nucleophilic ring-opening reactions with oxabicyclic alkenes have been reported with high yields and enantioselectivities however, comprehensive information is not available regarding such reactions on unsymmetrical substrates. From the preceding sections it is obvious that oxabicyclic alkenes can produce an array of different products by varying both the reaction conditions and catalyst used.
Introduction of a substituent at bridgehead carbon adds an extra element of excitement in product outcome due to the possibility of different regioisomer formation (Scheme 1.82).

The use of transition metal catalysts has tremendously improved the regioselectivity of nucleophilic ring opening on unsymmetrical substrates, in some cases to the point of single isomer formation. Despite this, subtle variation in catalyst/condition has been known to impact the regiochemical outcome. For instance, Pd-catalyzed ring opening of C1 methyl substituted benzoxanorbornene with alkylzinc reagents results in tertiary alcohol derivatives as the only isomer whereas Pd-catalyzed ring opening of 1-287 with ArI produces secondary alcohol derivatives exclusively.

Scheme 1.82 Ring opening of C1 bicyclic alkenes catalyzed by transition metals.
Moreover, the Ni catalyzed ring opening reaction of C\textsuperscript{1} methyl substituted oxanorbornenes resulted in the mixture of both tertiary and secondary alcohols. The relative stereochemistry was also dependent on the transition metal used; Pd, Ni and Rh afforded \textit{cis} isomers while the copper catalyzed reactions provided \textit{trans} isomers as the major product.

The Tam group has examined various aspects of isomerization, [2+2] cycloaddition, and cyclodimerization reactions with unsymmetrical oxabicyclic substrates.\textsuperscript{81, 82, 83} It was found that depending on the electronic nature of the substituent the metal will preferentially insert in one bond over the other (Scheme 1.7\textsuperscript{6}).\textsuperscript{6} This important finding can be applied to the proposed research on ring-opening reactions where different type of substituent is expected to affect the regioisomeric outcome of the final product.

Accumulation of regioisomeric data is useful information for predicting and understanding the reaction mechanisms of these metal catalysts. A superior understanding of what is exactly occurring in these reactions will not only facilitate further exploration into new reaction pathways but also aid in the design of new catalytic systems for other synthetically useful processes. For these reasons, it is the goal of this research project to expand the scope of transition metal-catalyzed ring-opening reactions through the synthesis of novel C\textsuperscript{1} substituted 7-oxabenzonorbornadienes and oxanorbornadienes which can then be studied in ring-opening reactions.

In specific, the nucleophilic ring-opening reactions this thesis will focus on will be performed with aryl iodides. Looking at the literature, it becomes apparent that the reactions that have been reported in the past few years are limited to symmetrical
structures. Therefore the regiochemical issues surrounding metal-catalyzed reactions of unsymmetrical substrates have still yet to be explored. Ring-opening reactions of unsymmetrical oxabicycles will be useful in generating novel optionally-substituted ring systems with different stereochemistries. Regiochemical information will help to determine the mechanisms of the reactions, and mechanistic information will be beneficial for reaction optimization.

The hydronaphthalene core can be found in a variety of natural and synthetic compounds, possessing a wide range of biological activities. Given the medicinal interest, investigations into the regioselectivity of opening unsymmetrical C^1 substituted oxabenzonorbornadienes is highly desirable. If we could establish the necessary requirements for highly regioselective opening, subsequent modification of the dihydronaphthalene products has potential to generate diverse structures within the hydronaphthalene scaffold.

1.7 References (Chapter 1)


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Chapter 2

Synthesis of 2-Substituted Furans
2.1 Introduction

The furan moiety is a key structural unit in many biologically active molecules, with applications ranging from pharmaceuticals to flavoring and fragrance compounds.\(^1\) Moreover, substituted furans are useful and versatile synthetic intermediates for the preparation of a variety of heterocyclic and acyclic organic compounds.\(^2\) Although some 2-substituted furans are commercially available (such as R = Me, t-Bu, COOMe etc.), 2-substituted furans with R = alkyl, cycloalkyl and substituted aryl groups are either not reported in the literature or not readily available from commercial suppliers.

2.2 Preparation of 2-Bromofuran

During the course of our efforts to prepare a series of 2-aryl furans, we identified 2-bromofuran as a key reagent which could be used for preparing a series of compounds by Suzuki coupling methodology. Currently, this reagent is not available from common fine chemical suppliers like Aldrich and as large quantities were required a new synthetic methodology needed to be developed.

2.2.1 Background

Several methods have been described in literature for bromination of furan 2-1 to 2-bromofuran 2-2.\(^3\) Bromination of furan using hexabromocyclopentadiene,\(^3b\) dioxane dibromide\(^3d\) and microwave assisted bromination using 2,4,4,6–tetrabromo-2,5-cyclohexadienone\(^3g\) are unsuitable for the preparation of 2-bromofuran in large quantities. The two methods developed by Brandsma, metallation with EtLi followed by reaction with Br\(_2\) in ether at -80°C\(^3d\) and bromination of furan with Br\(_2\) in DMF\(^3e\), were known to be more effective for the preparation of 2-bromofuran. Unfortunately, we and others\(^3f\)
found these methods difficult to work with and the isolation of the product proved troublesome.

We initially followed Brandsma’s procedure for the synthesis 2-bromofuran by treating furan 2-1 with Br₂ in DMF.³e We encountered similar difficulties as mentioned by Alper in isolation of bromofuran and subsequently modified its isolation by effecting direct steam distillation of the reaction mixture, isolating bromofuran in good yields (50-55 %).³f The residual reaction mass contained a green, dense, tarry solid. This is not surprising in view of the unusual sensitivity of furan towards mineral acids.

The addition of Br₂ to DMF was highly exothermic. It was very difficult to control the reaction temperature in the large scale reactions (20-30 g) during bromine addition. Furthermore, elemental bromine itself is not easy to handle because of its highly corrosive nature. Because of these inconveniences a new methodology to access 2-bromofuran was sought.

2.2.2 Results and Discussion

We developed a new and practical procedure for the bromination of furan, which offers simplified work-up and isolation techniques for large-scale preparation (20-50 g scale) using safe, inexpensive, and readily available reagents.⁴ The described preparation does not require extractive workup procedures or chromatographic purifications.

![Scheme 2.1 Synthesis of 2-bromofuran using NBS in DMF.](image)

We modified the procedure of bromination of furan using readily available and easy to handle N-bromosuccinimide (NBS) (Scheme 2.1). Interestingly, unlike elemental
Br$_2$ we found that addition of NBS to DMF was not exothermic. Bromination of furan was thus performed by controlled addition of NBS-DMF solution at room temperature followed by vigorous stirring overnight. Direct steam distillation of the reaction mixture resulted in isolation of 2-bromofuran in 65-75% yields. Optionally, the obtained product can be further purified by atmospheric distillation to get high quality 2-bromofuran. Thus, we have found a new, simple, straightforward and scalable procedure for the preparation of 2-bromofuran using NBS in DMF.

2.3 Synthesis of 2-Aryl Furans

2.3.1 Pd Catalyzed Suzuki Coupling Reactions

The cross-coupling reaction of the organometallic compounds with organic halides and related derivatives provides convenient synthetic methodology for C-C bond formation. Usually organoboronic acids are most often used as the organometallic reagent because they are thermally stable and inert to moisture and oxygen. These features enable the handling of organo boronic acids without special precautions. Since its discovery, the Suzuki-Miyaura reaction has become one of the most powerful and synthetically valuable processes for the construction of carbon-carbon bonds.$^5$ Its importance in organic synthesis is evident from its application in a number of areas, ranging from natural product synthesis to materials chemistry.$^6$ Professor Akira Suzuki was awarded the Nobel prize in Chemistry in 2010 (shared with Heck and Negishi) as recognition for his contributions in the discovery and development of the Suzuki coupling reaction.

The key advantages of the Suzuki coupling are the mild reaction conditions; high tolerance toward functional groups; commercial availability of boronic acids; stability of boronic acids to heat, oxygen, and water; and the ease of handling and separation of
boron-containing byproducts from the reaction mixtures. These desirable features make the Suzuki coupling an important tool in medicinal chemistry as well as the large-scale synthesis of pharmaceuticals and fine chemicals. However, despite considerable effort in developing more active catalysts for the Suzuki-Miyaura reaction over the past two decades, some limitations still remain. For example, whereas simple aryl halides and aryl boronic acids are successful coupling partners, reactions involving their heteroaryl analogues are less straightforward. Therefore, the development of a “universal” method for the cross-coupling of heteroaryl substrates would be highly advantageous.

2.3.2 General Mechanism of Suzuki Coupling Reaction

The mechanism of the Suzuki coupling starts with either a Pd(0) catalyst or Pd(II) catalyst which is reduced in situ to Pd(0) by one of many known mechanisms (Scheme 2.2). A very wide range of palladium catalysts or precursors can be used for cross coupling reactions. Pd(PPh₃)₄ is most commonly used but PdCl₂(PPh₃)₂ and Pd(OAc)₂ plus Ph₃P or other phosphine ligands are also efficient since they are stable to air and readily reduced to the active Pd(0) complex by the organometallics or phosphines used for the cross coupling reaction. Oxidative insertion of an organic halide 2-2 results in the stable trans- σ-Pd(II) complex 2-5. The oxidative addition is rate determining step in the catalytic cycle. The relative reactivity decreases in the order I> OTf> Br>> Cl. Following this, the halide ligand is exchanged with hydroxide, generated from the basic solution, to provide the palladium hydroxide 2-6. Reaction of the arylboronic acid 2-3 with hydroxide provides borate 2.7, capable of transmetallating the palladium center to yield borate 2-8 and the diorganopalladium species 2-9. Reductive elimination of this species regenerates the palladium (0) catalytic species and produces the cross-coupled product 2-10.
Scheme 2.2 General mechanism of Suzuki cross coupling reaction.

The most commonly employed bases for these processes are $\text{K}_3\text{PO}_4$ and $\text{K}_2\text{CO}_3$ but KOH or KF have also been reported. However, the choice of base is still empirical, and no general rule for their selection has been established. The role of the base in these reactions is to facilitate the otherwise slow transmetalation of the boronic acid 2-3 by forming a more reactive borate species 2-7 that can interact with the Pd center and transmetalate in an intermolecular fashion.\(^{15}\) Alternatively, it has also been proposed that the base replaces the halide in the coordination sphere of the palladium complex 2-5 and facilitates an intramolecular transmetalation.\(^{16}\)

2.3.3 Results and Discussion

2-Bromofuran was found to be a key starting material for the preparation of a wide range of 2-aryl furans 2-4 by palladium-catalyzed Suzuki coupling reactions with various aryl boronic acids.\(^4\)
Table 2.1 Synthesis of 2-aryl boronic acids by palladium-catalyzed Suzuki cross coupling reactions between 2-bromofuran and aryl boronic acids 2-3.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acid 2-3</th>
<th>Ar</th>
<th>Furan 2-4</th>
<th>Yield(%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-3a</td>
<td>C₆H₅</td>
<td>2-4a</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>2-3b</td>
<td>4-CH₃-C₆H₄</td>
<td>2-4b</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>2-3c</td>
<td>3-CH₃-C₆H₄</td>
<td>2-4c</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>2-3d</td>
<td>2-CH₃-C₆H₄</td>
<td>2-4d</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>2-3e</td>
<td>4-CH₂O-C₆H₄</td>
<td>2-4e</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>2-3f</td>
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<td>2-4f</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>2-3g</td>
<td>2-CH₂O-C₆H₄</td>
<td>2-4g</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>2-3h</td>
<td>4-Cl-C₆H₄</td>
<td>2-4h</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
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<td>2-4i</td>
<td>67</td>
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<td>10</td>
<td>2-3j</td>
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<td>2-4j</td>
<td>70</td>
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<td>56</td>
</tr>
<tr>
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<td>2-4l</td>
<td>59</td>
</tr>
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<td>13</td>
<td>2-3m</td>
<td>4-biphenyl</td>
<td>2-4m</td>
<td>77</td>
</tr>
<tr>
<td>14</td>
<td>2-3n</td>
<td>1-naphthyl</td>
<td>2-4n</td>
<td>85</td>
</tr>
</tbody>
</table>

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

In our labs, we found Suzuki coupling reaction between 2-bromofuran 2-2 and phenylboronic acid 2-3a (Ar = Ph) occurred smoothly at 80 °C in the presence of 2 mol % of PdCl₂(PPh₃)₂ and 2.5 equivalents of K₂CO₃ in DMF/H₂O (3:1), to provide 2-phenylfuran 2-4a in 62% isolated yield after column chromatography (Table 2.1, entry
1). Suzuki coupling reactions of 2-bromofuran **2-2** worked well with boronic acids containing both electron-donating groups attached to the Ar ring (Ar = CH$_3$-C$_6$H$_4$, entries 2, 3, 4; Ar = CH$_3$O-C$_6$H$_4$, entries 5, 6, 7; Ar = C$_2$H$_5$-C$_6$H$_4$ entry 11) as well as with electron-withdrawing groups attached to the Ar ring (Ar = Cl-C$_6$H$_4$, entries 8, 9, 10; Ar = COCH$_3$-C$_6$H$_4$, entry 12).

The position of the substituent on the Ar ring (*ortho* or *meta*) showed little effect on the yields of the Suzuki coupling reactions (compare entries 3, 4 and entries 6, 7). However, the *para* substituted aryl iodides containing electron donating showed lower yield while this trend was not noticeable with electron withdrawing chloro substituents (entries 8 to 10). In general, all the palladium-catalyzed Suzuki coupling reactions of 2-bromofuran **2-2** occurred smoothly, giving moderate to good yields of the 2-arylfurans.

**2.3.4 Pd Catalyst Screening Study**

After identifying the reasonable conditions for coupling 2-bromofuran with aryl boronic acids, we wanted to find the best Pd-catalyst for Suzuki coupling to get 2-arylfurans using mild reaction conditions and with low catalyst loading in good to excellent yields. Usually the most common catalysts for the Suzuki coupling contain triarylphosphine ligands. More recently, new bulky and electron-rich phosphine ligands, which can dramatically improve the efficiency and selectivity of such cross-coupling reactions, have been introduced. Alteration of phosphine ligands has become one standard processes for developing more active catalyst systems for palladium-catalyzed carbon-carbon and carbon-nitrogen bond-forming reactions.$^{11}$
2.3.5 Results and Discussion

We screened four different commercially available Pd(0) and Pd(II) catalysts for coupling reactions using Pd(OAc)$_2$, PdCl$_2$(PPh$_3$)$_2$, Pd(PPh$_3$)$_4$, and 5% Pd/C (Table 2.2) using variously substituted aryl boronic acids.

Table 2.2 Screening of different Pd-Catalysts in Suzuki coupling reaction.

![Chemical diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Yield (%)$^b$ using different Pd catalysts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pd(OAc)$_2$</td>
</tr>
<tr>
<td>1</td>
<td>C$_6$H$_5$</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>4-CH$_3$-C$_6$H$_4$</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>3-CH$_3$-C$_6$H$_4$</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>2-CH$_3$-C$_6$H$_4$</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>4-CH$_3$O-C$_6$H$_4$</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>3-CH$_3$O-C$_6$H$_4$</td>
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</tr>
<tr>
<td>7</td>
<td>2-CH$_3$O-C$_6$H$_4$</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>4-Cl-C$_6$H$_4$</td>
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<td>9</td>
<td>3-Cl-C$_6$H$_4$</td>
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<td>2-Cl-C$_6$H$_4$</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>4-Et-C$_6$H$_4$</td>
<td>38</td>
</tr>
<tr>
<td>12</td>
<td>4-C(O)CH$_3$-C$_6$H$_4$</td>
<td>40</td>
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<tr>
<td>13</td>
<td>4-Biphenyl</td>
<td>32</td>
</tr>
<tr>
<td>14</td>
<td>1-Naphthyl</td>
<td>36</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 2 mol% of the Pd catalyst was used with 2.5 eq of base with 2:1 DMF:water. $^b$Isolated yields after column chromatography. $^c$These results are presented in Table 2.1.
Generally, the combination of palladium catalysts with various phosphine ligands resulted in excellent yields and high efficiency.\textsuperscript{12} Unfortunately, most of the phosphine ligands are air-sensitive and expensive; which places significant limits on their synthetic applications. On the other hand, it is desirable to be able to employ low catalyst loadings particularly for pharmaceutical and industrial application. Thus, the development of new and efficient phosphine free palladium catalytic systems remains a potentially promising area for organic chemists.\textsuperscript{13}

2-Bromofuran \textbf{2-2} was reacted with various aryl boronic acids in the presence of several palladium sources, a solvent system of DMF and water, and K\textsubscript{2}CO\textsubscript{3} acting as a base. Low yields of less than 50\% were obtained in all cases when Pd(OAc\textsubscript{2}) was used. PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} and Pd(PPh\textsubscript{3})\textsubscript{4} functioned as effective catalysts with Pd(PPh\textsubscript{3})\textsubscript{4} providing slightly higher yields in most cases except for the coupling of 2-MeO-C\textsubscript{6}H\textsubscript{4}, 3-MeO-C\textsubscript{6}H\textsubscript{4}, and 4-biphenyl groups (Table 2.2, entries 6, 7, 13). Interestingly, when Pd/C was used as catalyst, the cross coupling reactions afforded products in 67-73\% yields for phenyl, 4-Cl -C\textsubscript{6}H\textsubscript{4}, and 1-naphthyl groups (entries 1, 8, 14). Indeed, the highest yield for the coupling of phenyl boronic acid was provided with Pd/C of 73\%. It is important to note that Pd/C as a source of palladium is not often used in Suzuki coupling reactions.

\begin{center}
\begin{tikzpicture}
\node at (-2,0) {\textbf{2-2}};
\node at (0,-0.5) {\textbf{2-11}};
\node at (5,0) {\textbf{2-12}};
\node at (1.75,0) {\textbf{Pd catalysts}};
\node at (0,-0.75) {\textbf{DMF-Water, K\textsubscript{2}CO\textsubscript{3} \ 75-85\degree C}};
\draw[->] (0,0) -- (0,-0.5) node[anchor=south] {\textbf{HO}};
\draw[->] (1.5,0) -- (1.5,-0.5) node[anchor=south] {\textbf{B-\textit{Alkyl}}};
\draw[->] (-0.5,0) -- (-0.5,-0.5) node[anchor=south] {\textbf{HO}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.3 Suzuki coupling with alkyl boronic acids.}

To expand the scope of this Pd-catalyzed reaction, Suzuki coupling between 2-bromofuran and 1\textdegree or 2\textdegree alkyl boronic acids \textbf{2-11} was attempted (Scheme 2.3). Unfortunately, none of the reactions were successful and did not afford any coupling
products 2-12. Thus, Pd catalyzed Suzuki coupling reaction methodology was found to be useful for the preparation of 2-aryl substituted furans 2-4 only.\(^{33}\)

### 2.4 Synthesis of 2-Alkyl Furans

#### 2.4.1 Background

When a Scifinder™ search was done for the preparation of 2-alkylfurans, very few methods were found. There are few reports for preparation of primary and secondary 2-alkyl substituted furans by the coupling of 2-lithiated furan and the corresponding organoboranes.\(^{17}\) In addition, there are indirect methods for preparation of 2-alkyl furans involving cyclization of advanced intermediates. For example, the synthesis of furans 2-14 \textit{via} metal catalyzed isomerization of 3-alkynylallyl alcohols 2-13 has been used as an important methodology to synthesize 2-alkyl furans 2-14. Gabriele et al. found that a catalytic system of K\(_2\)PdI\(_4\) heated in DMA provided the desired furan 2-14 in excellent yields. (Scheme 2.4).\(^{18}\)

![Scheme 2.4 Palladium-catalyzed cycloisomerizations.](image)

Later, this methodology was improved by Yin and coworkers by utilizing gold (I) and gold (III) catalysis.\(^{19}\) Unfortunately, these methods are limited for the synthesis of 2-substituted furans containing a methylene group directly bonded to the C\(^2\) position of the furan.
2.4.2 Alkyl-Aryl Cross Coupling

For preparing a series of 2-alkylfurans by a single step process from a common intermediate, we envisioned an alkyl–aryl cross-coupling protocol. This type of reaction can involve either an aryl nucleophile and alkyl electrophile or an alkyl nucleophile and aryl electrophile. Since 2-bromofuran 2-2 was chosen to be a common intermediate, the later route was chosen. One of the major challenges for the cross-coupling reactions with organometallic reagents that contain β-hydrogens is the problem of β-elimination. This process has a major impact on the catalytic cycle of various metal catalyzed cross-coupling reactions including Pd or Ni catalyzed Suzuki coupling, Stille coupling etc.20

2.4.3. Iron Catalyzed Cross Coupling Reaction

Even though palladium and nickel have been the most used metals for cross-coupling reactions, in recent times, iron catalyzed cross-coupling reactions has shown tremendous potential in forming $sp^3$-$sp^2$ bonds. The iron catalysis also gained popularity because of distinct advantages such as easy availability, low toxicity and economic viability for most of the iron salts. Iron catalysts might be employed as alternatives for more-expensive precious metals, such as palladium, or highly toxic metals, such as nickel. The substrate scope of iron-catalyzed cross-coupling reactions is complementary to that of palladium and nickel. Iron is capable of catalyzing the reaction of a broad range of chlorides, as well as a broad range of alkyl halides with organometallic donors, an area in which palladium is currently limited. Because of the low toxicity of magnesium reagents, combining Grignard reagents with iron catalysts could be used to develop an environmentally benign carbon-carbon bond forming processes.
The systematic, but largely mechanistic study of the influence of catalytic amounts of transition metal salts (cobalt (II) chloride, iron chloride) on the interaction of Grignard reagents with organic halides dates back to the work of Kharasch, but it was not until 1971–1972 that such catalytic reactions received much attention in the literature.

In 1971, Tamura and Kochi published the first paper on a series of studies and described that some ‘soluble catalysts’ containing silver, iron, or copper in THF were shown to be extremely effective for coupling of Grignard reagents with organic halides. Kochi originally proposed the use of catalytic a mount of iron salts for stereospecific cross-coupling of Grignard reagents with organic halides (Scheme 2.5). However, the fact that the alkenyl halide had to be employed in excess (3-5 equiv.) constituted a significant drawback in preparative terms for this protocol.

### 2.4.4. Mechanism of Iron Catalyzed Cross Coupling Reaction

Just like the mechanism in any other cross coupling reaction, the first step of the catalytic cycle involving iron is the formation of organometallic complex B (Alkyl-Fe-X) by oxidative addition of active metal on the organic electrophile (Alkyl-X). The transmetallation of metal complex with organometallic reagent (ArMgX) affords the complex containing Alkyl-Fe-Aryl linkage C, reductive elimination of this complex results in formation of cross-coupling product and the active metal species [Fe] is regenerated (Scheme 2.6).
Scheme 2.6 General mechanism of Fe catalyzed alky-aryl Coupling.

The formation of side products such as alkane, alkene and biaryl compounds can be rationalized by the disproportionation of alkyl iron intermediate B giving dialkyiron D and dihalide E. β-Hydride elimination from D, results in formation of alkene, while reductive elimination from D affords alkane as side product. Similarly dihalide E, can trigger homo-coupling resulting in formation of biaryl byproduct.

For the cross-coupling reaction of Grignard reagents containing β-hydrogens, Furstner and co-workers proposed that the catalytically active iron complex in reactions has a formal oxidation state of negative two. Negative oxidation states of iron have precedent in the literature such as Collman’s work on the highly nucleophilic Fe(-II) compound Na₂Fe(CO)₄. Bogdanovic and co-workers have established that FeCl₂ is reduced in situ by four equivalents of Grignard reagent to form an iron(-II) complex of formal composition [Fe(MgX)₂].
Furstner proposed that this reduced form of iron then enters the catalytic cycle as Fe(-II). Subsequent oxidative addition of the iron complex to the organic acceptor gives an Fe(0) complex. This complex then undergoes transmetallation with the organomagnesium reaction partner. This event is isohypsic and yields an iron complex that now has two organic groups attached to it. Reductive elimination then takes place forming a new carbon-carbon bond and regenerating the Fe(-II) catalytic species (Scheme 2.7).

To test this hypothesis, Furstner et al. examined the viability of iron powder as a catalyst. Iron (0) powder, reduced in situ by reduction of FeCl₃ with potassium does not react with an aryl halide and is therefore unable to enter the catalytic cycle. However, upon addition of a Grignard reagent the metal slowly dissolved to give a black solution that was then catalytically competent. Further support for this claim came from preparation of tetrakis(ethylene)ferrate, a well characterized Fe(−II) compound. This
complex is catalytically competent in cross-coupling reactions with efficiencies similar to the FeCl₂ catalysts synthesized in situ.

Interestingly, in most cases the iron precatalyst used has very little effect on the rate, yield, or selectivity of the iron-catalyzed reactions. Fe(acac)₃ is most commonly used as it is air stable and inexpensive. Only sec-alkyl Grignard reagents require the use of Fe(salen)Cl for effective reaction (Figure 2.1).²⁸

![Fe complexes used in cross-coupling reactions.](image)

Cahiez et al. reported the first iron-catalyzed cross-coupling of organomagnesium reagents of actual preparative interest with alkenyl halides in the presence of Fe(acac)₃ in THF with NMP as co-solvent.²⁹ When this reaction was done in NMP alone the yield was moderate (40%) but when NMP was used as co-solvent with THF the yield jumped to more than 80%.

Scheme 2.8 Iron catalyzed cross coupling reaction in the presence of THF-NMP.
Further investigation by the addition of various polar co-solvents such as sulfolane, diethyl carbonate, DMPU, DMF, DMA, tetramethylurea and DME also resulted in improved yield. However, the best result was obtained in the presence of NMP. The discovery of this solvent effect had significant consequences in the development of iron catalysed cross coupling reactions. No difference was observed by replacing Fe(acac)$_3$ by Fe(dpm)$_3$, Fe(dbm)$_3$ (Figure 2.1) or FeCl$_3$. One of the effects of NMP is most likely stabilization of the iron organometallic species, which are the real catalytic intermediates of this reaction, by limiting the decomposition processes via $\beta$-hydrogen elimination.

2.4.5. Tam Group’s Previous Work on Fe Catalyzed Reaction

Previously, the Tam group studied Fe catalyzed coupling reactions of numerous Grignard reagents with anti-tert-butoxynorbornadien-2-yl triflate (2-24). In the presence of five equivalents of cyclohexylmagnesium chloride (CyMgCl) and Fe(acac)$_3$ (10 mol% in Et$_2$O) at -25 °C, the desired coupling product 2-25e was formed in 22% isolated yield. Based on this result, the iron-catalyzed coupling reaction was optimized by investigating the effect of solvent, different iron catalysts, different Grignard halides and reaction temperature.

It was found that the best solvent for the reaction is THF/NMP (1:3) which afforded the desired product in 81% yield. It was also observed that a decrease in the amount of NMP used in the THF/NMP solvent mixture led to a decrease in the yield of the desired coupling product 2-25e but increased the yield of the undesirable reduced product 2-26. Several catalysts, like FeCl$_3$, Fe(acac)$_3$, Fe(dpm)$_3$, Fe(dbm)$_3$ etc, which are reported in the literature to be active in iron-catalyzed coupling reactions were screened.
It was found that the commercially available, air-stable Fe(acac)₃ catalyst seemed to be the best choice with respect to high yields and ease of handling. The reactions worked better at -25 to -40 °C and it was found that reaction above 0 °C led to decomposition of substrates.

The effect of different Grignard halides on the iron-catalyzed coupling reaction indicates when the halide of the Grignard reagent was changed from Cl to Br to I resulted in decrease in the yield of the desired coupling product 2-25e and increase in the yield of the undesired reduced product (2-26).

The scope of the iron-catalyzed cross-coupling reactions of triflate 2-24 with various Grignard reagents was explored (Scheme 2.9). It was found that various cycloalkyl magnesium halides underwent the reaction efficiently giving the corresponding cross-coupling products in moderate to good yields (50–81%). This iron-catalyzed coupling reaction of triflate worked well with acyclic primary, secondary and even t-alkyl groups, giving the anti-2,7-disubstituted norbornadienes with R = i-Pr, n-Bu, s-Bu, t-Bu groups in good yields (50-75%). The use of vinyl, aryl and alkynyl Grignard reagents in the iron-catalyzed coupling reaction of triflate 2-24 also afforded the corresponding anti-2,7-disubstituted norbornadienes in good yields (61–76%).

![Scheme 2.9 Iron catalyzed cross coupling of triflate and various Grignard reagents.](image-url)
2.4.6. Results and Discussion

We began our investigation of the reaction conditions of the Fe-catalyzed coupling reaction using 2-bromofuran 2-2 and cyclohexylmagnesium chloride (2.27). The yields were determined by GC using benzophenone as an internal standard. Various solvents, iron catalysts, reaction temperatures, reaction times, and equivalencies of Grignard reagent were investigated and reaction conditions were optimized. Amide, phosphoramidate, and urea based solvents provided the highest yields (Table 2.3, entries 1-8) whereas ether, amine, or pyridine based solvents provided low or no yield (entries 9-12). The solvents DMPU and DMA provided the highest yield of coupling product of 60% (entries 1,8).

Of the iron catalysts screened, Fe(acac)$_3$ provided the highest yield (entry 1). The bulkier malonate derived iron sources Fe(dbm)$_3$ or Fe(dpm)$_3$ furnished only 30% and 22% yields, respectively (entry 15, 16). FeCl$_3$ provided the second highest yield of 40% whereas the hydrate of FeF$_3$ provided no observed coupling product (entries 13, 14). Low yields (5%) were also obtained for Fe(Salen)Cl (entry 17). Reaction times of 15, 30, 60, and 120 minutes were screened with 120 minutes showing the highest yield (entries 1, 18, 19, 20). Prolonged reaction times beyond 120 minutes did not provide higher yields. Variation of reaction temperature at 0, -25, and -40 °C (entries 1, 21, 22) showed that the highest yield was obtained at -25 °C with no reaction observed at -78 °C.
Table 2.3 Optimization of conditions for the synthesis of 2-28.

![Chemical Reaction](image)

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

<sup>a</sup>GC yields with internal standard of benzophenone
After identifying suitable conditions for coupling of 2-bromofuran with cyclohexyl magnesium chloride, the coupling reactions with other Grignard reagents were investigated. Primary and secondary alkyl Grignard reagents, including small to medium – sized ring cycloalkyl groups provided moderate to low yields (35- 55%) of 2-substituted furans 2-4 (Table 2.4, entries 1-9). For smaller sized alkyl groups of less than five carbons, isolation of the product proved to be non-trivial due to their volatility.

Aryl groups could be coupled with 2-bromofuran; however, low yields were observed (4-26%, entries 10-18) with the lowest yields of 5-6% obtained for phenyl and the 4-fluoro, 2-methyl and 2-methoxy substituted aryl groups (entries 18, 13, 16). Higher yields of 20-26% were obtained for 4 and 3-methyl and methoxy substituted aryl groups (entries 11, 12, 14, 15). Low yields of 15% of 2-benzylfuran were obtained (entry 9). No coupling product was obtained from 3-chlorophenylmagnesium chloride, ethynylphenylmagnesium chloride, or tert-butylmagnesium chloride and thus this coupling methodology may not extend to halide substituted aryl, sp hybridized, or tertiary alkyl Grignard reagents. The variation of the halide within the Grignard reagents from chloride to bromide did not offer improved yields.

In the iron-catalyzed coupling of 2-bromofuran 2-2 with various alkyl and aryl Grignard reagents, low to moderate yields of the desired coupling product were obtained. Much of the non hetero-coupled 2-bromofuran 2-2 was converted to bifuran 2-30 which was detected in every reaction. The compound is likely a result of magnesium halide exchange to provide a 2-furylmagnesium halide which could undergo further unwanted homo-coupling with 2-bromofuran.
Table 2.4 Fe catalyzed cross coupling with various Grignard reagents.

\[
\text{2-2} + \text{RMgX} \xrightarrow{\text{DMPU, -25 °C}} \text{2-4a-x}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>X</th>
<th>Product</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cyclopropyl (2.29a)</td>
<td>Br</td>
<td>2-4o</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>(\text{\textsuperscript{t}}\text{Bu} (2.29b))</td>
<td>Cl</td>
<td>2-4p</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>(\text{\textsuperscript{t}}\text{Bu} (2.29c))</td>
<td>Cl</td>
<td>2-4q</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>Cyclobutyl (2.29d)</td>
<td>Cl</td>
<td>2-4r</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>Cyclopentyl (2.29e)</td>
<td>Cl</td>
<td>2-4s</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>Cyclohexyl (2.29f)</td>
<td>Cl</td>
<td>2-4t</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>Cycloheptyl (2.29g)</td>
<td>Br</td>
<td>2-4u</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>Dodecyl (2.29h)</td>
<td>Cl</td>
<td>2-4v</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>Bn (2.29i)</td>
<td>Cl</td>
<td>2-4w</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>C(_6)H(_5) (2.29j)</td>
<td>Br</td>
<td>2-4a</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>4-CH(_3)-C(_6)H(_4) (2.29k)</td>
<td>Br</td>
<td>2-4b</td>
<td>26</td>
</tr>
<tr>
<td>12</td>
<td>3-CH(_3)-C(_6)H(_4) (2.29l)</td>
<td>Br</td>
<td>2-4c</td>
<td>24</td>
</tr>
<tr>
<td>13</td>
<td>2-CH(_3)-C(_6)H(_4) (2.29m)</td>
<td>Br</td>
<td>2-4d</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>4-CH(_3)O-C(_6)H(_4) (2.29n)</td>
<td>Br</td>
<td>2-4e</td>
<td>22</td>
</tr>
<tr>
<td>15</td>
<td>3-CH(_3)O-C(_6)H(_4) (2.29o)</td>
<td>Br</td>
<td>2-4f</td>
<td>24</td>
</tr>
<tr>
<td>16</td>
<td>2-CH(_3)O-C(_6)H(_4) (2.29p)</td>
<td>Br</td>
<td>2-4g</td>
<td>6</td>
</tr>
<tr>
<td>17</td>
<td>4-biphenyl (2.29q)</td>
<td>Br</td>
<td>2-4m</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
<td>4-F-C(_6)H(_4) (2.29r)</td>
<td>Br</td>
<td>2-4x</td>
<td>6</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield after column chromatography;

The dimers 2-31 of the Grignard reagents were also observed in all cases. Both of these compounds often co-elute during column chromatography and have similar boiling
points to the desired coupled product thus isolation was non-trivial, often requiring quantification by NMR (Figure 2.2).

![Figure 2.2 Homocoupled products obtained during Fe catalyzed cross coupling reaction.](image)

In conclusion, our efforts have led to the synthesis of 2-aryl and 2-alkyl furans by palladium and iron catalyzed coupling methodologies. These furans are useful intermediates in the synthesis of C\textsuperscript{1}-substituted Diels-Alder cycloadducts by treatment with the appropriate dienophile. Iron catalyzed couplings of 2-bromofuran 2-2 with Grignard reagents (primary and secondary) provided the corresponding 2-alkylfurans in low to moderate yields. This coupling methodology has allowed access to 2-alkylfurans through a general methodology while previously reported syntheses for secondary 2-alkyl furans required more difficult methods. 2-Arylfurans were also attainable by this coupling methodology, however only at extremely low yields.

The limitations of this reaction were shown to be that tertiary alkyl or alkynyl Grignard reagents were not amenable coupling partners. Further improvement to this methodology may include the use of a less aggressive organometallic that is not prone to undergo metal-halide exchange reactions such as organozinc or organoboron reagents. The use of a 2-furyl organometallic coupling partner with an organic halide under transition metal catalysis may provide higher yields.
2.5 Synthesis of 2-Substituted Furans (Miscellaneous)

2.5.1 Preparation of 2-Trimethylsilylfuran

2-Trimethylsilylfuran was prepared by following a literature procedure starting from furan. Treatment of furan with \( n\)-butyllithium in refluxing ether generates 2-lithiofuran, which upon quenching with chlorotrimethylsilane, produces trimethylsilylfuran 2-32.\(^{31}\) Similarly, when the acetone was added to 2-lithiofuran in THF, 2-furyl-2-propanol 2-34 was obtained.\(^{32}\)

\[
\text{Furan} \xrightarrow{1. \text{n-BuLi, Et}_2\text{O, reflux, 3h}} \text{LiFuran} \xrightarrow{2. \text{Me}_3\text{SiCl, 0°C to 25°C, 1h}} \text{Trimethylsilylfuran (62%)}
\]

Scheme 2.10 Synthesis of 2-substituted furans via the production of an \( \alpha\) anion.

2.5.2 Preparation of 2-Acetylaminomethylfuran

2-Acetylaminomethylfuran 2-36 is prepared by treatment of commercially available furfurylamine 2-35 (2-aminomethyl furan) with acetic anhydride in dichloromethane.

\[
\text{Furfurylamine} \xrightarrow{\text{Ac}_2\text{O, CH}_2\text{Cl}_2, 0-25°C, 1h}} \text{Acetylaminomethylfuran (94%)}
\]

Scheme 2.11 Preparation of 2-Acetylaminomethyl furan 2-36.

In conclusion, from the methodology described in Chapter 2 for the synthesis of 2-substituted furans, novel \( \text{C}^1\)-substituted oxabicyclic alkenes bearing various alkyl and
aryl groups can be synthesized. These compounds will serve in the study of the regioselectivity of various reactions on the oxabenzonorbornadiene framework. The use of various alkyl and cycloalkyl substitutions at the C^1 position can provide steric bias, through variation of the size of the group. Furthermore, the electron donating character of the alkyl groups can be varied with primary, secondary, or tertiary groups for the previously outlined reactions.

2.6 EXPERIMENTAL

General considerations:

All reactions are done in septum-sealed, flame-dried flasks under nitrogen atmosphere. All commercial reagents were used as received from their respective suppliers. Reagent grade furan and NBS purchased from Aldrich were used without additional purification. Column chromatography was performed on 230-400 mesh silica gel using flash column chromatography techniques. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} plates. ^1H and ^13C NMR spectra were recorded on Bruker Avance-300 or 400 MHz spectrometer. Chemical shifts for ^1H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the residual proton resonance as the internal standard (chloroform: δ 7.26 ppm). Chemical shifts for ^13C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). Infrared spectra were taken on a Bomem MB-100 FTIR spectrophotometer. Unless stated otherwise, commercial reagents were used without purification. Solvents were purified by distillation under dry nitrogen: THF and Et₂O from
potassium/benzophenone; DME from CaH₂; DMPU, DMSO, TMEDA and TEA from 4Å molecular sieves.

**Preparation of 2-Bromofuran:** A solution of NBS (20 g, 0.112 mol) in DMF (60 mL) was added via addition funnel to a solution of furan (15.3 g, 0.225 mol) in DMF (40 mL) in a 500 mL three-neck RBF over a period of 40-60 minutes, keeping internal temperature between 25-35 °C under constant stirring. Addition of NBS solution to reaction mixture was found to be slightly exothermic. During addition, the reaction mixture went from brown solution to dark green. After the addition was complete, the reaction mixture was stirred at ambient temperature for an additional 2-4 h. The resulting clear brown solution was heated gradually to 100-110 °C, in order to distill out some of the unreacted furan. After maintaining at 100-110 °C temperature for 0.5-1 h, the reaction mixture was exposed to a constant jet of steam generated by heating distilled water to 100-120 °C in a separate two-neck RBF. Distillate consisting of water and bromofuran was collected in a receiver. The initial few drops contained mostly residual unreacted furan, and were therefore collected separately. Distillation was continued until no organic product was present in the distillate. The distillate was transferred to a separatory funnel along with water (20-30 mL). The suspension was shaken well to force traces of DMF to aqueous layer. After layer separation, the bromofuran **2-2** settled down as colorless lower layer. It was collected and stored in a dry bottle containing anhydrous K₂CO₃ (11.5 g, 70%).
2-Bromofuran, 2-2 Colorless liquid, Yield = 70% (11.5 g); IR (CH$_2$Cl$_2$): 3140; 2930; 1679; 1472; 1386; 1052 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.28 (dd, $J = 3.3, 2.3$ Hz, 1H); 6.35 (dd, $J = 4.9, 3.6$ Hz, 1H); 7.40 (dd, $J = 2.1, 1.1$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz): 111.5, 114.0, 124.0, 141.3; HRMS (EI) calcd. for C$_4$H$_4$BrO (M$^+$): 146.9446; found: 146.9452.

**General Procedure A – Palladium-Catalyzed Suzuki Coupling (Table 2.1):** To an oven-dried vial containing a stir bar inside an inert atmosphere (Ar) glove box, the Pd catalyst (0.02 equiv) was added. The vial was then removed from the glovebox. Anhydrous K$_2$CO$_3$ (2.5 equiv) and boronic acid (1.2 equiv) were then added followed by DMF and H$_2$O (v/v 2:1, ~1 M) and quickly capped. The reaction mixture was then heated to 75-85°C for 18-20 h. The crude product was then purified by column chromatography with hexanes or EtOAc-hexanes mixture.

**General Procedure B – Iron-Catalyzed Coupling (Table 2.4):** To an oven-dried, nitrogen flushed flask equipped with a magnetic stir and rubber septum was charged with Fe(acac)$_3$ (24 mg, 20 mol %) and DMPU (2.5 mL). The flask was cooled to -25°C and bromofuran 2-2 was added (584 mg, 4 mmol). RMgX (16 mmol, 400 mol %) was then added dropwise over a period of 20 minutes to provide a deep purple to brown solution. The solution was then stirred for 2.5 hours and water was added dropwise (2 mL) followed by saturated sodium bicarbonate (5 mL) and extracted with 3×10 mL Et$_2$O. The extract was then stirred for 2.5 hours and water was added dropwise (2 mL) followed by saturated sodium bicarbonate (5 mL) and extracted with 3×10 mL Et$_2$O. The extract was dried over Na$_2$SO$_4$ and concentrated under rotary evaporation. The crude products were then purified by silica gel column chromatography with a mixture of ethyl acetate and hexanes or diethyl ether and pentane.
2-(4-Methoxyphenyl)furan, 2-4e. Following general procedure A Pd-catalyzed coupling: Yield = 77% (100.0 mg);

Following general procedure B Fe-catalyzed coupling: Yield = 22% (267 mg); Off-white solid; Mp: 54-56 °C; Rf = 0.26 EtOAc:hexanes = 5:95; IR (CH₂Cl₂): 2959, 2937, 1617, 1218, 1047 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 3.82 (s, 3H), 6.43 (dd, J=3.4, 1.7 Hz, 1H), 6.51 (d, J=2.8 Hz, 1H), 6.91 (d, J=8.8 Hz, 2H), 7.41 (d, J=1.3 Hz, 1H), 7.61-7.56 (m, 2H); ¹³C (APT) NMR (CDCl₃, 75 MHz): δ 55.2 (CH₃), 103.3 (CH), 111.5 (CH), 114.1 (CH), 124.0 (qC), 125.2 (CH) 141.3 (CH), 154.0 (qC), 159.0 (qC). HRMS (EI) calcd. for C₁₁H₁₀O₂ (M⁺): 174.0681; found: 174.0686.

2-(3-Methoxyphenyl)furan, 2-4f. Following general procedure A Pd-catalyzed coupling: Yield = 72% (126.0 mg);
Following general procedure B Fe-catalyzed coupling: Yield = 24% (310 mg); Brown oil. 

\[ \text{Rf} = 0.45 \text{ (EtOAc:hexanes=5:95); IR (CH}_2\text{Cl}_2: 2938, 1605, 1504, 1290, 1226, 1038 \text{ cm}^{-1}; \]

\(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 3.77 (s, 3H), 6.38 (dd, \( J = 3.4, 1.8 \text{ Hz, } 1 \text{H} \)), 6.56 (d, \( J = 3.4 \text{ Hz, } 1 \text{H} \)), 6.71–6.75 (m, 1H), 7.13–7.21 (m, 3H), 7.37 (d, \( J = 1.7 \text{ Hz, } 1 \text{H} \)); \(^{13}\)C (APT) NMR (CDCl\(_3\), 75 MHz): \( \delta \) 55.3 (CH\(_3\)), 105.3 (CH), 109.2 (CH), 111.7 (CH), 113.2 (CH), 116.4 (CH), 129.8 (CH), 132.2 (qC), 142.1 (CH), 153.8 (qC), 159.9 (qC). HRMS (EI) calcd. for C\(_{11}\)H\(_{10}\)O\(_2\) (M\(^+\)): 174.0681; found: 174.0679.

\[ \text{2-} \text{(2-Methoxyphenyl)furan, 2-4g. Following general procedure A Pd-catalyzed coupling: Yield = 63% (110.0 mg); } \]

Following general procedure B Fe-catalyzed coupling: Yield = 6% (94 mg); Brown oil. 

\[ \text{Rf} = 0.42 \text{ EtOAc:hexanes } = 10:90; \text{ IR (CH}_2\text{Cl}_2): 3002, 2940, 2837, 1602, 1464, 1083 \text{ cm}^{-1}; \]

\(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 3.93 (s, 3H), 6.48–6.50 (m, 1H), 6.93–7.04 (m, 3H),
7.20-7.27 (m, 1H), 7.46 (d, J = 0.7 Hz, 1H), 7.85 (dd, J = 7.7, 1.3 Hz, 1H); $^{13}$C (APT) NMR (CDCl$_3$, 75 MHz): δ 55.4 (CH$_3$), 109.8 (CH), 111.0 (CH), 111.6 (CH), 119.9 (qC), 120.7 (CH), 126.0 (CH), 128.0 (CH), 141.1 (CH), 150.3 (qC), 155.3 (qC). HRMS (EI) calcd. for C$_{11}$H$_{10}$O$_2$ (M$^+$): 174.0681; found: 174.0685.

2-(4-Ethylphenyl)furan, 2-4k. Following general procedure A Pd-catalyzed coupling:
Yield=84% (96.0 mg); Brown oil. R$_f$ = 0.5 (EtOAc:hexanes=5:95); IR (CH$_2$Cl$_2$): 3023, 2965, 2931, 1516, 1457, 1157, 1007 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): δ 1.24 (t, J=7.6 Hz, 3H), 2.65 (q, J=7.6 Hz, 2H), 6.44 (dd, J=3.3, 1.8 Hz, 1H), 6.58 (d, J=3.3 Hz, 1H), 7.21 (d, J=8.2 Hz, 2H); 7.43 (d, J=1.6 Hz, 1H), 7.59 (d, J=8.2 Hz, 2H); $^{13}$C (APT) NMR (CDCl$_3$, 75 MHz): δ 15.5 (CH$_3$), 28.6 (CH$_2$), 104.2 (CH), 111.5 (CH), 123.8 (CH), 128.1 (CH), 128.5 (qC), 141.6 (CH), 143.5 (qC), 154.2 (qC); HRMS (EI) calcd. for C$_{12}$H$_{12}$O (M$^+$): 172.0888; found: 172.0886.

2-(4-Biphenyl)furan, 2-4m. Following general procedure A Pd-catalyzed coupling:
Yield=77% (170.0 mg);
Following general procedure B Fe-catalyzed coupling: Yield = 20% (277 mg); Light brown solid, Mp: 148-150 °C, Rf = 0.33 (EtOAc:hexanes =5:95); IR (CH₂Cl₂): 3054, 2987, 1600, 1478, 1265, 1158 cm⁻¹;¹H NMR (CDCl₃, 300 MHz): δ 6.42–6.40 (m, 1H), 6.69 (d, J=3.3 Hz, 1H), 7.32–7.37 (m, 1H), 7.33–7.50 (m, 3H), 7.62 (d, J=8.4 Hz, 4H), 7.75 (d, J=8.4 Hz, 2H); ¹³C (APT) NMR (CDCl₃, 75 MHz): δ 105.1 (CH), 111.7 (CH), 124.2 (CH), 126.9 (CH), 127.3 (CH), 128.8 (CH), 129.9 (qC), 140.0 (qC), 140.6 (qC), 142.1 (CH), 153.8 (qC). HRMS (EI) calcd. for C₁₆H₁₂O (M⁺): 220.0888; found: 220.0885.

2-(1-Naphthyl)furan, 2-4n. Following general procedure A Pd-catalyzed coupling: Yield; 87% (165.0 mg); Colorless oil. Rf = 0.45 (EtOAc:hexanes=10:90); IR (CH₂Cl₂): 3054, 2987, 1512, 1422, 1265, 1015 cm⁻¹;¹H NMR (CDCl₃, 300 MHz): δ 6.58 (dd, J=3.3, 1.9 Hz, 1H), 6.71 (d, J=3.3 Hz, 1H), 7.40–7.56 (m, 3H), 7.61 (d, J=1.7 Hz, 1H), 7.71 (dd, J=7.2, 1.0 Hz, 1H), 7.80–7.89 (m, 2H), 8.37–8.41 (m, 1H); ¹³C (APT) NMR (CDCl₃, 75MHz): δ 109.2 (CH), 111.3 (CH), 125.3 (CH), 125.6 (CH), 125.9 (CH), 126.2 (CH), 126.5 (CH), 128.5 (CH), 128.6 (CH), 128.7 (qC), 130.4 (qC), 134.0 (qC), 142.4 (CH), 153.4 (qC). HRMS (EI) calcd. for C₁₄H₁₀O (M⁺): 194.0732; found: 194.0726.
2-Butylfuran, 2-12a. Following general procedure B Fe-catalyzed coupling: Yield; 55% (345 mg); Orange liquid. Rf = 0.64 (EtOAc/hexanes=10:90); IR (CH₂Cl₂); 2967, 2870, 1539, 1457, 1378, 1111 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.81-0.86 (m, 3H), 1.18 (d, J = 7.0 Hz, 3H), 1.21-1.37 (m, 2H), 2.68 (m, 1H), 5.91 (d, J = 3.3 Hz, 1H), 6.20-6.22 (m, 1H), 7.30-7.35 (m, 1H). ¹³C (APT) NMR (CDCl₃, 100 MHz): δ 11.4 (CH₃), 18.4 (CH₃), 28.5 (CH₂), 38.2 (CH), 104.9 (CH), 109.7 (CH), 141.6 (CH), 160.5 (C). HRMS (EI) calcd. for C₈H₁₂O (M⁺): 124.0888; found: 124.0893.

2-Cyclopentylfuran (2-12b): Following general procedure B; Yield: 44% (244 mg). Colorless oil; Rf = 0.60 (EtOAc–hexanes, 10:90); IR (neat): 3150, 3120, 2952, 1741, 1650, 1594, 1237, 1000 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ = 1.43-1.92 (m, 6 H), 1.99-2.13 (m, 2 H), 3.12 (quint, J = 7.7 Hz, 1 H), 6.00 (d, J = 3.2 Hz, 1 H), 6.30 (m, 1 H), 7.33 (m, 1 H). ¹³C NMR (APT; CDCl₃, 100 MHz): δ = 25.3 (CH₂), 31.8 (CH₂), 38.7 (CH), 103.1 (CH), 109.8 (CH), 140.6 (CH), 160.0 (qC). HRMS (EI) calcd. for C₉H₁₂O (M⁺): 136.0888; found: 136.0890.

2-Trimethylsilylfuran (2-32)

To the solution of furan (4.0 g, 58.8 mmol) in anhydrous diethyl ether (100 mL), n-BuLi (33 mL, 1.78 M in hexanes, 58.8 m.mol) was charged slowly at 0-5 °C. The reaction mixture is slowly heated to reflux for 3-4 hours. A light brown suspension was obtained.
The reaction mixture was cooled to 0-5 °C, trimethylsilyl chloride (5.75 g, 52.9 mmols) was added dropwise and the resulting mixture was stirred for 12-16 hours at RT. The reaction mixture was cooled to 0-5 °C, water (75 mL) was charged slowly to quench the reaction. The layers were separated and the aqueous layer was extracted with ether (20 mL X 2). The combined organic layer was washed with brine (30 mL) and dried (MgSO₄). The organic solution was concentrated to low volume on rotavapour to get light brown oil. The trimethylsilylfuran (5.11 g, 62%) was collected by careful distillation using short path distillation at atmospheric pressure. ¹H NMR was compared with reported compound in literature to confirm the structure.³¹

2-Acetilaminomethylfuran 2-36

To the solution of furfurylamine (0.930 g, 10 mmol) dissolved in dichloromethane (15 mL) at 0-5 °C, a solution of acetic anhydride (1.23 g,12.0 mmol) in DCM (5 ml) was charged slowly. The reaction mixture was slowly warmed to room temperature and stirred for 2 hours. The completion of reaction was confirmed by disappearance of starting material on TLC. The reaction mixture was quenched by addition of crushed ice. The aqueous layer was extracted with DCM (2 X 10 mL). The combined organic layer was washed with 5% NaHCO₃ solution (10 mL) followed by water wash (10 mL). The organic solution was concentrated on rotary evaporator and used as is in the next step. (1.31g, 94% yield). Yellow Oil. Rₚ = 0.26 (EtOAc:hexanes=5:95); IR (CH₂Cl₂): 3390, 3079, 2923, 1667, 1549, 1431, 1370, 1288 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.96 (s, 3H), 4.37 (d, J = 5.5Hz, 2H), 6.19 (d, J = 2.8 Hz, 1H), 6.28 (d, J= 1.7 Hz, 1H), 6.41 (brs,
1H, NH), 7.32 (s, 1H); 13C (APT) NMR (CDCl3, 75 MHz): δ 23.0 (CH3), 36.5 (CH2), 107.3 (CH), 110.4 (CH), 142.1 (CH), 151.4 (qC), 170.1 (qC). HRMS (CI) calcd. for C7H10NO2 (M+H+): 140.0707; found: 140.0712.

2.6 References (Chapter 2)


Chapter 3

Synthesis of C\textsuperscript{1} Substituted Oxabicyclic Alkenes
3.1 Introduction

C\textsuperscript{1}-substituted oxabicycloalkenes are required in order to explore the regioselectivity of transition metal catalyzed ring opening reactions. One of the most straightforward methods for the construction of the 7-oxabicyclo[2.2.1]hept-2-ene skeleton is a Diels-Alder reaction between a 2-substituted furan and an appropriate dienophile (Scheme 3.1). The yields of Diels-Alder reactions involving furan are highly sensitive to both diene and dienophile substitution. In particular, substitution on the furan greatly affects the chemical reactivity during cycloaddition reactions.\textsuperscript{1}

\[
\begin{array}{c}
\text{R}_1 \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_2 \\
\text{R}_1 \\
\end{array}
\quad + 
\begin{array}{c}
\text{O} \\
\text{R}_2 \\
\text{R}_2 \\
\text{R}_1 \\
\text{R}_1 \\
\end{array}
\quad \text{[4+2] Cycloaddition}
\quad \begin{array}{c}
\text{O} \\
\text{R}_1 \\
\text{R}_2 \\
\text{R}_1 \\
\text{R}_2 \\
\end{array}
\]

Scheme 3.1 Synthesis of C\textsuperscript{1}-substituted oxabicycloalkenes.

Diels-Alder reactions using a furan as a diene to form oxanorbornene derivatives have been used in the syntheses of numerous complex targets.\textsuperscript{2} For our investigation we selected two different oxabicyclic alkenes skeletons for the preparation of a series of compounds with a wide range of substituents at C\textsuperscript{1} as shown in Figure 3.1.

![Figure 3.1 Structures of two different oxabicyclic alkene skeletons.](image-url)
3.1.1 Preparation of Dienophiles (Generation of Benzyne)

For the preparation of compounds comprising series 3-4 commercially available dimethyl acetylenedicarboxylate was used directly, whereas for the preparation of compounds of series 3-5, the benzyne was generated \textit{in situ}. Benzyne, which is a highly reactive intermediate, can be prepared \textit{in situ} using a variety of methods reported in literature.\textsuperscript{3} For our work we prepared benzyne by treatment of anthranilic acid with isoamyl nitrite to form a diazoniun salt which releases nitrogen gas and carbon dioxide upon heating. The other two methods shown in Scheme 3.2 involve organolithium precursors which undergo elimination or dehydrohalogenation reactions.

Scheme 3.2 Methods for generating benzyne \textit{in situ}, for preparation of C\textsuperscript{1} substituted oxabenzonorbornadiene.

3.1.2 Synthesis of 2-Substituted Furans (The Dienes partners)

As mentioned in chapter two, the 2-aryl substituted furans were prepared by Suzuki coupling protocol\textsuperscript{4} while 2-alkyl substituted furans were prepared by iron catalyzed cross coupling reactions.\textsuperscript{5} Both reactions took advantage of a common
precursor, 2-bromofuran; a chemical whose synthesis was specifically developed by our group for this purpose.

3.2 Synthesis of C\textsuperscript{1}-Substituted Oxanorbornadienes

We wanted to study the regioselectivity of the various transition metal catalyzed reactions using 7-oxanorbornadienes derivatives with a wide range of substituents on the C\textsuperscript{1} carbon. To our surprise, a search in the literature showed very few C\textsuperscript{1} substituted 7-oxanorbornadienes synthesized to date.

3.2.1 Background

The [4+2] Diels-Alder cycloaddition reaction of 2-substituted furans with dimethyl acetylenedicarboxylate can potentially lead to the formation of desired products. According to recent literature, dimethyl acetylenedicarboxylate (DMAD) (3-7) was used as the starting compound for the syntheses of phthalates via Diels–Alder reactions.\textsuperscript{6} It is well known that phthalic acid derivatives are important starting materials and building blocks for the syntheses of various dyes, typical resin paints, various pharmaceuticals, and biologically active agents.\textsuperscript{7} Therefore, development of convenient synthetic approach to phthalic acid derivatives is of current interest; however, it is important to note that furan adducts are considerably less stable and tend to undergo retro Diels-Alder reactions. This tendency can be attributed to the benefit of aromaticity of the furan upon cycloreversion.\textsuperscript{8}

Furan is a planar cyclic molecule with three pairs of delocalized $\pi$ electrons and is therefore aromatic. Two of the $\pi$ electron pairs are shown in Figure 3.2 as two double bonds and the third pair of $\pi$ electrons is from a lone pair on the oxygen atom.\textsuperscript{9}
According to Huckel, a cyclic system of sp\(^2\) atoms is probably aromatic if it contains 4n + 2 (n = positive integer or zero) electrons.

![Diagram of furan molecule]

Furan

**Figure 3.2 Participation of six \(\pi\) electrons in aromaticity of furan.**

Since furan is aromatic, when it undergoes the cycloaddition reaction it is destabilized due to loss of aromaticity. In the adduct, the furan moiety is similar to a non-aromatic 2,5-dihydrofuran system. The benefit of reforming the aromatic furan prompts the reverse reaction, a retro Diels-Alder, to take place since the barrier for the reverse reaction is much smaller than in the cyclopentadiene case.

To overcome the difficulties in Diels-Alder cycloadditions several methods have been developed such as the use of high pressure, high temperature, microwave assistance, and Lewis acid mediated reactions. Although several Lewis acids have been reported to promote the reaction efficiently, there are problems in terms of generality.
3.2.2 Results and Discussion

We employed the Diels-Alder reaction between 2-substituted furans and dimethyl acetylenedicarboxylate 3-1 for the preparation of C1-substituted-7-oxanorbornadienes 3-4a-j. 10 2-Substituted furans 3-8a-c and 3-8e-g are commercially available. 2-Phenylfuran 3-8d was prepared in 71-73% yield by Pd-catalyzed Suzuki coupling reaction between 2-bromofuran 2-2 and phenylboronic acid and 2-trimethylsilylfuran 3-8j was synthesized in 62% by deprotonation of furan followed by trapping with chlorotrimethylsilane11 (Scheme 3.3). 2-Acetylaminomethyl furan 3-8i was prepared by treatment of furfurylamine 3-8l (2-aminomethyl furan) with acetic anhydride in dichloromethane.

![Scheme 3.3 Synthesis of 2-trimethylfuran 3-8j and 2-acetylaminomethyl furan 3-8i.](image)

With the 2-substituted furans 3-8a-i in hand, we studied the Diels-Alder reactions of these 2-substituted furans with dimethyl acetylenedicarboxylate 3-7 and the results are shown in Table 3.1.
Table 3.1 Synthesis of C\textsuperscript{1}-substituted 7-oxanorbornadienes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Furan</th>
<th>Product</th>
<th>Yield (%)\textsuperscript{a}</th>
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</thead>
<tbody>
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<td><img src="image1" alt="Furan" /> (3-8a)</td>
<td><img src="image2" alt="Product" /> (3-4a)</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Furan" /> (3-8b)</td>
<td><img src="image4" alt="Product" /> (3-4b)</td>
<td>85</td>
</tr>
<tr>
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<td><img src="image5" alt="Furan" /> (3-8c)</td>
<td><img src="image6" alt="Product" /> (3-4c)</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Furan" /> (3-8d)</td>
<td><img src="image8" alt="Product" /> (3-4d)</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
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<td><img src="image10" alt="Product" /> (3-4e)</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Furan" /> (3-8f)</td>
<td><img src="image12" alt="Product" /> (3-4f)</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Furan" /> (3-8g)</td>
<td><img src="image14" alt="Product" /> (3-4g)</td>
<td>13</td>
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\textsuperscript{a}Yield corresponding to the product indicated.
<table>
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<th>Entry</th>
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<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
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<td><img src="" alt="Product.png" /></td>
<td>0 (92)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

<sup>b</sup>Compound 3-4k was unstable to isolate and was isomerized to form compound 12 in 92% yield (see Scheme 3.4).

We found C1-substituted 7-oxanorbornadienes 3-4a and 3-4b with primary alkyl groups (Y = Me and Et) were produced in excellent yields (85%, entries 1-2). The yields of the Diels-Alder reactions were significantly lowered with a tertiary alkyl group (3-4c, Y = tBu, 34%) or with an aromatic group (3-4d, Y = Ph, 42% (entry 4). With carbonyl substituents (ester 3-4e, Y = COOMe; ketone 3-4f, Y = COMe; and amide 3-4g, Y = CONH₂), low to moderate yields of the Diels-Alder reactions were observed (13-50% yields, entries 5-7). C1-substituted 7-oxanorbornadienes 3-4h and 3-4i containing a primary alcohol and protected primary amine group (Y = CH₂OH and CH₂NHAc) were produced in good yields (75% and 51%, entries 8-9).

The Diels-Alder reaction with a non-protected free primary amine group 3-8l (CH₂NH₂) led to a complicated mixture of products and decomposition was observed.
C\textsuperscript{1}-Silyl substituted 7-oxanorbornadienes 3-4j can also be produced in 35% yield (entry 10). However, the C\textsuperscript{1}-methoxy substituted 7-oxanorbornadienes 3-4k were found to be unstable and aromatized to phenol 3-9k in 92% yield (Table 1, entry 11 and Scheme 3). We have attempted the Diels-Alder reactions of 2-substituted furans with \( Y = \text{CN, NO}_2, \text{COOH and Br} \), but in each case a complicated mixture of products was obtained with considerable decomposition and no desired C\textsuperscript{1}-substituted 7-oxanorbornadienes were isolated.

Thus, we synthesized some C\textsuperscript{1}-substituted 7-oxanorbornadienes 3-4a to 3-4j, by the Diels-Alder reaction between 2-substituted furans 3-8a to 3-8j and dimethyl acetylenedicarboxylate 3-7. Moderate to good yields (13-85%) of the Diels-Alder reactions were observed. These C\textsuperscript{1}-substituted 7-oxanorbornadienes will find applications as valuable synthetic intermediates and useful in the studies of transition metal-catalyzed reactions.

3.3 Synthesis of C\textsuperscript{1}-Substituted Oxabenzonorbornadienes

3.3.1 Background

Oxabenzonorbornadienes 3-5 can be synthesized by benzyne-furan cycloaddition. Benzyne (3-13) is a popular intermediate used in organic synthesis, mechanistic studies,
and the synthesis of functional materials. The aryne (in this case, benzyne) can be generated by one of several methods as shown in Scheme 3.2.³

To our surprise, a search in the literature showed that very few unsymmetrical C¹-substituted oxabenzonorbornadienes have been synthesized to date (3-5a-f, Figure 3.3),¹² and 1-trimethylsilyloxabenzonorbornadiene 3-5f was only obtained in very low yield.¹²b

![Chemical structures](image)

**Figure 3.3 Known C¹-substituted oxabenzonorbornadienes 3-5a-f in the literature.**

### 3.3.2 Results and Discussion

With the 2-substituted furans in hand, (syntheses described in Chapter 2) we studied the Diels-Alder reactions of these 2-substituted furans with benzyne 3-13 generated *in situ* from anthranilic acid 3-10 and isoamyl nitrite (Table 3-2).¹³ For the synthesis of 2-trimethylsilylfuran 3-8j (Scheme 3.3) and 2-furanyl-2-propanol 3-16ab previously described literature procedures were employed. Both were produced via deprotonation of the α-furan proton with "BuLi followed by the trapping of the anion with an electrophile. Trapping of the anion with TMSCl resulted in 3-8j in a 62% yield. Alternatively, the use of acetone followed by water to quench resulted in 3-16ab at 65% yield.¹⁴
The yields of the Diels-Alder reactions involving furan are sensitive to both diene and dienophile substitution. In the procedure involving cycloaddition with benzyne, the substitution on furan greatly affects the chemical reactivity. 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 the yield of the cycloadduct. In the case of 2-ethylfuran 3-8b, the product was obtained in 80% yield (Table 3.2, entry 1) whereas the larger 2″-butylfuran 3-16h and 2-dodecylfuran 3-16i provided yields of 55 and 58%, respectively (entries 2 and 3). Interestingly, when secondary linear alkyl groups were examined the size of the substituent seemed to have a profound effect. This effect was easily seen in comparison between 2-i-propylfuran 3-14j and 2-sbutylfuran 3-16k (entries 4 and 5). 2-SButylfuran 3-16k has a bulkier substituent which resulted in a much lower yield of the C1-norbornadiene than when 2-i-propylfuran 3-16j was used in the cycloaddition. The secondary 2-i-propylfuran 3-16j and 2-sbutylfuran 3-16k provided 70 and 29% of their respective C1-oxabenzonorbornadiene.

The tertiary alkyl group, 2-tbutylfuran 3-8c was also explored with the expectation that the yield of its cycloadduct would be lower than the other systems previously explored.

Surprisingly, the bulkier 2-tbutylfuran 3-8c underwent cycloaddition in higher yield than 2-sbutylfuran 3-16k in 66% yield (entry 6). The scope of secondary alkyl groups explored was expanded to include cycloalkyl substituents. The corresponding cycloadducts were obtained in low to moderate yields. 1-i-propyloxabenzonorbornadiene and 1-sbutyloxabenzonorbornadiene remained the highest and lowest yielding C1 secondary linear alkyl oxabenzonorbornadienes with all of the cycloalkyl substituent yields falling between these two extremes. 2-Cyclobutylfuran 3-16n (entry 8) 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 3-16m, 2-cyclopentylfuran, 3-16o, and 2-cycloheptylfuran 3-16q of 29, 33, and 32%, respectively (entries 7, 9 and 11). A slightly higher yield of 45% was obtained for 2-cyclohexylfuran 3-16p (entry 10).

The cycloaddition of a variety of 2-arylfurans 3-16r-3-16x provided the corresponding 1-aryloxabenzonorbornadiene in moderate yields. The unsubstituted 2-phenylfuran 3-8r underwent cycloaddition in 43% yield (entry 12). Comparison of other aryl substituents to this standard resulted in an increase or decrease in yield depending on the substituent. For example, arylfurans containing an extended π-system, 2-(1-naphthyl)furan 3-16y and 2-(4-biphenyl)furan 3-16z both provided much lower yields of 24 and 16% respectively (entries 19 and 20). Examination of the ortho-, meta-, and para-tolyl 3-16s-u (entries 13-15) and chloro 3-16v-x (entries 16-18) systems provided insight into the electron donating or withdrawing substituent effects on the phenyl group. Both of these cases provided generally higher yields than the unsubstituted 2-phenylfuran. Of the tolyl systems, a range of yields from 31% for the p-tolyl to 53% for the m-tolyl 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 3-5v-x which ranged from 51-63%.
Table 3.2 Synthesis of C\(^1\)-substituted oxabenzonorbornadienes.

![Chemical structure]

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

In our investigations three other systems were explored resulting in a wide range of yields. 2-Trimethylsilylfuran 3-8j furnished the bicyclic alkene 3-5f in 75% yield (entry 21) which was higher than the 66% yield from the comparable system of 2-tbutylfuran 3-16k. Though TMS group is bulkier than t-Bu group, the yield of 3-5f is
higher. Because of longer C-Si bond compared with C-C bond of \( t\)-Bu, the effective steric effect is larger with \( t\)-Bu substituent, hence lower yield (66%) of 3-5l.

2-Bromofuran 2-2 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 was thought that the electronic effects of this substituent are responsible for its low yield. Slight decomposition was observed during the purification (column chromatography) of 3-16aa. Finally, the tertiary alcohol-containing furan 3-16ab underwent cycloaddition in 47% yield (entry 23) which was much lower than its tertiary counterparts.

In conclusion, we have successfully synthesized some novel C\(^1\)-substitued oxabenzonorbornadienes with a variety of alkyl and aryl substituents. These compounds may prove useful for further studies into the scope and mechanism of reactions of oxabenzonorbornadienes.

3.4 Experimental

All reactions were performed in septum-sealed, flame-dried flasks under nitrogen atmosphere. All commercial reagents were used as received from their respective suppliers. \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded at 300/400 and 75/100 MHz, respectively. Chemical shifts are reported in parts per million (\( \delta \)) using internal solvent signals as references and coupling constants are reported in hertz (Hz). 2-Ethylfuran and 2-\( t\)-butylfuran were used as received. Other 2-substituted furans were synthesized according to literature procedures.
General procedure for the Diels-Alder reaction between 2-substituted furans 3-8a-j and dimethyl acetylenedicarboxylate 10:

The 2-substituted furan (1.1 eq.) was slowly charged into dimethylacetylene dicarboxylate (1.0 eq.) at room temperature. The resulting solution was heated to 90-100 °C in a screw capped vial for 12-16 hours. Reaction completion was monitored by TLC. The crude product was directly purified by column chromatography (EtOAc–hexanes mixtures) to give the product.

1-Methyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 3-4a

Light brown oil. Yield = 85% (1333 mg, 7.0 mmol); R_f = 0.40 (EtOAc–hexanes, 1:4); IR (CH_2Cl_2); 2955, 1716, 1641, 1473, 1267, 1132 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 400 MHz): \(\delta\) 1.76 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 5.58 (d, \(J = 2.0\) Hz, 1H), 6.96 (d, \(J = 5.2\) Hz, 1H), 7.16 (dd, \(J = 5.2\) & 1.9 Hz, 1H); \(^{13}\)C (APT) NMR (CDCl_3, 100 MHz): 15.1 (CH_3), 52.2 (CH_3), 52.3 (CH_3), 83.3 (CH), 93.9 (qC), 144.6 (CH); 145.9 (CH); 151.2 (qC), 156.5 (qC), 162.8 (qC), 164.9 (qC); HRMS (CI) calcd. for C_{11}H_{13}O_5 (M+H): 225.0763; found: 225.0770.

1-Ethyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 3-4b
Brown oil. Yield = 85% (809 mg, 4.0 mmol); R<sub>f</sub> = 0.40 (EtOAc–hexanes, 1:4); IR (CH<sub>2</sub>Cl<sub>2</sub>); 2955, 1726, 1639, 1437, 1273, 1122 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 0.99 (t, J = 7.4 Hz, 3H), 2.07-2.22 (m, 2H), 3.74 (s, 3H), 3.81 (s, 3H), 5.62 (d, J = 1.9 Hz, 1H), 6.95 (d, J = 5.2 Hz, 1H), 7.15 (dd, J = 5.2 & 1.9 Hz, 1H); <sup>13</sup>C (APT) NMR (CDCl<sub>3</sub>, 100 MHz): 9.0 (CH<sub>3</sub>), 21.9 (CH<sub>2</sub>), 52.2 (CH<sub>3</sub>), 52.3 (CH<sub>3</sub>), 83.2 (CH), 98.4 (qC), 144.7 (CH); 144.8 (CH); 151.4 (qC), 156.2 (qC), 162.7 (qC), 165.3 (qC); HRMS (CI) calcd. for C<sub>12</sub>H<sub>15</sub>O<sub>5</sub> (M+H): 239.0919; found: 239.0926.

1-<i>tert</i>-Butyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 3-4c

Light brown oil. Yield = 34% (66 mg, 0.73 mmol); R<sub>f</sub> = 0.26 (EtOAc–hexanes, 1:5); IR (CH<sub>2</sub>Cl<sub>2</sub>); 2957, 1717, 1634, 1482, 1399, 1273, 1201 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 1.08 (s, 9H), 3.71 (s, 3H), 3.82 (s, 3H), 5.62 (d, J = 1.6 Hz, 1H), 7.10 (d, J = 5.3 Hz, 1H), 7.16 (dd, J = 5.3 & 1.6 Hz, 1H); <sup>13</sup>C (APT) NMR (CDCl<sub>3</sub>, 75 MHz): 26.3(3 X CH<sub>3</sub>), 32.8 (qC), 52.1 (CH<sub>3</sub>), 52.5 (CH<sub>3</sub>), 82.3 (CH), 105.7 (qC), 142.8 (CH), 145.2 (CH), 149.6 (qC), 159.3 (qC), 162.3 (qC), 167.8 (qC) ; HRMS (CI) calcd. for C<sub>14</sub>H<sub>19</sub>O<sub>5</sub> (M+H):267.1232; found: 267.1233

1-Phenyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 3-4d
Amber coloured oil. Yield = 42% (250 mg, 2.1 mmol); \( R_f = 0.31 \) (EtOAc–hexanes, 1:4); IR (CH\(_2\)Cl\(_2\)) 2955, 1717, 1700, 1635, 1436, 1362, 1286, 1238 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 3.62 (s, 3H), 3.77 (s, 3H), 5.82 (d, \( J = 1.9 \) Hz, 1H), 7.31 (dd, \( J = 5.2 \) & 1.9 Hz, 1H), 7.44-7.33 (m, 4H), 7.50 (m, 2H); \(^13\)C (APT) NMR (CDCl\(_3\), 75 MHz): 51.9 (CH\(_3\)), 52.1 (CH\(_3\)), 83.4 (CH), 97.8 (qC), 126.6 (CH), 128.4 (CH), 128.7(CH), 133.6 (qC), 143.9 (CH), 144.8 (CH), 149.0 (qC), 158.5 (qC), 162.2 (qC), 164.8 (qC); HRMS (ESI) calcd. for C\(_{16}\)H\(_{15}\)O\(_5\) (M+H\(^+\)): 287.0919; found: 287.0915

![Diagram](image)

1,2,3-Trimethoxycarbonyl-7-oxanorbornadiene, 3-4e

Brown oil. Yield = 37% (1085 mg, 10.9 mmol); \( R_f = 0.48 \) (EtOAc–hexanes, 1:1); IR (CH\(_2\)Cl\(_2\)) 3008, 2957, 2851, 1741, 1644, 1438, 1269, 1204, 1148 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 3.78 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 5.72 (d, \( J = 2.1 \) Hz, 1H), 7.25-7.29 (m, 2H); \(^13\)C (APT) NMR (CDCl\(_3\), 100 MHz): 52.5 (CH\(_3\)), 52.6 (CH\(_3\)), 53.1 (CH\(_3\)), 84.6 (CH), 94.0 (qC), 142.2 (CH); 144.3 (CH); 150.8 (qC), 153.6 (qC), 162.3 (qC), 162.9 (qC), 166.0(qC); HRMS (CI) calcd. for C\(_{12}\)H\(_{13}\)O\(_7\) (M+H): 269.0661; found: 269.0666.

![Diagram](image)

1-acetyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 3-4f
Amber coloured oil. Yield = 50% (1386 mg, 11.0 mmol); R_t = 0.26 (EtOAc–hexanes, 1:5); IR (CH_2Cl_2); 2957, 1738, 1723, 1717, 1645, 1436, 1268, 1116 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 400 MHz): \(\delta\) 2.30 (s, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 5.72 (d, J = 1.8 Hz, 1H), 7.20 (d, J = 5.2 Hz, 1H), 7.24 (dd, J = 5.2 & 1.8 Hz, 1H); \(^13\)C (APT) NMR (CDCl_3, 100 MHz): 26.6 (CH_3), 52.4 (CH_3), 52.6 (CH_3), 84.0 (CH), 99.2 (qC), 141.9 (CH), 144.3 (CH), 149.7 (qC), 154.6 (qC), 162.3 (qC), 163.3 (qC), 201.7 (qC); HRMS (CI) calcd. for C_{12}H_{13}O_6 (M+H): 253.0712; found: 253.0719.

\[\text{COO} + \text{H}_2\text{N} \xrightarrow{\text{neat}} \text{MeOOC} \]

\[\text{3-7} \xrightarrow{\text{100°C, 12-16h}} \text{MeOOC} \text{O} \]

\[\text{3-8g} \xrightarrow{} \text{3-4g}\]

**1-Aminocarbonyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 3-4g**

Dark brown oil. Yield = 13% (33 mg, 3.6 mmol); R_t = 0.46 (EtOAc–hexanes, 1:1); IR (CH_2Cl_2); 3177, 2955, 1717, 1669, 1433, 1297, 1254, 1202 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 300 MHz): \(\delta\) 3.75 (s, 3H), 3.83 (s, 3H), 5.73 (d, J = 1.9 Hz, 1H), 5.98 (br s, 1H), 6.28 (br s, 1H), 7.23 (dd, J = 5.2 & 1.9 Hz, 1H), 7.29 (d, J = 5.2 Hz, 1H); \(^13\)C (APT) NMR (CDCl_3, 75 MHz): 52.4 (CH_3), 52.7 (CH_3), 83.5 (CH), 94.8 (qC), 142.8 (CH), 143.9 (CH), 147.5 (qC), 155.8 (qC), 162.1 (qC), 163.8 (qC), 167.4 (qC); HRMS (CI) calcd. for C_{11}H_{12}NO_6 (M+H): 254.0665; found: 254.0660.

\[\text{COO} + \text{OH} \xrightarrow{\text{neat}} \text{MeOOC} \]

\[\text{3-7} \xrightarrow{\text{100°C, 12-16h}} \text{MeOOC} \text{O} \]

\[\text{3-8h} \xrightarrow{} \text{3-4h}\]

**1-Hydroxymethyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 3-4h**

135
Amber coloured oil. Yield = 75% (1080 mg, 6.0 mmol); R_f = 0.16 (EtOAc–hexanes, 1:1); IR (CH_2Cl_2): 3493, 2955, 1716, 1637, 1438, 1302, 1271 cm^{-1}; ^1H NMR (CDCl_3, 400 MHz): δ 3.78 (s, 3H), 3.82 (s, 3H), 4.25 (m, 2H), 5.65 (d, J = 1.8 Hz, 1H), 7.03 (d, J = 5.3 Hz, 1H), 7.22 (dd, J = 5.3 & 1.8 Hz, 1H); ^13C (APT) NMR (CDCl_3, 100 MHz): 52.3 (CH_3), 52.5(CH_3), 59.9 (CH_2), 83.9 (CH), 98.3 (qC), 142.5 (CH), 144.9 (CH), 152.6 (qC), 153.6 (qC), 162.9 (qC), 164.6 (qC); HRMS (CI) calcd. for C_{11}H_{13}O_{6} (M+H): 241.0712; found: 241.0719.

![Diagram of reaction](image)

1-Acetylaminomethyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 3-4i

Amber coloured oil. Yield = 51% (257 mg, 1.8 mmol); R_f = 0.24 (EtOAc pure); IR (CH_2Cl_2): 3390, 2954, 1716, 1674, 1530, 1436, 1267, 1124 cm^{-1}; ^1H NMR (CDCl_3, 300 MHz): δ 1.92 (s, 3H), 3.74 (s, 3H), 3.77 (s, 3H), 3.85-4.14 (m, 2H), 5.59 (d, J = 1.7 Hz, 1H), 5.96 (br s, 1H), 6.95 (d, J = 5.3 Hz, 1H), 7.17 (dd, J = 5.2 & 1.6 Hz, 1H); ^13C (APT) NMR (CDCl_3, 75 MHz): 23.0 (CH_3), 37.8 (CH_2), 52.4 (CH_3), 52.6 (CH_3), 83.7 (CH), 96.9 (qC), 142.9 (CH), 145.3 (CH), 152.8 (qC), 153.6 (qC), 162.6 (qC), 163.9 (qC), 170.1(qC); HRMS (CI) calcd. for C_{13}H_{15}NO_{6} (M+H): 282.0978; found: 282.0982

![Diagram of reaction](image)

1-Trimethylsilyl-2,3-dimethoxycarbonyl-7-oxanorbornadiene, 3-4j
Amber coloured oil. Yield = 35% (353 mg, 3.6 mmol); \( R_f = 0.4 \) (EtOAc–hexanes, 1:5) IR (CH\(_2\)Cl\(_2\)); 2954, 1717, 1436, 1251, 1111 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta 0.16 \) (s, 9H), 3.73 (s, 3H), 3.70 (s, 3H), 5.68 (d, \( J = 1.5 \) Hz, 1H), 7.14 (d, \( J = 5.2 \) Hz, 1H), 7.19 (dd, \( J = 5.2 \) &1.5 Hz, 1H); \(^{13}\)C (APT) NMR (CDCl\(_3\), 75 MHz): -3.3 (3 X CH\(_3\)), 52.0 (2 X CH\(_3\)), 85.3 (CH), 91.5 (qC), 143.3 (CH), 146.1 (CH), 150.4 (qC), 159.3 (qC), 163.0 (qC), 165.7 (qC), HRMS (Cl) calcd. for C\(_{13}\)H\(_{19}\)SiO\(_5\) (M+H): 283.1002; found: 283.1008.

2,3-Dimethoxycarbonyl-4-methoxyphenol, 3-4k

White Solid. Yield = 92% (238 mg, 1.1 mmol); \( R_f = 0.48 \) (EtOAc–hexanes, 1:1); IR (CH\(_2\)Cl\(_2\)); 3145, 3025, 1738, 1677, 1475, 1456, 1227, 1119 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta 3.75 \) (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 6.97 (d, \( J = 9.2 \) Hz, 1H), 7.11 (d, \( J = 9.2 \) Hz, 1H), 10.44 (s, 1H); \(^{13}\)C (APT) NMR (CDCl\(_3\), 75 MHz): 52.5 (CH\(_3\)), 52.9 (CH\(_3\)), 57.2 (CH\(_3\)), 109.4 (qC), 119.4 (CH), 120.5 (CH), 124.1(qC), 148.8 (qC), 155.6 (qC), 167.4 (qC), 168.9 (qC); HRMS (Cl) calcd. for C\(_{11}\)H\(_{13}\)O\(_6\) (M+H)\(^+\): 241.0712; found: 241.0719

**General procedure for furan-benzyne Diels-Alder cycloaddition:** To a round bottom flask under an atmosphere of N\(_2\) and equipped with a reflux condenser and addition funnel was added a 2-substituted furan (1 equiv.) and THF (~0.5M). To this solution was added isoamyl nitrite (2.5 equiv.). Anthranilic acid (2 equiv.) in THF (~0.5M) was then added dropwise over a period of 20 minutes. The flask was then heated to 45-55 °C for 3 hours. The reaction mixture was then poured into EtOAc to which H\(_2\)O was added. The layers were separated and the aqueous layer extracted with EtOAc. The combined
organic extracts were washed with brine, dried over MgSO₄, and concentrated. The crude extract was then purified by flask chromatography over silica (EtOAc/hexanes mixtures).

1-Ethylxabenzonorbornadiene, (3-5g). Amber colored oil. Yield = 80% (628 mg, 3.6 mmol); R_f = 0.50 (EtOAc:hexanes = 1:4); IR (NaCl, cm⁻¹): 3065, 3008, 2972, 2937, 2879, 1463, 1453, 1364, 1289, 1144, 1082, 982, 904, 761, 735, 634 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.22 (dd, 1H, J = 1.4 & 5.8 Hz), 7.16 (d, 1H, J = 6.3 Hz), 7.04 (dd, 1H, J = 1.6, 5.4 Hz), 6.97 (dm, 2H, J = 1.2 Hz), 6.79 (d, 1H, J = 5.5 Hz), 5.66 (d, 1H, J = 1.6 Hz), 2.44-2.25 (m, 2H), 1.18 (t, 3H, J = 7.5 Hz); ¹³C NMR (APT, CDCl₃, 100MHz): δ 151.1, 150.5, 144.6, 144.4, 124.9, 124.7, 120.0, 119.2, 93.4, 81.7, 22.2, 9.0. HRMS (CI) calcd. for C₁₂H₁₂O (M⁺): 172.0888; found: 172.0884.

1-Cyclobutylxabenzonorbornadiene, 3-5n. Light yellow oil. Yield = 62% (377 mg, 1.9 mmol); R_f = 0.39 (EtOAc:hexanes = 10:90); IR (CH₂Cl₂): 3073, 2961, 1600, 1508, 1284, 1087, 1050, 988, 908, 878, 758, 734 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.26-7.23 (m, 1H), 7.15-7.13 (m, 1H), 7.08 (dd, J = 1.8, 5.5 Hz, 1H), 7.00-6.98 (m, 2H), 6.88 (d, J = 5.5 Hz, 1H), 5.72 (d, J = 5.5 Hz, 1H), 3.41 (pent, J = 8.5 Hz, 1H), 2.40-2.31 (m,
2H), 2.27-2.19 (m, 2H), 2.16-2.10 (m, 1H), 2.06-2.01 (m, 1H); $^{13}$C NMR (APT, CDCl$_3$, 100MHz): $\delta$ 151.3, 149.9, 144.8, 143.3, 124.8, 124.7, 120.0, 119.4, 94.8, 81.6, 34.1, 23.9, 23.7, 18.6. HRMS (EI) calcd. for C$_{14}$H$_{14}$O (M$^+$): 198.1045; found: 198.1041.

### 3.5 References (Chapter 3)


Chapter 4

Palladium Catalyzed Ring Opening Reactions of C1 Substituted Oxabicyclic Alkenes
4.1 Introduction

A large number of palladium catalyzed reactions have been developed with oxabicycloalkenes for preparing a wide range of organic templates. The ring opening reactions using carbon as well as heteroatoms have been utilized successfully to create a carbon frameworks with multiple stereocenters in a single step.\(^1\) Palladium catalyzed stereoselective reactions have been developed for opening oxabicyclic alkene 4-1 with aryl triflates,\(^2\) aryl iodides,\(^3\) dialkylzinc reagents,\(^4\) aryl boronic acids\(^5\) and organozinc halides (Scheme 4.1).\(^6\) Most of these reactions proceed under very mild conditions, providing products with excellent enantio- and diastereoselectivities when in the presence of chiral ligands.

Scheme 4.1 Palladium catalyzed ring opening reactions of oxabicyclic alkenes.

For the present work, we selected arylative ring opening reactions on oxabicyclic alkenes leading to the formation of highly substituted, 1,2-dihydronaphthyl derivatives. The dihydronaphthalene skeleton is found in naturally occurring compounds that exhibit
an array of diverse biological activities.\textsuperscript{7} Arylative openings of oxabicyclic alkenes are accomplished with many transition metals like rhodium, nickel and copper in addition to palladium. Except for copper, all the transition metal catalyzed additions provide \textit{cis} products \textbf{4-13}. Carretero \textit{et al.} reported Grignard reagents in combination with catalytic amount of copper (I) salts are effective for alkyllative and arylative ring opening reactions of oxabicyclic alkenes with high levels of \textit{anti} selectivity (Scheme 4.2).\textsuperscript{8}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.2.png}
\caption{Arylative ring opening reactions of oxabicyclic alkenes.}
\end{figure}

The first highly stereoselective palladium-catalyzed reactions of oxabenzonorbornadiene \textbf{4-1} with organic halides to give 2-substituted dihydronaphthol derivatives was reported by Cheng’s group.\textsuperscript{3} This catalytic reaction provided a novel method for the preparation of \textit{cis}-1,2-dihydro-1-naphthyl derivatives, which are otherwise very difficult to access. The initial asymmetric version of this reaction using palladium (0) BINAP complex and phenyl triflate (\textbf{4-6}) led to the formation of two products (Scheme 4.1).\textsuperscript{2} The ring opened product \textbf{4-7} was minor, with only 13\% yield but 96\% ee, while the major product \textbf{4-8}, arising from carbopalladation without ring-opening, was isolated in 71\% yield and 64\% ee.
Lautens’ group reported palladium catalyzed ring opening of heterobicyclic alkenes with organoboronic acids.\textsuperscript{5} The addition of a variety of aryl groups proceeded in excellent yield. The ring opening using heteroaryl groups which was found to be problematic with other catalyst systems also worked well. The chiral phosphine-containing palladacycle was shown to have high catalytic activity as well as asymmetric induction ability in ring-opening reaction of oxabicyclic alkenes with arylboronic acids. A similar reaction using aryl boronic acids was reported by Murakami and Igawa using a catalytic amount of a rhodium complex, Rh[(cod)Cl]\textsubscript{2} having P(OEt)\textsubscript{3} ligands, to form \textit{cis} 2-aryl-1,2-dihydro-1-naphthols stereoselectively in good yields.\textsuperscript{9}

The ring opening reaction of the oxabenzenorbornadiene with aryl iodides was carried out in THF in the presence of Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}, Zn, ZnCl\textsubscript{2}, and Et\textsubscript{3}N (\textbf{Scheme 4.3}).\textsuperscript{3} Both electron rich and electron deficient aromatic iodides used with symmetrical benzoanorbornadiene \textbf{4-1} to give \textit{cis}-1,2-dihydro-1-naphthol derivatives \textbf{4-5} in good to excellent yields.

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_4.3.png}
\end{center}

\textbf{Scheme 4.3 Pd catalyzed addition of organic iodides on oxabicyclic alkene.}

It was found that the presence of electron withdrawing substituent resulted in lower yield. The ring opening reactions were successful with β-iodoenone, benzyl bromide and methyl iodide form the corresponding naphthol derivatives. The
stereochemistry of all the dihydronaphthalenol derivatives obtained from the ring opening reactions were found to be cis.

Martin et al. optimized the ring opening reaction of 7-oxabenzonorbornadienes 4-14 using a combination of Pd(OAc)$_2$, PPh$_3$, Zn, and PMP in dry DMF with aryl and vinyl halides to afford the corresponding cis-2-substituted 1,2-dihydronaphthols in good to excellent yields.$^{10}$ Using this protocol, Martin’s group reported improved route to C-aryl glycosides such as 4-17 using ring opening with glycal iodide 4-15 as the key step, followed by oxidation (Scheme 4.4).

![Scheme 4.4 Pd catalyzed ring opening followed by oxidation.](image)

These reactions occurred under mild conditions with a variety of aryl halides bearing an electron withdrawing or donating groups. Oxidation of the intermediate 1,2-dihydro-1-naphthols 4-16 using IBX yielded the corresponding 2-substituted 1-naphthols 4-17 in excellent yields.

4.1.1 Mechanism of Pd Catalyzed Ring Opening Reactions with Aryl Iodides

The ring opening of bicyclic alkenes with aryl iodides has close resemblance to Heck coupling, but there are a few distinct mechanistic differences between the two due to the unique structure of bicyclic alkenes. The oxidative addition of aryl halides to form organopalladium species and insertion of an alkene into a palladium-carbon bond (carbopalladation) is similar to a typical Heck pathway. The syn elimination of a β-hydrogen cannot occur in the case of bicyclic alkenes 4-18 due to two reasons. First, the
cyclic structure of molecule puts a restriction on rotation of C-C bond which is necessary for getting the β-hydrogen in syn conformation. The second possibility is the elimination of a hydrogen from bridgehead carbon, however this would result in the formation of the unstable species 4-20 and thus is forbidden as per Bredt’s rule (Scheme 4.5). Therefore, in arylative ring opening of oxabicyclic alkenes the cleavage of C-O bond occurs instead of β-hydrogen elimination. Examples of this type of β-oxygen elimination are not very common in the literature.12

Scheme 4.5 β-Hydride elimination vs. β-oxygen elimination.

The mechanism proposed by Cheng for palladium catalyzed hydrophenylation of oxabenzonorbornadienes in the presence of Zn powder and ZnCl$_2$ is initiated by reduction of Pd (II) to Pd (0) by the zinc metal. This reduction is then followed by oxidative addition of the aryl halide to give 4-21 (Scheme 4.6).3b The aryl palladium species 4-21 undergoes an exo selective carbopalladation at the oxabicycle olefin to generate intermediate 4-22. Chelation of the olefin and the oxygen atom of the oxabicycle may help to contribute to the high exo selectivity with 4-1. The cleavage of β-oxygen results in
ring-opened intermediate 4-23 which then undergoes hydrolysis to liberate the ring-opened product 4-5 and palladium (II). The palladium (II) undergoes a reduction to Pd (0) thus continuing the catalytic cycle.

Scheme 4.6 Mechanism of ring opening reaction.

It was found that inclusion of ZnCl₂ enhances the activity of the catalyst system. Based on the mechanism two possible roles of ZnCl₂ are proposed. One possibility is that ZnCl₂ acts as a Lewis acid associated with the bridging oxygen thus facilitating β-heteroatom elimination. The other possible role is attachment of ZnCl₂ to the coordinated iodide of Pd(Ph₃P)₂ArI (4-21), thereby assisting the removal of this ligand and enhancing coordination of 4-1 to the palladium center and insertion of 4-1 into the R-Pd bond. The observed rate determining step of these catalytic reactions is the insertion of 4-1 into the
R-Pd bond, the role of ZnCl$_2$ is more likely to assist removal of iodide and to enhance the rate of the insertion.

### 4.1.2 Regioselectivity in C$^1$ Substituted Oxabicycloalkenes

As stated previously, introduction of substituents on the bridgehead carbon removes the plane of symmetry in the oxabicyclic systems. The addition of an organic group to the carbon-carbon double bond of C$^1$ substituted oxabenzonorbornadiene potentially results in the formation two possible cis-1,2-dihydro-1-naphtol products. Very few examples are reported in literature where C$^1$ carbon possessing substituents are used for ring opening reactions.

Cheng’s group reported a ring opened example of benzoxanorbornadiene in which a methyl group was attached to one of the bridgehead carbons. It was shown that the palladium catalyzed reaction of compound 4-24 with RI was highly regioselective, forming exclusively 4-28a with cis geometry (Scheme 4.7)$^{3b}$ The other regioisomer 4-28b originating from the attack of nucleophile close to methyl substituent was not detected.

![Scheme 4.7 Pd catalyzed reaction on C$^1$ substituted oxabicyclic alkene.](image)

The presence of a methyl group on a bridgehead carbon appears to block the addition of an organic group to the nearby double-bond carbon. Of the three RI tested, all organic groups added to the olefin carbon distal to the methyl group giving the
corresponding product 4-28a. However, the nickel catalyzed ring opening reaction of unsymmetrical 7-oxanorbornene 4-30 with phenyl iodide 4-10 in acetonitrile gave a mixture of the two regioisomers 4-31a and 4-31b in a 2:1 ratio in 72% total yield (Scheme 4.8). The major product 4-31a was formed from exo addition of the phenyl group to the olefin carbon distal to the bridgehead methyl group while 4-31b was formed as result of addition on olefin carbon close to C¹ methyl group.¹³ No explanation was provided to account for formation of mixture of products under Ni catalysis.

Scheme 4.8 Ni catalyzed ring opening reaction on C¹ oxabicyclic alkene.

Interestingly, in the ring opening reaction of compound 4-33 with dialkylzinc in the presence of Pd(dppf)Cl₂ the product obtained was exclusively the tertiary alcohol derivative 4-34b. The formation of 4-34b was due to addition of the alkyl group to the olefin carbon close to the bridgehead methyl group.

Scheme 4.9 Pd catalyzed reaction on C¹ oxabicyclic alkene with dialkyl zinc.
As discussed in chapter 1 (Scheme 1-67, page 52) to explain the formation of 4-34b, Lautens proposed a carboxpalladation mechanism according to which the more sterically encumbered palladium would migrate to the less hindered carbon, while the smaller alkyl group would be transferred to the carbon next to the substituted bridgehead. If a Lewis acid promoted reaction were to be taking place ionization at the tertiary center would be expected to predominate.\(^{14}\)

Murakami and Igawa reported formation of cis-4-methyl-2-phenyl-1,2-dihyronaphthalenol 4-35a by rhodium-catalyzed a nucleophilic addition of phenyl boronic acid 4-9 on compound 4-33 in excellent yield (Scheme 4.10).\(^{9}\)

![Scheme 4.10 Rh catalyzed reaction on C\(^1\) oxabicyclic alkene with boronic acid.](image)

During recent investigations by our group toward the synthesis of 1,2-naphthalene oxides, it was found that the substituents present on the oxabenzonorbornadiene determined the product formed. This was thought to be due to their ability to preferentially stabilize one intermediate over the other.\(^{15}\) The 1-methyl-7-oxabenzonorbornadiene 4-33 and 1-carboxymethyl-7-oxabenzonorbornadiene 4-36 were used to examine the effects of an unsymmetrical bicyclic alkene on this reaction.
Scheme 4.11 Mechanisms for the synthesis of 1,2-naphthalene oxides.

The opposite regioselectivity was seen in these two examples, presumably due to the electron donating nature of the methyl substituent in comparison to the electron withdrawing nature of the methyl ester 4-36. In each case, oxidative insertion of the Ru catalyst occurred into the opposite side of the C-O bond.

4.2 Optimization Study using C¹-Substituted Electron Rich and Electron Deficient Oxabicyclic Alkenes

In order to understand the impact of substituents on the C¹ carbon of oxabicyclic alkenes in the palladium catalyzed ring opening reactions, we selected two model compounds with electronically different types of substituents on the C¹ carbon. As discussed in Chapter 3, generation of benzyne from 2-aminobenzoic acid and in situ Diels–Alder reaction with 2-substituted furans provided C¹-substituted 7-oxanorbornadienes 4-36 and 4-40.

Figure 4.1 Structures of model compounds.
Compound \textbf{4-36} was substituted with an electron withdrawing ester group whereas compound \textbf{4-40} has an electron donating ethyl substituent (\textbf{Figure 4.1}). It is important to note that steric bulk of both substituents is similar. We were also interested in studying the effect of the nature of substituent on the electrophile (ArI) had on the outcome of the ring opening reaction. We selected aryl iodides possessing an electron donating and an electron withdrawing functional groups for our study. To understand the effect of sterics, the aryl groups were selected with substituents on either the \textit{ortho}, \textit{meta} or \textit{para} position with respect to iodo group.

Based on the mechanisms proposed for the ring opening reactions, the key step is carbopalladation of aryl palladium species \textbf{4-21} on the olefinic carbons of oxabicyclic alkenes. Because of the substituent on the allylic carbon, the symmetry of the olefin is lost. The question that needs to be answered is; how does this loss of symmetry impact the carbopalladation step? Does the electronic or steric bulk of C\textsuperscript{1} substituent effect the orientation of aryl palladium species (\textbf{Scheme 4.12})? Or does the nature of substituents on the aromatic ring influence the alignment of aryl palladium species during carbopalladation step? It has been reported that the electronic nature of palladium complex affects the regiochemical outcome in Heck reactions.\textsuperscript{16} When the reaction goes through a neutral palladium pathway the regiochemistry is governed by the sterics of the substrate, however, when the reaction involves cationic palladium complexes the electronic nature of the substituent is thought to influence the regiochemical outcome. The regioselectivities resulting from the cationic palladium complexes are thought to come about by an increase in the polarization of the alkene which favors the transfer of vinyl or aryl group to the site of least electron density.
Scheme 4.12 Influence of substituent on C₁ carbon during carbopalladation.

In addition to the possible inherent effect of C₁ substituent on regiochemical outcome of the reaction we were also equally curious to know the effect of external factors like the ligands and oxidation state of the palladium catalyst, additives and the reaction media (solvents) on ring opening of oxabenzenorbornadienes. Is there a possibility of preparing tertiary alcohol derivative exclusively in one conditions and secondary alcohol in other? Or in other words, is it possible to achieve reversal of selectivity? Will there be change in mode of reaction (mechanism) with changes in reaction conditions and with variations in electronics and steric in substrate and reagents? Intrigued by these questions, we set out to study the reactions of oxabicyclic alkenes as described in the following sections. Using model compounds 4-36 and 4-40 we conducted studies as discussed in the following subsections.

4.2.1 Ring Opening Reactions with Different Palladium Catalysts

To the best of our knowledge, compounds 4-36 and 4-40 have not been used in transition metal catalyzed ring opening reactions and as such we wanted to find the best palladium catalyst system for these ring openings. Cheng et al. used the catalyst PdCl₂(PPh₃)₂ whereas Martin’s group reported the use of Pd(OAc)₂/PPh₃ as the catalyst of choice.
Complicating matters is the fact that the roles of phosphines in this reaction are not clearly understood, therefore, in surveying the optimum conditions we also tested the activity of \( \text{Pd}(\text{PPh}_3)_4 \) in addition to the above catalysts. It is important to note that all of these catalysts have different steric effects and electronic properties, for example, the oxidation state of palladium in \( \text{Pd}(\text{PPh}_3)_4 \) is \( \text{Pd}(0) \) whereas it is \( \text{Pd}(II) \) in \( \text{PdCl}_2(\text{PPh}_3)_2 \) and \( \text{Pd(OAc)}_2 \).

We initially studied the reaction of 1-ethyl-7-oxabenzenorboranadiene 4-40 with 4-iodoanisole 4-45 in THF as a model reaction in the presence of zinc (10 equivalents), zinc chloride (0.5 equivalent) and triethylamine (10 equivalents) with various palladium catalysts. The ring opening reaction in the presence of \( \text{PdCl}_2(\text{PPh}_3)_2 \) formed \( \text{cis}-1,2\)-Dihydro-4-ethyl-2-(4-methoxyphenyl)-1-naphthol 4-46a exclusively in 72% yield (Scheme 4.13).

![Scheme 4.13 Pd catalyzed ring opening reaction on 4-40.](image)

The structure of 4-46a was characterized by \(^1\text{H}, \ ^{13}\text{C} \) and HRMS data. Since this compound is not reported in literature, it was further confirmed by comparing with spectral data of closely related compound 4-44 reported in the literature (Figure 4.2).\(^{3b} \)
Figure 4.2 Structure of reference compound 4-44 and structure of compound 4-96 prepared for single crystal X-ray analysis.

The presence of a multiplet at 4.85-4.99 ppm is characteristic of a methine proton H\(^1\) attached to free hydroxyl group which is not possible for structure of 4-46b. The presence of single olefin proton H\(^3\) and absence of second olefin proton peak clearly rules out the possibility of tertiary alcohol derivative 4-46b. The other regioisomer 4-46b is expected to show two olefin proton peaks. The H\(^1\) NMR peaks of 4-46a prepared from the ring opening reaction were compared with reference compound 4-44 to confirm the structure of the obtained regioisomer (Table 4.1).

**Table 4.1 Comparison H\(^1\) NMR peaks of 4-46a with reference compound 4-44.**

<table>
<thead>
<tr>
<th>Proton Assignment</th>
<th>Reference Compound 4-44</th>
<th>Obtained Compound 4-46a</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(^1)</td>
<td>4.99 (dd, J = 4.0 Hz &amp; 1.6 Hz)</td>
<td>4.85-4.89 (app t)</td>
</tr>
<tr>
<td>H(^2)</td>
<td>3.61-365 (m)</td>
<td>3.73-3.78 (m)</td>
</tr>
<tr>
<td>H(^3)</td>
<td>5.83 (dq, J = 4.2 Hz &amp; J = 1.2 Hz)</td>
<td>5.91 (d, J = 4.6 Hz)</td>
</tr>
</tbody>
</table>

Single crystal X-ray analysis of 4-96 (Figure 4.2), one of the molecules in the series of 1,2-dihyronaphthol derivatives prepared, was performed in order to confirm the relative stereochemistry (Refer appendix for X-ray result). The crystal structure results of
496 and the observed proton-proton coupling constant of ca. 5.0 Hz between H¹ and H² for the 1,2-dihydronaphthol analogues are in accordance with the values of compounds having similar structure and stereochemistry reported in the literature.¹⁷

The ring opening reaction using Pd(OAc)₂ in the presence of Ph₃P afforded 4-46a in lower yield (60%) (Table 4.2). It was found that when 1-ethyl-7-oxabenzonorboranadiene 4-40 was reacted with 4-iodoanisole in the presence of Pd(OAc)₂ naphthol derivative 4-51 (Figure 4.3) was obtained as a major side product, resulting from aromatization of 4-40 before addition of aryl iodide.

![Figure 4.3 Structure of the by-product 4-51.](image)

The ring opening reaction of 4-40 using Pd(OAc)₂ without Ph₃P did not proceed (entry 3). No reaction was observed in the absence of a Ph₃P with catalytic Pd(OAc)₂, the unreacted starting material was recovered. When 1-ethyl-7-oxabenzonorboranadiene 4-40 was treated with Pd(PPh₃)₄, the reaction was clean and the yield was improved. These results suggest the phosphine ligands on the palladium catalyst have a direct effect in the course of reaction irrespective of initial oxidatation state of palladium.
Table 4.2 Results of ring opening of 4-40 with different Pd catalysts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (4-46a)</th>
<th>4-46a : 4-46b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂(PPh₃)₂</td>
<td>72%</td>
<td>100 : 0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂, Ph₃P</td>
<td>60%</td>
<td>100 : 0</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>0ᵃ</td>
<td>0ᵃ</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh₃)₄</td>
<td>74%</td>
<td>100 : 0</td>
</tr>
</tbody>
</table>

ᵃNo reaction, starting material recovered.

Both Pd(PPh₃)₄ and PdCl₂(PPh₃)₂ gave excellent yields while the Pd(OAc)₂ in the presence of triphenylphosphine was least productive. In all the cases a secondary naphthol derivative 4-46a was obtained as single regio isomer, i.e. the addition of aryl group occurred exclusively on the olefin carbon away from the ethyl substituent on C₁ carbon. Thus, irrespective of palladium catalyst, the reactions were all highly regioselective, affording a single product in each case with cis configuration.

To increase the scope we extended the reaction of 4-iodoanisole on an electron deficient 1-methoxycarbonyl-7-oxabenzonorbornadiene 4-36. THF was used as the solvent in the model reaction in the presence of zinc, zinc chloride and triethylamine with various palladium catalysts. When 7-oxabenzonorbornadiene 4-36 containing an electron withdrawing-CO₂Me substituent on the bridgehead carbon was reacted with 4-
iodoanisole 4-45 in the presence of Pd(Ph₃P)₂Cl₂ (5 mol%) in THF at 60-65°C, the expected dihydronaphthol 4-47 was not obtained (Scheme 4.14). This seems to be a result of the dihydronaphthol 4-47 formed in this reaction undergoing rapid dehydration to form the naphthalene derivative 4-48a.

Scheme 4.14 Pd catalyzed ring opening reaction on 4-36.

The structure of 4-48a was characterized by ¹H, ¹³C and HRMS data and further confirmed by comparisons with the known molecule reported in an independent Suzuki coupling reaction as shown in Scheme 4.15.¹⁸

Scheme 4.15 Suzuki coupling protocol to prepare 4-48a.

The ¹H and ¹³C NMR of 4-48a prepared from ring opening reaction is compared with literature data in Table 4.3 and Table 4.4, respectively.
Table 4.3 Comparison H\textsuperscript{1} NMR of 4-48a with reference compound.

<table>
<thead>
<tr>
<th>Proton Assignment</th>
<th>Reference Compound</th>
<th>Obtained Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>H\textsuperscript{16}</td>
<td>3.83 (s, 3H)</td>
<td>3.83 (s, 3H)</td>
</tr>
<tr>
<td>H\textsuperscript{1}</td>
<td>3.99 (s, 3H)</td>
<td>3.97 (s, 3H)</td>
</tr>
<tr>
<td>H\textsuperscript{14, 17}</td>
<td>7.10 (d, J = 8.5 Hz, 2H)</td>
<td>7.10 (d, J = 8.7 Hz, 2H)</td>
</tr>
<tr>
<td>H\textsuperscript{6, 7}</td>
<td>7.56-7.70 (m, 2H)</td>
<td>7.56-7.70 (m, 2H)</td>
</tr>
<tr>
<td>H\textsuperscript{13, 18}</td>
<td>7.79 (d, J = 8.5 Hz, 2H)</td>
<td>7.80 (d, J = 8.6 Hz, 2H)</td>
</tr>
<tr>
<td>H\textsuperscript{8}</td>
<td>8.09 (d, J = 6.7 Hz, 1H)</td>
<td>8.08 (d, J = 2.1 Hz, 1H)</td>
</tr>
<tr>
<td>H\textsuperscript{19, 10}</td>
<td>8.41 (m, 2H)</td>
<td>8.41 (m, 2H)</td>
</tr>
<tr>
<td>H\textsuperscript{5}</td>
<td>8.71 (d, J = 7.6 Hz, 1H)</td>
<td>8.70 (d, J = 9.6 Hz, 1H)</td>
</tr>
</tbody>
</table>

Table 4.4 Comparison C\textsuperscript{13} NMR of 4-48a with reference compound.

<table>
<thead>
<tr>
<th>C\textsuperscript{13} Assignment</th>
<th>Reference Compound</th>
<th>Obtained Compound</th>
<th>C\textsuperscript{13} Assignment</th>
<th>Reference Compound</th>
<th>Obtained Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\textsuperscript{1}</td>
<td>52.30 (CH\textsubscript{3})</td>
<td>52.37 (CH\textsubscript{3})</td>
<td>C\textsuperscript{8}</td>
<td>128.94 (CH)</td>
<td>128.98 (CH)</td>
</tr>
<tr>
<td>C\textsuperscript{16}</td>
<td>55.23 (CH\textsubscript{3})</td>
<td>55.25 (CH\textsubscript{3})</td>
<td>C\textsuperscript{4}</td>
<td>129.15 (qC)</td>
<td>129.14 (qC)</td>
</tr>
<tr>
<td>C\textsuperscript{14, 17}</td>
<td>114.59 (CH)</td>
<td>114.60 (CH)</td>
<td>C\textsuperscript{19}</td>
<td>129.41 (CH)</td>
<td>129.46 (CH)</td>
</tr>
<tr>
<td>C\textsuperscript{3}</td>
<td>124.96 (CH)</td>
<td>124.97 (CH)</td>
<td>C\textsuperscript{12}</td>
<td>131.05 (qC)</td>
<td>131.03 (qC)</td>
</tr>
<tr>
<td>C\textsuperscript{7}</td>
<td>126.71 (CH)</td>
<td>126.76 (CH)</td>
<td>C\textsuperscript{9}</td>
<td>134.02 (qC)</td>
<td>134.03 (qC)</td>
</tr>
<tr>
<td>C\textsuperscript{3}</td>
<td>127.18 (qC)</td>
<td>127.53 (qC)</td>
<td>C\textsuperscript{11}</td>
<td>135.99 (qC)</td>
<td>135.98 (qC)</td>
</tr>
<tr>
<td>C\textsuperscript{6}</td>
<td>127.54 (CH)</td>
<td>127.59 (CH)</td>
<td>C\textsuperscript{15}</td>
<td>159.34 (qC)</td>
<td>159.34 (qC)</td>
</tr>
<tr>
<td>C\textsuperscript{13,18}</td>
<td>128.08 (CH)</td>
<td>128.11 (CH)</td>
<td>C\textsuperscript{2}</td>
<td>167.27 (qC)</td>
<td>167.30 (qC)</td>
</tr>
<tr>
<td>C\textsuperscript{10}</td>
<td>128.42 (CH)</td>
<td>128.44 (CH)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The electron deficient, 1-methoxycarbonyl-7-oxabenzonorboranadiene was treated with 4-iodoanisole in the presence of Pd(PPh₃)₄ in THF to form compound 4-48a in 74% yield. The results are presented in Table 4.5. The same reaction with Pd(OAc)₂ afforded a lower yield (54%). In all the cases the reaction proceeded regioselectively as a result of addition of the aryl group onto the olefin carbon away from –CO₂Me group to form 3-(4-methoxyphenyl)-naphthalene-1-carboxylic acid methyl ester 4-48a exclusively. The other regio isomer 4-48b was not obtained.

Based on the results obtained from catalyst screening, it appears that both PdCl₂(PPh₃)₂ and Pd(PPh₃)₄ gave good results. The most active palladium complex for this reaction appears to be PdCl₂(PPh₃)₂, furnishing 4-48a in 85% yield. The ring opening reactions in Pd(OAc)₂ gave poor results for both electron rich and electron deficient substrates. In all cases, the palladium catalyzed ring opening occurred regioselectively affording a single product as result of addition of aryl group on olefin carbon distal to C¹ substituent.

**Table 4.5 Results of ring opening of 4-36 with different Pd catalysts.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield</th>
<th>4-48a : 4-48b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂(PPh₃)₂</td>
<td>85%</td>
<td>100 : 0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₄</td>
<td>74%</td>
<td>100 : 0</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>54%</td>
<td>100 : 0</td>
</tr>
</tbody>
</table>
Comparison of the reaction between 4-iodoanisole and an electron deficient or electron rich oxabicycle reveals the yields obtained from 1-methoxycarbonyl-7-oxabenzonorboranadiene are slightly better. This is not surprising based on the literature available for the Heck reaction where alkenes bearing an electron withdrawing groups are known to be most reactive for insertion.

4.2.2 Ring Opening Reactions in Different Solvents

The choice of solvent is vital to many catalytic reactions. In some cases, changes in solvent polarities can have a dramatic effect on the activity of one catalytic species in competition with another resulting in a complete selectivity reversal.\(^\text{19}\) Polar solvents usually have a greater basicity and nucleophilicity than non-polar solvents. Thus, there might be coordination of the polar donor solvent to the palladium species in the transition state. For example, the nickel catalyzed reaction of oxabicyclic alkenes with aryl iodides worked only in acetonitrile while in other solvents such as toluene, dichloromethane, methanol, DMF, and DMSO, the reaction yielded no product.

The lack of catalytic activity in toluene and dichloromethane was attributed to ready decomposition of the Ni(0) catalyst in these essentially non-coordinating solvents. The lack of reaction in methanol was due to the fact that the Ni(0) catalyst is protonated by methanol to yield undesirable by-products \(^\text{4-52}\) as result of reductive ring opening (Figure 4.4).

In solvents such as DMF and DMSO which are strongly coordinating, the bicyclic alkene is unable to effectively compete with solvent molecules for coordination to the nickel center, precluding the addition reaction. It is interesting to note that for the
same addition reaction catalyzed by PdCl$_2$(PPh$_3$)$_2$ and zinc metal, THF was found to be the best solvent.

![Structures of the by-products 4-52 and 4-53.](image)

**Figure 4.4 Structures of the by-products 4-52 and 4-53.**

To understand the effect of solvent on the present catalytic reactions we carried out the reaction of 4-iodoanisole with model compounds 4-36 and 4-40 in the presence of Pd(PPh$_3$)$_2$Cl$_2$ in various solvents as shown in Table 4.6 and Table 4.7.
Table 4.6 Results of ring opening of an electron deficient C¹ benzoxanorbornadiene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>41% a</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>80%</td>
</tr>
<tr>
<td>4</td>
<td>Acetonitrile</td>
<td>68%</td>
</tr>
<tr>
<td>5</td>
<td>Hexane</td>
<td>9%</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>71%</td>
</tr>
<tr>
<td>7</td>
<td>Dichloroethane</td>
<td>75%</td>
</tr>
</tbody>
</table>

\*16% of ethyl ester 4-53 was formed due to transesterification with ethanol

The solvents chosen were polar aprotic, polar protic and non-polar solvents. The ring opening of C¹-methoxy ester-oxabenzonorboranadiene 4-40 with 4-iodoanisole, in the presence of PdCl₂(PPh₃)₂ gave the best yields in polar aprotic solvents. The reaction in THF afforded 85% yield while in DMF it was 80%. The ring opening reaction in acetonitrile gave 68% yield (entry 4).

The results were reasonable in non-polar solvents, like toluene (71%) and dichloroethane (75%). However, the reaction in hexanes did not proceed as well providing a yield of only 9% (entry 5). The reaction of C¹-methoxy ester-oxabenzonorbornadiene 4-36 in polar protic solvent (ethanol) gave a moderate yield (41%). Part of the product loss was due to transesterification with solvent ethanol to form.
ethyl ester derivative of naphthalene 4-53 in 16% yield (Figure 4.4). This product was separated by column chromatography and fully analyzed by NMR and HRMS.

**Table 4.7 Results of ring opening of an electron rich C\(^1\) substituted benzoxanorbornadiene.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>88%</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>95%</td>
</tr>
<tr>
<td>4</td>
<td>ACN</td>
<td>63%</td>
</tr>
<tr>
<td>5</td>
<td>Hexane</td>
<td>19%</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>54%</td>
</tr>
<tr>
<td>7</td>
<td>Dichloroethane</td>
<td>55%</td>
</tr>
</tbody>
</table>

Similarly, the ring opening of 1-ethyl-7-oxa-benzonorbornadiene 4-40 with 4-iodoanisole in the presence of Pd(PPh\(_3\))\(_2\)Cl\(_2\) gave the best yields in polar aprotic solvents. The reaction in THF afforded 72% yield while in DMF it was 95%. The same reaction in acetonitrile gave 63% yield (entry 4). However, the yields were moderate in non-polar solvents, the reaction in toluene and dichloroethane gave 54% and 55% yield respectively. The reaction in hexanes afforded moderate yield of 19% (entry 5). The
reaction of 1-ethyl-7-oxa-benzonorbornadiene 4-40 in polar protic solvent (ethanol) also gave good yield (88%).

4.2.3 Ring Opening Reactions in the Presence of Different Lewis Acids

Based on the results of catalyst and solvent screening for both the electron rich and an electron deficient oxabicyclic systems, Pd(PPh₃)₂Cl₂ in DMF was selected as the best combination for optimum yield of the ring opened product. Interestingly, zinc chloride, a Lewis acid, was found to enhance the reaction rate. This effect has been previously reported in the literature; in one such example it was reported that the ring opening of oxabenzonorbonadiene 4-54 with 4-iodotoluene afforded 57% yield of ring opened product after 22 hours of reaction in the absence of ZnCl₂, while the inclusion of ZnCl₂ resulted in quicker reaction rate (9 hours) and improved yield (85%) (Scheme 4.16).

Unfortunately the use of the ZnCl₂ additive alone proved problematic as the starting material 4-54 was prone to isomerization into the 1-naphthol 4-56 when under these condition. This problem was overcome however, through the use of excess Et₃N as it appears to suppress the Lewis acidity of ZnCl₂ thus inhibiting the formation of the isomerized product.
To further optimize the palladium-catalyzed ring opening reaction of 4-36 and 4-40 with 4-iodoanisole the effect of Lewis acid on the product outcome was investigated. We were also curious to see how the regiochemical outcome was affected by the presence of different Lewis acids. To investigate this, the reaction of 1-methoxycarbonyl-7-oxabenzonorbornadiene with 4-iodoanisole in the presence of Zn, Et$_3$N and Pd(PPh$_3$)$_2$Cl$_2$ in DMF was conducted using wide range of Lewis acids (0.5 equivalent).

The comparison of screening data of different Lewis acids with result of reaction in the presence of standard zinc chloride (85%) reveals no dramatic impact on the yield with 1-methoxycarbonyl-7-oxabenzonorbornadiene.

Table 4.8 Results of ring opening of an electron deficient C$^1$benzoxanorbornadiene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZnCl$_2$</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>FeCl$_3$</td>
<td>59%</td>
</tr>
<tr>
<td>3</td>
<td>AlCl$_3$</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>ZnI$_2$</td>
<td>70%</td>
</tr>
<tr>
<td>5</td>
<td>CuCl$_2$</td>
<td>86%</td>
</tr>
<tr>
<td>6</td>
<td>ZrCl$_4$</td>
<td>74%</td>
</tr>
</tbody>
</table>
The best result was achieved with copper chloride (86%) while aluminum chloride (78%) was second best. The reaction with zinc iodide (70%) and zirconium chloride (74%) gave moderate yields (entry 4 & 6). The reaction in the presence of iron chloride afforded the least yield (59%).

The reaction of an electron rich 1-ethyl-7-oxabenzenonorbornadiene 4-40 with 4-iodoanisole in the presence of Pd(PPh₃)₂Cl₂ in DMF was done at 60 °C using a wide range of Lewis acids (0.5 equivalent). The comparison of results of different Lewis acids with result of ring opening reaction in presence of zinc chloride (95%) reveals a big impact on the yield with 1-ethyl-7-oxabenzenonorbornadiene (Table 4.9). Among all the Lewis acids screened, zinc iodide gave the best result (78%), though it is comparatively much lower with respect to zinc chloride.

**Table 4.9 Results of ring opening of 4-40 in the presence of different Lewis acids.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Yield of 4-46a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZnCl₂</td>
<td>95%</td>
</tr>
<tr>
<td>2</td>
<td>ZrCl₄</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃</td>
<td>58%</td>
</tr>
<tr>
<td>4</td>
<td>ZnI₂</td>
<td>78%</td>
</tr>
<tr>
<td>5</td>
<td>FeCl₃</td>
<td>66%</td>
</tr>
<tr>
<td>6</td>
<td>CuCl₂</td>
<td>67%*</td>
</tr>
</tbody>
</table>

* Entry 6, the product appears to be the mixture of cis-trans isomers 4-46a and 4-46a’*
The reaction with copper chloride, which afforded a slightly higher yield compared to zinc chloride when using an electron deficient oxabicycle, gave a moderate yield (67%) with an electron rich oxabicycle (entry 6). However, the product obtained from the reaction of 4-40 in the presence of copper chloride appears to be mixture of cis-trans isomer of 4-46a and 4-46a’. Though the formation of the trans product in the presence of copper salt was not expected it is not surprising considering the literature precedent of copper catalyzed ring opening reaction which afford the trans product as the major.  \(^8\)

The ring opening reaction in the presence of iron chloride afforded a moderate yield (66%) while the yield from aluminum chloride was the lowest (58%). The reaction in the presence of zirconium chloride resulted in aromatization of 1-ethyl-7-oxabenzonorbornadiene to naphthalene derivative along with some unidentifiable by-product.

4.3 Ring Opening of C\(^1\) Substituted Oxabicyclic Alkenes with Different Aryl Iodides

The electronic effect exerted by the substituent on the aromatic ring has been reported to effect the regioselectivity during Heck reaction of aryl iodides using Pd(OAc)\(_2\) as a catalyst. \(^20\) A series of commercially available electron-rich and electron-deficient aryl iodides were screened. The effect of a substituent in either the ortho, para or meta position with respect to iodo group in the phenyl ring was also studied, thus covering both electronic and steric effect of the reaction.

The results of reaction of 1-carbomethoxy-7-oxabenzonorbornadiene 4-36 in the presence of Zn, Et\(_3\)N and Pd(PPh\(_3\))\(_2\)Cl\(_2\) in DMF at 60 °C with different aryl iodides are summarized in Table 4.10.
Table 4.10 Results of ring opening of 4-36 with different aryl iodides.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ar-I</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-36</td>
<td>4-I</td>
<td>4-45</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-48a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-36</td>
<td>4-I</td>
<td>4-66</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-57</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4-36</td>
<td>4-I</td>
<td>4-67</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4-58</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4-36</td>
<td>4-I</td>
<td>4-68</td>
<td>17%</td>
</tr>
<tr>
<td>Entry</td>
<td>Substrate</td>
<td>Ar-I</td>
<td>Product</td>
<td>Yield</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>5</td>
<td>4-36</td>
<td>4-69</td>
<td>4-59</td>
<td>14%</td>
</tr>
<tr>
<td>6</td>
<td>4-36</td>
<td>4-70</td>
<td>4-60</td>
<td>11%</td>
</tr>
<tr>
<td>7</td>
<td>4-36</td>
<td>4-71</td>
<td>4-61</td>
<td>71%</td>
</tr>
<tr>
<td>8</td>
<td>4-36</td>
<td>4-72</td>
<td>4-62</td>
<td>68%</td>
</tr>
<tr>
<td>9</td>
<td>4-36</td>
<td>4-73</td>
<td>4-63</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>Substrate</td>
<td>Ar-I</td>
<td>Product</td>
<td>Yield</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>10</td>
<td>4-36</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td>68%</td>
</tr>
</tbody>
</table>

From the data it is clear that the presence of an electron donating groups like methyl or methoxy on the aromatic ring are favorable for ring opening reactions. In fact, the highest yield (85%) was obtained when the methoxy group was present on the para position (entry 1). The presence of the methoxy group in the meta position gave slightly lower yield (80%) but the 2-iodoanisole gave the least yield (77%) in the series with methoxy substituted aryl iodides. This trend is most likely due to increased steric hindrance near the reactive site.

In the series of methyl substituted aryl iodides the highest yield was obtained with 2-iodotoluene (73%) followed closely by 4-iodotoluene (71%). This trend in the ring opening of an electron deficient oxabicyclic alkene suggests the steric bulk of methyl substituent was less dominating than the electronic effect. The ring opening reaction with 3-iodotoluene afforded the lowest yield (68%) in iodotoluene series (entry 8). This trend was further confirmed by the reaction of iodobenzene with 1-carbomethoxy-7-oxabenzonorbornadiene which afforded 68% of 4-65 (entry 10). Thus an electron donating group in para and ortho position favors ring opening more effectively than in meta position.
It is well known that an electron withdrawing substituent on the aryl halide enhances the rate of oxidative addition from the substrate to the Pd atom. However we found the reaction of iodo nitrobenzene with 1-carbomethoxy-7-oxabenzonorbornadiene (4-36) to be sluggish affording very low yields of corresponding naphthalene derivatives along with an unidentified mixture of products. The presence of electron withdrawing groups decreased the efficiency of the catalytic cycle toward the ring opening reactions. Among the nitro series, the best yield was obtained with \( p \)-iodo nitrobenzene (17%) followed by \( meta \) derivative 4-69. The reaction of 2-iodonitrobenzene gave the lowest yield of 4-61, possibly as result of both electronic and steric disfavor.

Irrespective of the nature and position of the substituent, the ring opening reactions of 1-carbomethoxy-7-oxabenzonorbornadiene were found to be highly regioselective, affording naphthalene derivatives through the dehydration of corresponding 1,2-dihydronaphthalenols.

The results of the reaction of 1-ethyl-7-oxabenzonorbornadiene 4-40 in the presence of Zn, ZnCl\(_2\), Et\(_3\)N and Pd(PPh\(_3\))\(_2\)Cl\(_2\) in DMF at 60 °C with different aryl iodides are summarized in Table 4.11. Again, from the data it is quite apparent that the presence of an electron donating groups like methyl or methoxy on the aromatic ring was favorable for the ring opening reaction. In fact the highest yield (95%) was obtained when the methoxy group was present on the \( para \) position (entry 1). The presence of the methoxy group in the \( ortho \) position 4-67 gave a slightly lower yield (91%) but 3-iodoanisole gave the least yield (80%) of 4-75 in the series with methoxy substituted aryl iodides. This trend in the ring opening of the electron rich oxabicyclic alkenes suggests that the steric bulk of the methoxy substituent was less dominating then the electronic effect.
In the series of methyl substituted aryl iodides, the highest yield obtained was with 3-iodotoluene (95%) followed closely by 4-iodotoluene (93%). The ring opening reaction with 2-iodotoluene (4-73) afforded the lowest yield (88%) in iodotoluene series (entry 9). This trend in the ring opening of ethyl substituted oxabicyclic alkenes indicates the methyl substituent in ortho position was increasing the steric bulk at the reactive site. However, the reaction of iodobenzene with 1-ethyl-7-oxabenzonorbornadiene 4-40 afforded only 75% of the 1,2-dihydronapthol derivative 4-83. This imply that the electron donating groups on the aromatic ring favor ring opening of oxabicyclic alkenes to produce 4-substituted-1,2-dihydro naphthalenol derivatives.

Table 4.11 Results of ring opening of 4-40 with different aryl iodides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ar-I</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-40</td>
<td></td>
<td>4-45</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>4-46a</td>
<td></td>
<td>4-46a</td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>Substrate</td>
<td>Ar-I</td>
<td>Product</td>
<td>Yield</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>2</td>
<td>4-40</td>
<td><img src="image1" alt="Substrate" /></td>
<td><img src="image2" alt="Product" /></td>
<td>80%</td>
</tr>
<tr>
<td>3</td>
<td>4-40</td>
<td><img src="image3" alt="Substrate" /></td>
<td><img src="image4" alt="Product" /></td>
<td>91%</td>
</tr>
<tr>
<td>4</td>
<td>4-40</td>
<td><img src="image5" alt="Substrate" /></td>
<td><img src="image6" alt="Product" /></td>
<td>61%</td>
</tr>
<tr>
<td>5</td>
<td>4-40</td>
<td><img src="image7" alt="Substrate" /></td>
<td><img src="image8" alt="Product" /></td>
<td>30%</td>
</tr>
<tr>
<td>6</td>
<td>4-40</td>
<td><img src="image9" alt="Substrate" /></td>
<td><img src="image10" alt="Product" /></td>
<td>0%</td>
</tr>
</tbody>
</table>
The reaction of iodonitrobenzenes with 1-ethyl-7-oxabenzonorbornadiene 4-40 in the presence of Zn, Et₃N and Pd(PPh₃)₂Cl₂ in DMF at 60 °C did not afford the expected 1,2-dihyronaphthalenol derivatives. It appears that the presence of the strong electron withdrawing nitro group triggers the dehydration of the intermediate naphthalenol to
form corresponding 2-arylated naphthalenol derivative. The spontaneous dehydration appears to be feasible irrespective of position of nitro group in iodo nitrobenzene.

Just like with an electron deficient oxabicycle, the ring opening reaction with iodo nitrobenzenes and 1-ethyl-7-oxabenzonorbornadiene 4-40 provided low yields of corresponding naphthalene derivatives along with an unidentified mixture of products. Among the nitro series, the best yield was obtained with p-iodonitrobenzene (60%) followed by the meta derivative (30%). However, no product was obtained (entry 6) in the reaction of 2-iodonitrobenzene on ethyl substituted oxabicycle possibly due to unfavorable electronic and steric effects of the nitro group in the aromatic ring. Thus, the electronic nature of the substituent dictates the product outcome of arylative ring opening of an electron rich oxabicycle.

The electron withdrawing functional group, irrespective of its position on the aromatic ring, led to the formation of 2-aryl naphthalenes while the unsubstituted or electron donating functional group containing aryl ring yielded 1,2-dihydronaphthalenols. Irrespective of the nature and position of the substituent, the ring opening reactions of 1-ethyl-7-oxabenzonorbornadiene were found to be highly regioselective forming a single product as a result of addition of the aryl group to the olefin carbon away from C1 substituent.

4.4 Ring Opening C1-Substituted Oxabicyclic Alkenes with different Halobenzenes

Aryl iodides have been used in the literature on ring opening reactions of oxabicyclic alkenes but there are few reported examples of reactions that succeeded with aryl bromides as well. For most of this work we used aryl iodides but we were interested in seeing the reactivity of other aryl halides using the conditions optimized in our labs on
C\textsuperscript{1} substituted oxabenzonorbornadienes. The results of the reaction of 1-carbomethoxy-7-oxabenzonorbornadiene 5-36 in the presence of Zn, Et\textsubscript{3}N and Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} in DMF at 60°C with different halobenzenes are summarized in Table 4.12.

**Table 4.12 Results of ring opening of 4-36 with different aryl halides.**

<table>
<thead>
<tr>
<th>#</th>
<th>Substrate</th>
<th>Ph-X</th>
<th>Product A</th>
<th>Product B</th>
<th>Ratio A:B</th>
<th>Combined Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-36</td>
<td>I</td>
<td>4-74</td>
<td>Not Formed</td>
<td>100:0</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-36</td>
<td>Br</td>
<td>4-84</td>
<td>4-65</td>
<td>80:20</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4-36</td>
<td>Cl</td>
<td>4-86</td>
<td>Not Formed</td>
<td>0:100</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4-36
The reaction of iodobenzene with oxabicyclic alkenes afforded 3-phenylnaphthalene 4-65 in 68% yield, while the reaction with bromobenzene yielded an inseparable mixture of products as result of ring opening with aryl addition (2,4-disubstituted naphthalene 4-65) as well as aromatized product (2-substituted naphthalene 4-85) without aryl addition (entry 2). Due to lower reactivity of bromobenzene, the competitive isomerization of oxabicyclic alkene also occurs (without aryl addition) and the obtained product undergoing spontaneous dehydration to form 2-substituted naphthalene derivatives. Based on $^1$H NMR the major product (80%) in the reaction of bromobenzene with oxabicycle was the arylated ring opened product (2,4-disubstituted naphthalene), while the minor (20%) corresponded to the isomerized, 2-substituted naphthalene derivative. This observation indicates that the oxidative addition of bromobenzene with palladium is slower than aromatization of 4-36 to form naphthalene derivative. Overall, the combined yield of both products was 55%.

The ring opening of 1-carbethoxy-7-oxabenzonorbornadiene using chlorobenzene resulted in exclusive formation of the 1-substituted naphthalene derivative 4-85 in 65% yield as a result of isomerization of 4-36. The oxabicycle is thought to undergo isomerization followed by elimination of water thus forming the naphthalene derivative.

The results of the reaction of 1-ethyl-7-oxabenzonorbornadiene (4-40) in the presence of Zn, Et$_3$N and Pd(PPh$_3$)$_2$Cl$_2$ in DMF with different halobenzenes is summarized in Table 4.13. The reaction of iodobenzene with oxabicyclic alkene gives 3-phenyl-1,2-dihydronaphthol derivative 4-83 in 75% yield, while the reaction with bromobenzene yields a mixture of products as a result of ring opening with aryl addition.
4-83 as well as ring opening without aryl addition 4-51. As a result of the lower reactivity of bromobenzene, the competitive opening of oxabicycle occurs without aryl addition, with subsequent aromatization to form 5-substituted naphthalenol derivative 4-51. Based on $^1$H NMR, the major product (80%) in the reaction of bromobenzene with oxabicycle was the 2-phenyl ring opened product while the minor (20%) corresponds to the non-arylated naphthalenol derivative as result of aromatization (entry 2). Overall, the combined yield of both products was 53%.

**Table 4.13 Results of Ring opening of 4-40 with different aryl halides**

<table>
<thead>
<tr>
<th>#</th>
<th>Substrate</th>
<th>Ph-X</th>
<th>Product A</th>
<th>Product B</th>
<th>Ratio A:B</th>
<th>Combined Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-40</td>
<td></td>
<td>4-74</td>
<td>Not Formed</td>
<td>100:0</td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td>4-40</td>
<td></td>
<td>4-83</td>
<td>4-51</td>
<td>80:20</td>
<td>53%</td>
</tr>
</tbody>
</table>
The ring opening of 1-ethyl-7-oxabenzonorbornadiene using chlorobenzene resulted in exclusive formation of naphthalenol derivative 4-51 in 61% yield. The oxabicycle is thought to undergo ring opening followed by aromatization to form the naphthalenol derivative. Thus, when an electron withdrawing substituent was not present in the molecule, dehydration of the ring opened product does not occur. It is henceforth safe to conclude that dehydration of the ring opened product is not due reaction conditions, but rather, can be attributed to the presence of an electron withdrawing functional groups in the 1,2-dihyronaphthalenol intermediates. In the absence of an electron withdrawing groups, aromatization can lead to naphthalenol derivatives.

### 4.5 Ring Opening Reactions of Various C¹ Substituted-7-Oxabenzonorbornadienes

The substrate scope of the ring opening reaction was evaluated using optimized conditions with various substituents on the bridgehead carbon. In order to understand the reactivity and regioselectivity of the ring opening reaction a wide range of C¹ substituents were selected that include both electron withdrawing and donating groups, sterically bulky groups, aromatic rings, cycloalkyl substituents and substituents with reactive
functional groups. The details on the preparation of all these C1 substituted oxabicyclic alkenes are provided in chapter 3.

The results of the reaction of 4-iodoanisole in the presence of Zn, ZnCl₂, Et₃N and Pd(PPh₃)₂Cl₂ in DMF with different 1-substituted-7-oxabenzenonorbornadienes are summarized in Table 4.14, these results are compared with standard reaction with 4-40.

**Table 4.14 Results of ring opening reaction with various C1 substituted oxabenzenonorbornadiene**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ar-I</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>4-87</td>
<td>4-45</td>
<td>4-96</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>4-40</td>
<td>4-45</td>
<td>4-46a</td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>Substrate</td>
<td>Ar-I</td>
<td>Product</td>
<td>Yield</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>------</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>3</td>
<td>4-88</td>
<td>I-</td>
<td></td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-45</td>
<td>4-97</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4-89</td>
<td>I-</td>
<td></td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-45</td>
<td>4-98</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4-90</td>
<td>I-</td>
<td></td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-45</td>
<td>4-99</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4-91</td>
<td>I-</td>
<td></td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-45</td>
<td>4-100</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4-36</td>
<td>I-</td>
<td></td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entry</td>
<td>Substrate</td>
<td>Ar-I</td>
<td>Product</td>
<td>Yield</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>8</td>
<td><img src="4-92" alt="Image" /></td>
<td><img src="4-45" alt="Image" /></td>
<td><img src="4-101" alt="Image" /></td>
<td>27%</td>
</tr>
<tr>
<td>9</td>
<td><img src="4-93" alt="Image" /></td>
<td><img src="4-45" alt="Image" /></td>
<td><img src="4-102" alt="Image" /></td>
<td>19%</td>
</tr>
<tr>
<td>10</td>
<td><img src="4-94" alt="Image" /></td>
<td><img src="4-45" alt="Image" /></td>
<td><img src="4-103" alt="Image" /></td>
<td>65%</td>
</tr>
</tbody>
</table>

The ring opening with 1-methyl-7-oxabenzonorbornadiene with 4-iodoanisole afforded the corresponding *cis*-1,2-dihydronaphthalenol 4-96 in 85% yield. This was slightly lower than the yield with ethyl substituent (95%) however, with the sterically crowded *t*-butyl substituent on C¹ carbon of bicyclic alkene 4-88, the yield of ring opened
product 4-97 was only 54%. This is not surprising considering the fact that steric bulk of t-butyl can interfere with palladium complex during bond making step of the catalytic cycle.

Similarly, when the cyclobutyl substituent was present at C\textsuperscript{1} position of alkene 4-94, the ring opened product was obtained in 65% yield. However, when the hydroxymethyl substituted oxabicycle 4-90 was subjected to ring opening conditions with 4-iodoanisole the resulting cis-1,2-dihydronaphthol derivative 4-99 was obtained in only 43% yield. The free hydroxyl functional group of 4-90 may be chelating with the active palladium species, thus affecting the progress of ring opening reaction. The ring opening reaction of the sterically bulky biphenyl substituent on oxabicyclic alkene 4-93 afforded the corresponding cis-1,2-dihydronaphthol derivative 4-102 in only 19% yield.

When an electron withdrawing substituent was introduced at the C\textsuperscript{1} position, the ring opening reaction with 4-iodoanisole resulted in the formation of the naphthalene analogue via dehydration of 1,2-dihydronaphthol intermediate. As we have seen in several instances, when 1-carbomethoxy-7-oxabenzonorbornadiene was treated with 4-iodoanisole in the presence of Zn, Et\textsubscript{3}N and Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} in DMF at 60 °C, it afforded the corresponding 2,4-disubstituted naphthalene derivative in 80-90% yield. Similarly when C\textsuperscript{1} carbon was substituted with –COCH\textsubscript{3}, CONH\textsubscript{2} was subjected to arylative ring opening with 4-iodoanisole, the corresponding disubstituted naphthalene analogues were obtained. However the yields of this reaction were very low, probably due to instability of 4-91 and 4-92 which undergo retro-Diels-Alder reactions under the reaction conditions. The ring
opening reaction of trimethylsilyl substituted oxabicyclic alkene 4-89 afforded a moderate yield (62%) of corresponding disubstituted naphthalene derivative 4-98.

4.6 Ring Opening Reactions of Various C¹-Substituted-7-Oxanorbornadienes

The arylative ring-opening strategy was further applied to non-aromatic C¹ substituted bicyclic systems. Even though several reactions are reported in literature on ring opening reactions of benzoxanorbornadienes, only one example was reported where 7-oxanorbornadiene 4-104 was reacted with p-iodotoluene 4-71 in the presence of palladium catalyst (Scheme 4.17).³b Stoichiometrically, this product may be considered to result from addition of the aryl group to the unsubstituted double bond of 4-104, followed by dehydration to give the unsymmetrical biaryl derivative 4-105. It was reported that due to the tendency of oxanorbornadienes derivatives to undergo retro-Diels-Alder reactions under the reaction conditions the yield was low (37%).

![Scheme 4.17 Pd catalyzed ring opening of 4-104 with p-iodotoluene.](image)

To the best of our knowledge, there are no reports of the ring opening reaction of C¹ substituted oxanorbornadiene derivatives. In order to understand the reactivity and regioselectivity of the ring opening reaction, a wide range of C¹ substituents were selected; electron withdrawing and donating groups, sterically bulky groups, aromatic rings, and substituents with reactive functional groups. The details on the preparation of all these C¹ substituted oxabicyclic alkenes are provided in chapter 3.
The ring opening with 1-methyl-7-oxanorbornadiene (4-106) with 4-iodoanisole afforded dimethyl 4′-methoxy-1, 1′-biphenyl-5-methyl-3, 4-dicarboxylate (4-108a) in 72% yield (Scheme 4.18). The formation of highly substituted unsymmetrical biaryl derivative occurs as result of addition of aryl group to unsubstituted double bond of 4-106, followed by dehydration of intermediate 4-107.

Scheme 4.18 Regioselectivity in Pd catalyzed ring opening reaction of 4-106.

The structure of 4-108a was characterized by \(^1\)H, \(^{13}\)C and HRMS data. We prepared a series of biaryl derivatives using this procedure. None of the molecules prepared by ring opening of 1-substituted-7-oxanorbornadienes with 4-iodoanisole are reported in the literature, therefore, the structure was confirmed through comparison with the closely related molecule (4-128)\(^{28}\) whose independent synthesis is shown in Scheme 4.19.
Scheme 4.19 Synthesis of biaryl derivatives using cross enyne metathesis protocol.

The H\textsuperscript{1} NMR peaks of 4-108\textsubscript{a} prepared from the ring opening reaction is compared with the reference compound 4-128 to confirm the structure of obtained regio isomer (Table 4.15). The presence of characteristic doublets at 7.58 and 8.00 ppm with small 1.8 to 2.0 Hz coupling typical of meta protons confirms the structure of regio isomer 4-108\textsubscript{a}. The other regio isomer 4-108\textsubscript{b} would have large coupling constant due to the presence of H\textsuperscript{a} and H\textsuperscript{b} proton ortho to each other.

**Table 4.15 Comparison H\textsuperscript{1} NMR peaks of 4-108\textsubscript{a} with reference compound 4-128.**

<table>
<thead>
<tr>
<th>Proton Assignment</th>
<th>Reference Compound 4-128</th>
<th>Obtained Compound 4-108\textsubscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>H\textsuperscript{a} and H\textsuperscript{c}</td>
<td>7.58 (d, J = 2.0 Hz, 1H)</td>
<td>7.59 (d, J = 1.8 Hz, 1H)</td>
</tr>
<tr>
<td></td>
<td>8.02 (d, J = 2.0 Hz, 1H)</td>
<td>8.00 (d, J = 1.8 Hz, 1H)</td>
</tr>
</tbody>
</table>

The synthesis of unsymmetrical biaryls is of the utmost importance in organic synthesis in view of their numerous potential applications\textsuperscript{21} and is generally achieved by
Ullman coupling,$^{22}$ Stille reaction,$^{23}$ Suzuki coupling$^{24}$ etc. The biaryl derivatives obtained as result of ring opening contain the dicarboxylate functionalities, which are categorized as phthalic acid derivatives. It has been well known that phthalic acid derivatives are important starting materials or building blocks for the syntheses of various dyes,$^{25}$ typical resin paints,$^{26}$ various pharmaceuticals, and biologically active agents.$^{27}$ Therefore, a development of convenient synthetic approach to phthalic acid derivatives has still been the current interest.

The results of the reaction of 4-iodoanisole in the presence of Zn, ZnCl$_2$, Et$_3$N and Pd(PPh$_3$)$_2$Cl$_2$ in DMF with different 1-substituted-7-oxa-norbornadienes are summarized in Table 4.16.

**Table 4.16 Results of ring opening reaction with various C$^1$ substituted oxanorbornadienes.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ar-I</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 4-106" /></td>
<td><img src="image2" alt="Substrate 4-45" /></td>
<td><img src="image3" alt="Product 4-108" /></td>
<td>72%</td>
</tr>
<tr>
<td>Entry</td>
<td>Substrate</td>
<td>Ar-I</td>
<td>Product</td>
<td>Yield</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="4-109" /></td>
<td><img src="image" alt="4-45" /></td>
<td><img src="image" alt="4-117" /></td>
<td>69%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="4-110" /></td>
<td><img src="image" alt="4-45" /></td>
<td><img src="image" alt="4-118" /></td>
<td>19%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="4-111" /></td>
<td><img src="image" alt="4-45" /></td>
<td><img src="image" alt="4-119" /></td>
<td>64%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="4-112" /></td>
<td><img src="image" alt="4-45" /></td>
<td><img src="image" alt="4-120" /></td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="4-113" /></td>
<td><img src="image" alt="4-45" /></td>
<td><img src="image" alt="4-121" /></td>
<td>15%</td>
</tr>
<tr>
<td>Entry</td>
<td>Substrate</td>
<td>Ar-I</td>
<td>Product</td>
<td>Yield</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="4-114" /></td>
<td><img src="image" alt="4-45" /></td>
<td><img src="image" alt="4-122" /></td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="4-115" /></td>
<td><img src="image" alt="4-45" /></td>
<td><img src="image" alt="4-123" /></td>
<td>33%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="4-116" /></td>
<td><img src="image" alt="4-45" /></td>
<td><img src="image" alt="4-124" /></td>
<td>0%</td>
</tr>
</tbody>
</table>

The palladium catalyzed arylative ring opening of C\(^1\) ethyl substituted bicyclic alkene afforded corresponding biaryl derivative \(4-117\) in 69% yield, which was slightly lower compared with its methyl analogue. However, with a bulky \(t\)-butyl substituent in C\(^1\) position of oxabicycle \(4-110\), the yield dropped drastically to 19%. This can be attributed to the fact that steric bulk of tertiary butyl can interfere with palladium complex during bond making step of the catalytic cycle.
It is interesting to note that the ring opening reaction of the equally sterically crowded TMS substituted oxabicyle 4-111 provided a moderate yield (64%) of the biaryl derivative 4-119. When hydroxymethyl substituted oxabicycle 4-113 was subjected to ring opening conditions with 4-iodoanisole the resulting biaryl derivative 4-121 was obtained in only 15% yield. The free hydroxyl functional group may be chelating with active palladium species, thus affecting the progress of ring opening reaction. The ring opening reaction of the sterically bulky phenyl substituent on oxanorbornadiene 4-115 afforded the corresponding triaryl derivative 4-123 in 33% yield.

The reactions of 1-carbomethoxy-7-oxabenzonorbornadienes 4-36 provided excellent yields of ring opened 2, 4-disubstituted naphthalene derivatives but the reaction of corresponding non-aromatic bicycle 4-114 did not lead to expected biaryl derivative. The palladium catalyzed ring opening reaction of 1-carbomethoxy-7-oxanorbornadienes gave a complex mixture of products. Similarly, the reaction of 1-acetyl-7-oxanorbornadiene 4-112 did not yield the desired ring opened product. It appears that the presence of three strong electron withdrawing groups in bicyclic ring made the olefin too electron deficient to undergo arylative ring opening.

The ring opening reactions of C\(^1\) substituted oxanorbornadienes are highly regioselective irrespective of the steric bulk of the substituent at the bridgehead carbon. The product obtained is an unsymmetrical biaryl derivative as result of addition of aryl group on olefin carbon away from C\(^1\) substituent. It appears that the presence of two electron withdrawing ester groups in the oxabicycle ring triggers the dehydration of a cyclohexenol intermediate irrespective of the nature of substituent on the bridgehead carbon.
4.7 Experimental

All reactions were performed in septum-sealed, flame-dried flasks under nitrogen atmosphere. All commercial reagents were used as received from their respective suppliers. $^1$H NMR and $^{13}$C NMR spectra were recorded at 300/400 and 75/100 MHz, respectively. Chemical shifts are reported in parts per million (δ) using internal solvent signals as references and coupling constants are reported in hertz (Hz). All aryl iodides were used as received.

**General procedure for the palladium catalyzed reaction between 1-substituted- 7-oxabzenzonorbornadiene and aryl iodides:**

PdCl$_2$(PPh$_3$)$_2$ (0.018 g, 0.05 mmol), zinc powder (0.315 g, 5 mmol), 1-substituted oxabzenzonorbornadiene derivative (0.50 mmol) and zinc chloride (0.025 mmol) were weighed out in dry flask equipped with magnetic stirring bar. After the flask was sealed with a rubber septum the system was evacuated and purged with nitrogen gas three times followed by addition of solvent (3.0 mL). The flask was charged with triethylamine (4.0 mmol) and aryl halide (0.55 mmol) via a syringe through the rubber septum into the flask. The mixture was heated with stirring at 60-65 °C until the bicyclic alkene derivative was consumed as indicated by TLC analysis of the solution.

The reaction mixture was then cooled and stirred under air for 15-20 minutes at room temperature. The reaction mixture was diluted with dichloromethane (10-15 mL) and filtered through a pad of Celite™. The obtained filtrate was concentrated on a rotary evaporator to obtain a brown oily residue. The crude residue was purified by flash
chromatography, eluting with mixtures EtOAc/hexanes in the ratio given to provide the product.

Preparation of cis-1,2-Dihydro-4-methyl-2-(4-methoxyphenyl)-1-naphthol (4-96)

Yield: 85% (113 mg, 0.5 mmol). Off-white solid, Mp: 58-60 °C; Rf = 0.42 (EtOAc–hexanes, 1:4); IR (CH2Cl2); 3556, 3446, 3060, 2980, 1607, 1507, 1421, 1308, 1168, 1181 cm⁻¹; ¹H NMR (CDCl3, 300 MHz): δ 1.45 (brs, 1H, OH); 2.16 (t, J = 1.6 Hz, 3H), 3.70-3.80 (m, 4H), 4.88 (dd, J = 6.3 & 8.4 Hz, 1H), 5.87-5.93 (m, 1H), 6.81 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 7.21-7.30 (m, 2H), 7.31-7.39 (m, 3H); ¹³C (APT) NMR (CDCl3, 75 MHz): 19.1 (CH3), 46.3 (CH), 55.1 (CH3), 71.4 (CH), 113.9(CH), 123.1 (CH), 126.3 (CH), 126.7 (CH), 127.7(CH), 127.9(CH), 129.7 (qC), 130.2(CH), 132.6 (qC), 134.2 (qC), 136.8(qC), 158.8 (qC); HRMS (ESI) calcd. for C18H18O2 (M⁺): 266.1307; found: 266.1312.

Preparation of cis-1,2-Dihydro-4-ethyl-2-(4-methoxyphenyl)-1-naphthol (4-46a)

Yield: 95% (119 mg, 0.45 mmol). Off-white solid, Mp: 63-65 °C; Rf = 0.30 (EtOAc–hexanes, 1:5); IR (CH2Cl2); 3444, 2962, 2931, 1641, 1473, 1267, 1132 cm⁻¹; ¹H NMR (CDCl3, 400 MHz): δ 1.23 (t, J = 7.3 Hz, 3H), 1.45 (d, J = 8.6 Hz, 1H, OH), 2.57 (dq, J =
7.3 & 1.4 Hz, 2H), 3.73-3.78 (m, 4H), 4.85-4.89 (at, 1H), 5.91 (d, J = 4.6 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H), 7.22-7.26 (at, 1H), 7.29-7.34 (at, 1H), 7.35-7.37 (m, 2H); $^{13}$C (APT) NMR (CDCl$_3$, 100 MHz): 12.9 (CH$_3$), 25.1 (CH$_2$), 46.0 (CH), 55.2 (CH$_3$), 71.4 (CH), 114.0 (CH); 122.8 (CH); 124.7 (CH), 126.4(CH), 127.6(CH), 127.9(CH), 129.6 (qC), 130.3(CH), 133.6(qC), 137.1(qC), 138.3(qC), 158.8(qC); HRMS (ESI) calcd. for C$_{19}$H$_{20}$O$_2$Na (M+Na$^+$): 303.1360; found: 303.1364.

Preparation of cis-1,2-Dihydro-4-tert-butyl-2-(4-methoxyphenyl)-1-naphthol (4-97)
Yield: 54% (83 mg, 0.5 mmol). Light brown solid, Mp: 111-112 °C; $R_f$ = 0.31 (EtOAc–hexanes, 1:5); IR (CH$_2$Cl$_2$); 3559, 3054, 2987, 1512, 1265, 1180, 1035 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.41 (s, 9H), 1.47 (d, J = 9.1 Hz, 1H), 3.70 (t, J = 5.4 Hz, 1H), 3.75 (s, 3H), 4.76 (dd, J=8.2 & 6.0 Hz, 1H), 6.09(d, J = 4.9 Hz, 1H), 6.80 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 7.22 (dt, J=1.0 & 7.3 Hz, 1H), 7.29 (dt, J=7.8 & 1.3 Hz, 1H), 7.34(d, J=7.3 Hz, 1H), 7.72(d, J= 7.8 Hz, 1H); $^{13}$C (APT) NMR (CDCl$_3$, 100 MHz): 31.1 (CH$_3$), 35.2 (CH$_2$), 46.1 (CH), 55.2 (CH$_3$), 71.6 (CH), 114.0 (CH); 124.9 (CH); 126.2 (CH), 126.5(CH), 126.9(CH), 127.1(CH), 129.7 (qC), 130.3 (CH), 133.1 (qC), 138.5 (qC), 145.4 (qC), 158.8 (qC); HRMS (EI) calcd. for C$_{21}$H$_{24}$O$_2$ (M$^+$): 308.1776; found: 308.1172.
Preparation of \textit{cis-1,2-Dihydro-4-hydroxymethyl-2-(4-methoxyphenyl)-1-naphthol (4-99)} Yield: 43\% (61 mg, 0.5 mmol). Off-white solid, Mp: 147-148 °C; R$_f$ = 0.25 (EtOAc–hexanes, 1:1); IR (CH$_2$Cl$_2$); 3688, 3054, 2987, 1550, 1422, 1265, 738 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 400 MHz): 3.64 (s, 1H), 3.66 (s, 3H), 4.42 (d, J = 5.3 Hz, 2H), 4.79 (t, J = 5.8 Hz, 1H), 4.97 (t, J = 5.3 Hz, 1H), 5.09 (d, J = 5.3 Hz, 1H), 6.09 (d, J = 4.8 Hz, 1H), 6.74 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H), 7.16-7.26 (m, 2H), 7.29 (d, J = 7.3 Hz, 1H), 7.34 (d, J = 6.9 Hz, 1H); $^{13}$C (APT) NMR (DMSO-d$_6$, 100 MHz): 45.0 (CH), 54.9 (CH$_3$), 61.2 (CH$_2$), 69.9 (CH), 113.0 (CH); 122.5 (CH); 125.8 (CH), 126.8 (CH), 126.9 (CH), 127.1(CH), 130.3 (CH), 130.8 (qC), 132.3 (qC), 136.1 (qC), 138.2 (qC), 157.9 (qC); HRMS (EI) calcd. for C$_{18}$H$_{18}$O$_3$ (M$^+$): 282.1256; found: 282.1259.

Preparation of \textit{cis-1,2-Dihydro-4-ethyl-2-(2-methoxyphenyl)-1-naphthol (4-76)} Yield: 91\% (127 mg, 0.5 mmol). Off-white solid, Mp: 70-72 °C; R$_f$ = 0.24 (EtOAc–hexanes, 1:5); IR (CH$_2$Cl$_2$); 3565, 3054, 2986, 1600, 1491, 1463, 1439, 1422, 1264, 739 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.16 (t, J = 7.4 Hz, 3H), 2.05 (d, J = 5.3 Hz, 1H, OH), 2.48-2.54 (m, 2H), 3.76 (s, 3H), 4.29-4.31 (m, 1H), 4.80 (t, J = 5.3 Hz, 1H), 5.77 (d, J = 3.6 Hz, 1H), 6.79-6.85 (m, 2H), 7.10-7.20 (m, 3H), 7.22-7.26 (app. dt, 1H), 7.31 (d, J=
7.9Hz, 2H); $^{13}$C (APT) NMR (CDCl$_3$, 100 MHz): 12.9 (CH$_3$), 25.1(CH$_2$), 39.6 (CH), 55.4 (CH$_3$), 70.4(CH), 110.4(CH); 120.7 (CH); 122.8 (CH), 124.2(CH), 127.2 (qC), 127.3(CH), 127.4(CH), 128.0(CH), 128.1(CH), 130.0 (CH), 133.2 (qC), 136.6 (qC), 138.3 (qC), 157.2(qC); HRMS (EI) calcd. for C$_{19}$H$_{20}$O$_2$ (M$^+$): 280.1463; found: 280.1467.

Preparation of cis-1,2-Dihydro-4-ethyl-2-(3-methyl-phenyl)-1-naphthol (4-81) Yield: 95% (125 mg, 0.5 mmol). Light brown oil; $R_f = 0.35$ (EtOAc–hexanes, 1:5); IR (CH$_2$Cl$_2$); 3560, 3054, 2986, 1605, 1264, 1094, 896 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.28 (t, J = 7.4Hz, 3H), 1.62 (d, J = 8.1 Hz, 1H), 2.35 (s, 3H), 2.62 (dq, J = 1.5 & 7.4 Hz, 2H), 3.80-3.82 (m, 1H), 4.87 (dd, J = 6.0 & 7.8 Hz, 1H), 5.96 (d, J = 4.1 Hz, 1H), 7.05 (d, J = 7.4 Hz, 1H), 7.09 (d, J = 7.3 Hz, 2H), 7.20 (at, 1H), 7.28 (dt, J= 7.3 & 1.3 Hz, 1H), 7.33-7.45 (m, 3H); $^{13}$C (APT) NMR (CDCl$_3$, 100 MHz): 12.9 (CH$_3$), 21.4 (CH$_3$), 25.1 (CH$_2$), 46.9 (CH), 71.4 (CH), 122.9 (CH); 124.3 (CH); 126.1 (CH), 126.7 (CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 130.0 (CH), 133.5 (qC), 136.9 (qC), 138.0 (qC), 138.30 (qC), 138.32 (qC); HRMS (EI) calcd. for C$_{19}$H$_{20}$O (M$^+$): 264.1514; found: 264.1517.
Preparation of *cis*-1,2-Dihydro-4-ethyl-2-(4-phenyl)-1-naphthol (4-83) Yield: 75% (94 mg, 0.5 mmol); Light brown oil; R<sub>f</sub> = 0.35 (EtOAc–hexanes, 1:5); IR (CH<sub>2</sub>Cl<sub>2</sub>); 3564, 3054, 2986, 1602, 1452, 1422, 1265, 896, 739 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 1.17 (t, J = 7.4 Hz, 3H), 1.41 (d, J = 8.4 Hz, 1H), 2.52 (s, 3H), 2.62 (dq, J = 1.3 & 7.4 Hz, 2H), 3.76 (dd, 5.8 & 4.4 Hz, 1H), 4.81 (dd, J = 8.3 & 5.9 Hz, 1H), 5.87 (d, J = 4.4 Hz, 1H), 7.12-7.35 (m, 9H); <sup>13</sup>C (APT) NMR (CDCl<sub>3</sub>, 100 MHz): 12.9 (CH<sub>3</sub>), 25.1 (CH<sub>2</sub>), 47.0 (CH), 71.5 (CH), 122.9 (CH); 124.3 (CH); 126.6 (CH), 127.3 (CH), 127.6 (CH), 128.1 (CH), 128.5 (CH), 129.3 (CH), 133.6 (qC), 136.9 (qC), 138.2 (qC), 138.5 (qC); HRMS (EI) calcd. for C<sub>19</sub>H<sub>20</sub>O (M<sup>+</sup>): 250.1358; found: 250.1354.

Preparation of *cis*-1,2-Dihydro-4-ethyl-2-(2-methyl-phenyl)-1-naphthol (4-82) Yield: 88% (116 mg, 0.5 mmol); Off-white solid, Mp: 95-96 °C; R<sub>f</sub> = 0.40 (EtOAc–hexanes, 1:5); IR (CH<sub>2</sub>Cl<sub>2</sub>); 3562, 3054, 2986, 1602, 1488, 1422, 1265, 896, 739 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 1.17 (t, J = 7.4 Hz, 3H), 1.44 (d, J = 7.2 Hz, 1H), 2.34 (s, 3H), 2.52 (q, J = 7.4 Hz, 2H), 4.05-4.15 (m, 1H), 4.70 (t, J = 6.0 Hz, 1H), 5.79 (d, J = 2.2 Hz, 1H), 7.07-7.12 (m, 2H), 7.13-7.16 (m, 1H), 7.19 (app. dt, 2H), 7.28 (at, 2H), 7.34 (d, J=7.7 Hz, 1H); <sup>13</sup>C (APT) NMR (CDCl<sub>3</sub>, 100 MHz): 12.9 (CH<sub>3</sub>), 19.8 (CH<sub>3</sub>), 25.1 (CH<sub>2</sub>), 42.7 (CH), 70.0 (CH), 123.0 (CH); 125.0 (CH); 126.2 (CH), 127.1 (CH), 127.5 (CH), 127.6 (CH), 128.4 (CH), 129.2 (CH), 130.6 (CH), 133.4 (qC), 136.3 (qC), 136.6 (qC), 137.3 (qC), 138.1 (qC); HRMS (EI) calcd. for C<sub>19</sub>H<sub>20</sub>O (M<sup>+</sup>): 264.1514; found: 264.1518.
Preparation of \textit{cis-1,2-Dihydro-4-ethyl-2-(3-methoxyphenyl)-1-naphthol} (4-75) Yield: 80\% (112 mg, 0.5 mmol). Light brown oil. \(R_f = 0.27\) (EtOAc–hexanes, 1:5); IR (CH\(_2\)Cl\(_2\)); 3559, 3054, 2986, 1599, 1486, 1422, 1264, 1155, 1050 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.22 (t, \(J = 7.4\) Hz, 3H), 1.49 (d, \(J = 8.4\) Hz, 1H), 2.56 (app. q, 2H), 3.71 (s, 3H), 3.79 (dd, \(J = 5.6\) & 4.4 Hz, 1H), 4.88 (dd, \(J = 6.1\) & 8.2 Hz, 1H), 5.91 (d, \(J = 4.3\) Hz, 1H), 6.73-6.85 (m, 3H), 7.20 (t, \(J = 7.9\) Hz, 1H), 7.23-7.27 (m, 1H), 7.31 (dt, \(J = 7.6\) & 1.3 Hz, 1H), 7.37 (t, \(J = 6.2\) Hz, 2H); \(^{13}\)C (APT) NMR (CDCl\(_3\), 100 MHz): 12.9 (CH\(_3\)), 25.1(CH\(_2\)), 46.9 (CH), 55.0 (CH\(_3\)), 71.4(CH), 112.5(CH); 114.8 (CH); 121.5 (CH), 124.2 (CH), 126.5 (CH), 127.6 (CH), 128.0 (CH), 129.4 (CH), 133.5 (qC), 136.9 (qC), 138.5 (qC), 139.8 (qC), 159.6 (qC); HRMS (EI) calcd. for C\(_{19}\)H\(_{20}\)O\(_2\) (M\(^+\)): 280.1463; found: 280.1465.

Preparation of \textit{cis-1,2-Dihydro-4-ethyl-2-(4-methyl-phenyl)-1-naphthol} (4-80) Yield: 93\% (123 mg, 0.5 mmol); light brown oil. \(R_f = 0.35\) (EtOAc–hexanes, 1:5); IR (CH\(_2\)Cl\(_2\)); 3560, 3054, 2986, 1603, 1514, 1422, 1266, 896, 735 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.38 (t, \(J = 7.4\) Hz, 3H), 1.71 (d, \(J = 8.5\) Hz, 1H), 2.45 (s, 3H), 2.74 (app. q, 2H), 3.92 (dd, \(J = 5.6\) & 4.6 Hz, 1H), 5.01 (dd, \(J = 7.8\) & 6.5 Hz, 1H), 6.07 (d, \(J = 4.3\) Hz, 1H),
7.20-7.30 (m, 4H), 7.34-7.42 (m, 1H), 7.44-7.58 (m, 3H), $^{13}$C (APT) NMR (CDCl$_3$, 100 MHz): 12.9 (CH$_3$), 21.0 (CH$_3$), 25.1 (CH$_2$), 46.5 (CH), 71.4 (CH), 122.8 (CH); 124.5 (CH); 124.6 (CH), 126.5 (CH), 127.5 (CH), 127.9 (CH), 129.1 (CH), 129.2 (CH), 133.6 (qC), 134.9 (qC), 136.8 (qC), 137.0 (qC), 138.3 (qC); HRMS (ESI) calcd. for C$_{19}$H$_{20}$ONa (M+Na$^+$): 287.1411; found: 287.1420.

Preparation of cis-1,2-Dihydro-4-cyclobutyl-2-(4-methoxyphenyl)-1-naphthol (4-103)

Yield: 65% (99 mg, 0.5 mmol); Off-white solid, Mp: 115-117 °C; R$_{f}$ = 0.30 (EtOAc–hexanes, 1:5); IR (CH$_2$Cl$_2$); 3554, 3054, 2967, 1609, 1511, 1463, 1265, 1250, 1036, 764 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.49 (d, J = 8.7 Hz, 1H), 1.70-1.80 (m, 1H), 1.89-2.07 (m, 3H), 2.17-2.30 (m, 2H), 3.40-3.52 (m, 1H), 3.65 (s, 3H), 3.69 (m, 1H), 4.78 (dd, J = 8.5 & 6.3 Hz, 1H), 5.80 (dd, J = 4.6 & 1.7 Hz, 1H), 6.71 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 7.10-7.23 (m, 3H), 7.26 (d, J = 7.3 Hz, 1H); $^{13}$C (APT) NMR (CDCl$_3$, 100 MHz): 18.3 (CH$_2$), 28.0 (CH$_2$), 28.2 (CH$_2$), 37.3 (CH), 46.0 (CH), 55.1 (CH$_3$), 71.3 (CH), 113.9 (CH); 123.3 (CH), 123.5 (CH), 126.2(CH), 127.5(CH), 127.8(CH), 129.7 (qC), 130.3 (CH), 133.1 (qC), 137.1 (qC), 140.3 (qC), 158.8 (qC); HRMS (ESI) calcd. for C$_{21}$H$_{23}$O$_2$ (M+H$^+$): 307.1692; found:307.1698.
Preparation of cis-1,2-Dihydro-4-biphenyl-2-(4-methoxyphenyl)-1-naphthol (4-102)

Yield: 19% (38 mg, 0.5 mmol); Light brown solid, Mp: 138-140 °C; R_f = 0.37 (EtOAc–hexanes, 1:5); IR (CH_2Cl_2): 3550, 3052, 3030, 1608, 1509, 1485, 1263, 1178, 1035, 824, 763 cm⁻¹; ¹H NMR (CDCl_3, 400 MHz): δ 1.49 (d, J = 8.7 Hz, 1H), 1.70-1.80 (m, 1H), 1.89-2.07 (m, 3H), 2.17-2.30 (m, 2H), 3.40-3.52 (m, 1H), 3.65 (s, 3H), 3.69 (m, 1H), 4.78 (dd, J = 8.5 & 6.3 Hz, 1H), 5.80 (dd, J = 4.6 & 1.7 Hz, 1H), 6.71 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 7.10-7.23 (m, 3H), 7.26 (d, J = 7.3 Hz, 1H); ¹³C (APT) NMR (CDCl_3, 100 MHz): 53.9 (CH), 55.2 (CH₃), 77.2 (CH), 113.8(CH), 114.1(CH), 114.3(CH), 126.3(CH), 126.4(CH), 127.0(CH), 127.1(CH), 127.2(CH), 127.7(CH), 127.9(CH), 128.3(CH), 128.4(qC), 128.4 (CH), 128.5(CH), 128.7(CH), 128.8(CH), 130.6 (CH), 131.1 (CH), 133.5 (qC), 139.3 (qC), 139.8 (qC), 140.8(qC), 145.1(qC), 159.1 (qC); HRMS (ESI) calcd. for C_{29}H_{25}O_{2}(M+H⁺): 405.1849; found: 405.1856.

Preparation of 3-(4-Methoxyphenyl)-naphthalene-1-carboxylic acid methyl ester (4-48a)

Yield: 80% (105 mg, 0.45 mmol); White solid, Mp: 76-77 °C; R_f = 0.38 (EtOAc–
hexanes, 1:5; IR (CH\textsubscript{2}Cl\textsubscript{2}); 3054, 2987, 1716, 1610, 1517, 1437, 1422, 1265, 1181, 739 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): CDCl\textsubscript{3} δ 3.85 (s, 3H), 4.02 (s, 3H), 7.02 (d, J = 8.8 Hz, 2H), 7.53 (at, 1H), 7.59 (dt, J = 8.4 & 1.3 Hz, 1H), 7.66 (d, J = 8.7 Hz, 2H), 7.89 (d, J= 8.0 Hz, 1H), 8.13(d, J = 1.1 Hz, 1H), 8.44(d; J= 1.9 Hz, 1H); 8.91(d, J = 8.5 Hz, 1H);
\textsuperscript{13}C (APT) NMR (CDCl\textsubscript{3}, 100 MHz): 52.1 (CH\textsubscript{3}), 55.3 (CH\textsubscript{3}), 114.3(CH), 125.6 (CH), 126.5 (CH), 127.4(CH), 127.5 (qC), 128.3 (CH); 128.6 (CH); 129.6(CH), 129.9 (CH), 130.0 (qC), 132.3 (qC), 134.3(qC) 136.8 (qC), 159.4 (qC), 167.9 (qC); HRMS (ESI) calcd. for C\textsubscript{19}H\textsubscript{16}O\textsubscript{3} (M+H\textsuperscript{+}): 293.1177; found: 293.1176.

Preparation of 3-(4-Nitro-phenyl)-naphthalene-1-carboxylic acid methyl ester (4-59)
Yield: 17% (26 mg, 0.5 mmol);Yellow solid, Mp: 141-143 °C; R\textsubscript{f} = 0.50 (EtOAc–hexanes, 1:4); IR (CH\textsubscript{2}Cl\textsubscript{2}); 3080, 1715, 1597, 1519, 1434, 1350, 1250, 1193 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz):δ 4.03 (s, 3H), 7.55-7.70 (m, 2H), 7.85 (d, J= 8.9 Hz, 2H), 7.95 (d, J = 8.6 Hz, 1H), 8.23 (d, J = 1.6 Hz, 1H), 8.32 (d, J = 8.9 Hz, 2H), 8.42(d, J =2.0 Hz, 1H), 8.91 (d, J=8.6 Hz, 1H); \textsuperscript{13}C (APT) NMR (CDCl\textsubscript{3}, 100 MHz): 52.4 (CH\textsubscript{3}), 124.2(CH), 125.8 (CH), 127.1(CH), 127.9(CH), 128.3 (qC), 128.7 (CH); 129.0 (CH); 131.0(qC), 131.6 (CH), 134.1 (qC), 134.7 (qC), 146.2 (qC), 147.3 (qC), 167.5 (qC); HRMS (ESI) calcd. for C\textsubscript{18}H\textsubscript{13}NO\textsubscript{4} (M+H\textsuperscript{+}): 308.0922 Found; 308.0936.
Isolation of 3-(4-Methoxy-phenyl)-naphthalene-1-carboxylic acid ethyl ester (4-53)
Yield: 16% (25 mg, 0.5 mmol); Off-white solid, Mp: 79-80 °C; R_f = 0.40 (EtOAc–hexanes, 1:5); IR (CH_2Cl_2): 2957, 2924, 1713, 1609, 1516, 1248, 1187, 1035, 829 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 400 MHz): \(\delta\) 1.47 (t, J= 7.2 Hz, 3H); 3.87 (s, 3H), 4.52 (q, J= 7.2 Hz, 2H); 7.03 (dd, J = 6.7 & 2.1 Hz, 2H), 7.50-7.60 (m, 2H), 7.66 (dd, J = 6.7 & 2.1 Hz, 2H), 7.90 (d, J = 8.7 Hz, 1H), 8.13 (d, J= 1.7 Hz, 1H), 8.40 (d, J =2.0 Hz, 1H), 8.86 (d, J= 8.4 Hz, 1H); \(^{13}\)C (APT) NMR (CDCl_3, 100 MHz): 114.4 (CH), 125.7 (CH), 126.5 (CH), 127.4 (CH), 128.1 (qC), 128.4 (CH); 128.7 (CH); 129.5 (CH), 129.9 (CH), 130.1 (qC), 132.5 (qC), 134.3 (qC), 136.9 (qC), 159.5 (qC), 167.7 (qC); HRMS (ESI) calcd. for C_20H_19O_3 (M+H\(^+\)): 307.1329 Found: 307.1324.

Preparation of 3-(2-Methoxy-phenyl)-naphthalene-1-carboxylic acid methyl ester (4-58)
Yield: 77% (112 mg, 0.5 mmol); Light brown oil; R_f = 0.38 (EtOAc–hexanes, 1:5); IR (CH_2Cl_2): 3054, 2987, 1714, 1495, 1437, 1422, 1264, 1027, 743 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 300 MHz): \(\delta\) 3.83 (s, 3H), 4.01 (s, 3H), 7.03 (d, J = 9.9 Hz, 1H), 7.09 (dt, J=0.7 & 7.5 Hz, 1H), 7.34-7.46 (m, 2H), 7.54 (at, 1H), 7.60 (dt, J=8.5 & 1.4 Hz, 1H), 7.91(d, J =7.8 Hz, 1H), 8.16 (s, 1H), 8.43(d, J= 1.7 Hz, 1H), 8.95 (d, J= 8.5 Hz, 1H); \(^{13}\)C (APT) NMR (CDCl_3, 75 MHz): 52.1 (CH_3), 55.6 (CH_3), 111.3(CH), 121.0 (CH), 125.6 (CH), 126.2(CH), 126.5 (qC), 127.5 (CH); 128.7 (CH); 129.1(CH), 129.5 (qC), 130.2 (qC), 130.9 (CH), 132.5 (CH), 133.4 (CH), 133.9 (qC), 134.9 (qC), 156.6 (qC), 168.1 (qC); HRMS (ESI) calcd. for C_19H_16O_3Na (M+Na\(^+\)): 315.0997; found: 315.0993.
Preparation of 3-(4-Methoxy-phenyl)-naphthalene-1-carboxylic acid methyl ester (4-57) Yield: 80% (117 mg, 0.5 mmol); Off-white solid, Mp: 55-56 °C; Rf = 0.43 (EtOAc–hexanes, 1:5); IR (CH₂Cl₂); 3054, 2987, 1716, 1599, 1422, 1264, 1207 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 3.89 (s, 3H), 4.02 (s, 3H), 6.95 (ddd, J = 10.6, 0.8 & 0.7 Hz, 1H), 7.26 (at, 1H), 7.31 (dd, J = 7.6 & 0.9 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.54 (at, 1H), 7.61 (at, 1H), 7.92 (d, J = 7.9 Hz, 1H), 8.19 (d, 1.6 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.91 (d, J = 8.6 Hz, 1H); ¹³C (APT) NMR (CDCl₃, 100 MHz): 52.2 (CH₃), 55.3 (CH₃), 113.0 (CH), 113.1 (CH), 119.8 (CH), 125.7 (CH), 126.6 (CH), 127.6 (qC); 127.7 (CH); 128.8 (CH), 129.8 (CH), 130.0 (CH), 130.5 (qC), 130.8 (CH), 134.2 (qC), 137.1 (qC), 141.4 (qC), 160.1 (qC), 167.9 (qC); HRMS (ESI) calcd. for C₁₉H₁₆O₃Na (M+Na⁺): 315.0997; found: 315.0992.

Preparation of 3-(3-Nitro-phenyl)-naphthalene-1-carboxylic acid methyl ester (4-60) Yield: 14% (22 mg, 0.5 mmol); Light yellow oil; Rf = 0.38 (EtOAc–hexanes, 1:5); IR (CH₂Cl₂); 3054, 2987, 1716, 1436, 1422, 1265, 896, 739 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 4.04 (s, 3H), 7.55-7.63 (m, 2H), 7.67 (t, J = 7.8 Hz, 1H), 7.88 (app. dd, 1H), 7.99 (app. dd, 1H), 8.33 (d, 1.7 Hz, 1H), 8.35 (t, J =1.7 Hz, 1H), 8.55 (d, J = 1.9 Hz, 1H), 8.91 (d, 8.7 Hz, 1H); ¹³C (APT) NMR (CDCl₃, 100 MHz): 52.3 (CH₃), 122.0 (CH), 125.8 (CH), 126.8 (CH), 127.9 (qC), 128.0 (CH), 128.9 (CH); 129.7 (CH); 129.8 (CH), 129.9
(CH), 130.7 (qC), 130.1 (CH), 134.3 (qC), 136.4 (qC), 141.1 (qC), 153.2 (qC), 167.9 (qC); HRMS (ESI) calcd. for C_{18}H_{13}NO_{4}Na (M+Na^+): 330.0743; found: 330.0750.

Preparation of 3-(4-Methoxy-phenyl)naphthalene-1-trimethylsilane (4-98) Yield: 62% (95 mg, 0.5 mmol); light brown solid, Mp: 94-96 °C; R_f = 0.52 (EtOAc–hexanes, 1:5); IR (CH_2Cl_2); 3054, 2959, 1609, 1515, 1464, 1265, 1250, 1033, 739 cm^{-1}; ^1H NMR (CDCl_3, 400 MHz): 0.50 (s, 9H), 3.87 (s, 3H), 7.03 (dd, J = 6.8 & 2.0 Hz, 2H), 7.49 (dd, J = 6.2 & 3.4 Hz, 2H), 7.65 (dd, J = 6.8 & 2.0 Hz, 2H), 7.86-7.92 (m, 2H), 7.98 (d, J= 1.4 Hz, 1H), 8.07-8.14 (m, 1H); ^13C (APT) NMR (CDCl_3, 100 MHz): 0.3 (CH_3), 55.4 (CH_3), 114.2 (CH), 114.3 (CH), 125.4 (CH), 125.7 (CH), 126.9 (CH), 127.9 (CH), 128.1 (CH), 128.5 (CH); 129.3 (CH); 132.8 (CH), 133.7 (qC), 133.9 (qC), 135.7 (qC), 137.1 (qC), 138.7 (qC), 159.2 (qC); HRMS (EI) calcd. for C_{20}H_{22}OSi (M^+): 306.1440 Found: 306.1447.

Preparation of 3-(4-Methoxy-phenyl)naphthalene-1-carboxamide (4-100) Yield: 12% (17 mg, 0.5 mmol); R_f = 0.57 (EtOAc–hexanes, 1:1); IR (CH_2Cl_2); 3054, 2987, 1670, 1654, 1517, 1422, 1265, 896, 749 cm^{-1}; ^1H NMR (CDCl_3, 400 MHz): 3.87 (s, 3H), 7.01 (d, J = 8.8 Hz, 2H), 7.58-7.64 (m, 4H), 7.94 (d, J = 7.4 Hz, 1H), 8.14 (d, J = 1.7 Hz, 1H), 8.19 (s,1H), 8.22 (d, J = 8.1 Hz, 1H) ^13C (APT) NMR (CDCl_3, 100 MHz): 55.4 (CH_3),
114.1 (CH), 114.6 (CH), 117.9 (qC), 125.0 (CH), 127.7 (CH), 127.9 (CH); 128.2 (CH); 128.4 (CH), 128.8 (CH), 130.0 (CH), 131.1 (qC), 131.3 (qC), 132.0 (CH), 133.4 (qC), 137.8 (qC), 159.9 (qC), 162.2 (qC); HRMS (EI) calcd. for C_{18}H_{15}NO_2 (M^+): 277.1103, found: 277.1112.

Preparation of 3-(2-Methyl-phenyl)-naphthalene-1-carboxylic acid methyl ester (4-64) Yield: 73% (101 mg, 0.5 mmol); R_f = 0.50 (EtOAc–hexanes, 1:5); IR (CH_2Cl_2): 3054, 2987, 1715, 1436, 1422, 1265, 1212, 1197, 896, 742 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 400 MHz): \(\delta\) 2.33 (s, 3H), 4.01 (s, 3H), 7.26-7.38 (m, 4H), 7.57 (dt, 6.9 and 1.1 Hz, 1H), 7.65 (at, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 1.4 Hz, 1H), 8.24 (d, J = 1.9 Hz, 1H), 8.98 (d, J = 8.7 Hz, 1H); \(^13\)C (APT) NMR (CDCl_3, 100 MHz): 20.4 (CH_3), 52.1 (CH_3), 125.7 (CH), 125.9 (CH), 126.5 (CH), 126.8 (qC), 127.7 (CH), 127.7 (CH); 128.6 (CH); 129.9 (CH), 130.2 (qC), 130.4 (CH), 131.9 (CH), 132.9 (CH), 133.8 (qC), 135.5 (qC), 138.2 (qC), 140.6 (qC), 167.9 (qC); HRMS (ESI) calcd. for C_{19}H_{16}O_2 (M^+): 276.1150; found: 276.1145.

Preparation of 3-(3-Methylphenyl)-naphthalene-1-carboxylic acid methyl ester (4-63) Yield: 68% (94 mg, 0.5 mmol); R_f = 0.50 (EtOAc–hexanes, 1:5); IR (CH_2Cl_2); 3054, 2987, 1716, 1436, 1422, 1265, 1198, 1021, 739 cm\(^{-1}\); \(^1\)H NMR (CDCl_3, 400 MHz): \(\delta\)
2.47 (s, 3H), 4.04 (s, 3H), 7.22 (d, 7.8 Hz, 1H), 7.39 (t, 7.6 Hz, 1H), 7.50-7.58 (m, 3H),
7.62 (app. t, 1H), 7.92 (d, J= 8.0 Hz, 1H), 8.19 (d, J =1.5 Hz, 1H), 8.48 (d, J = 1.9 Hz,
1H), 8.93 (d, J = 8.6 Hz, 1H); ¹³C (APT) NMR (CDCl₃, 100 MHz): 21.5 (CH₃), 52.2
(CH₃), 124.4 (CH), 125.7 (CH), 126.5 (CH), 127.5 (qC), 127.6 (CH), 128.0 (CH); 128.5
(CH); 128.8 (CH), 128.8 (CH), 129.9 (CH), 130.4 (qC), 130.7 (CH), 134.2 (CH), 137.3
(qC), 138.5 (qC), 139.8 (qC), 167.9 (qC); HRMS (ESI) calcd. for C₁₉H₁₆O₂ (M⁺):
276.1150; found: 276.1147.

Preparation of 3-(4-Methyl-phenyl)-naphthalene-1-carboxylic acid methyl ester (4-62) Yield: 71% (98 mg, 0.5 mmol); Rᵣ = 0.60 (EtOAc–hexanes, 1:5); IR (CH₂Cl₂): 3054,
2987, 1716, 1602, 1518, 1436, 1265, 1211, 1152, 1137 cm⁻¹; ¹H NMR (CDCl₃, 400
MHz): δ 2.43 (s, 3H), 4.04 (s, 3H), 7.31 (d, J =7.9 Hz, 2H), 7.54 (dt, 6.9 and 1.1 Hz, 1H),
7.60 (d, J = 8.5, 1.5 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.5 Hz, 1H), 8.18 (d, J
= 1.7 Hz, 1H), 8.48 (d, J=2.0 Hz, 1H), 8.93 (d, J=8.7 Hz, 1H); ¹³C (APT) NMR (CDCl₃,
100 MHz): 21.1 (CH₃), 52.1 (CH₃), 125.6 (CH), 126.5 (CH), 127.0 (CH), 127.5 (qC),
127.5 (CH), 128.7 (CH); 129.6 (CH); 129.8(CH), 130.2 (qC), 130.4 (CH), 134.2 (qC),
136.9 (CH), 137.1 (qC), 137.5 (qC), 167.9 (qC); HRMS (ESI) calcd. for C₁₉H₁₆O₂ (M⁺):
276.1150; found: 276.1146.
Preparation of 3-Phenyl-naphthalene-1-carboxylic acid methyl ester (4-83) Yield: 68% (89 mg, 0.5 mmol); \( R_f = 0.50 \) (EtOAc–hexanes, 1:5); IR (CH\(_2\)Cl\(_2\)); 3054, 2987, 1716, 1436, 1265, 1197, 1152, 897 cm\(^{-1}\); \( ^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 4.03 (s, 3H), 7.40 (t, \( J = 7.3 \) Hz, 1H), 7.43 (t, 1.1 Hz, 1H), 7.50 (t, \( J = 7.3 \) Hz, 1H), 7.45-7.58 (m, 3H), 7.62 (app. t, 1H), 7.74 (app. dd, 2H), 7.92 (d, \( J = 8.1 \) Hz, 1H), 8.20 (d, \( J = 1.6 \) Hz, 1H), 8.48 (d, 1.9 Hz, 1H), 8.93 (d, 8.7 Hz, 1H); \( ^{13}\)C (APT) NMR (CDCl\(_3\), 100 MHz): 52.2 (CH\(_3\)), 125.7 (CH), 126.5 (CH), 127.3 (CH), 127.6 (qC), 127.7 (CH), 128.8 (CH); 128.9 (CH); 129.8 (CH), 130.4 (qC), 130.8 (CH), 134.2 (qC), 137.2 (CH), 139.9 (qC), 167.9 (qC); HRMS (EI) calcd. for C\(_{18}\)H\(_{14}\)O\(_2\) (M\(^+\)): 262.0994; found: 262.0998.

![Chemical structure](image)

Preparation of 3-(4-Nitro-phenyl)-1-ethyl-naphthalene (4-77) Yield: 61% (85 mg, 0.5 mmol); \( R_f = 0.15 \) (EtOAc–hexanes, 1:5); IR (CH\(_2\)Cl\(_2\)); 3471, 3386, 2970, 1674, 1621, 1519, 1265, 1184 cm\(^{-1}\); \( ^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 1.46 (t, \( J = 7.6 \) Hz, 3H), 3.19 (q, \( J = 7.6 \) Hz, 2H), 6.81 (d, \( J = 8.5 \) Hz, 2H), 7.47-7.53 (m, 2H), 7.59 (d, \( J = 8.5 \) Hz, 2H), 7.62 (d, \( J = 1.6 \) Hz, 1H), 7.87 (d, \( J = 1.2 \) Hz, 1H), 7.90 (dd, \( J = 6.1 \) & 3.4 Hz, 1H), 8.07 (dd, \( J = 6.1 \) & 3.4 Hz, 1H); \( ^{13}\)C (APT) NMR (CDCl\(_3\), 100 MHz): 15.1 (CH\(_3\)), 26.0 (CH\(_2\)), 115.4 (CH), 122.9 (CH), 123.5 (CH), 124.4 (CH), 125.2 (CH), 125.7 (CH); 128.2 (CH); 128.8 (CH), 130.5 (qC), 131.5 (qC), 134.2 (qC), 138.1 (qC), 140.6 (qC), 145.8 (qC); HRMS (ESI) calcd. for C\(_{18}\)H\(_{15}\)NO\(_2\) (M+H\(^+\)): 278.1183; found: 278.1185.
Preparation of **3-(3-Nitro-phenyl)-1-ethyl-naphthalene (4-78)** Yield: 30% (42 mg, 0.5 mmol); Rf = 0.24 (EtOAc–hexanes, 1:5); IR (CH2Cl2): 3466, 3384, 3053, 2970, 1620, 1600, 1496, 1421, 1265 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): 1.42 (t, J = 7.6 Hz, 3H), 3.16 (q, J = 7.6 Hz, 2H), 6.70 (dd, 7.9 & 1.5 Hz, 1H), 7.04 (t, 1.9 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.44-7.53 (m, 2H), 7.58 (s, 1H), 7.83-7.92 (m, 2H), 8.01-8.09 (m, 2H); ¹³C (APT) NMR (CDCl₃, 100 MHz): 15.1 (CH₃), 26.0 (CH₂), 114.1 (CH), 117.9 (CH), 123.6 (CH), 124.1 (CH), 124.7 (CH), 125.7 (CH), 125.8 (CH); 129.0 (CH), 129.7 (CH), 131.0 (qC), 134.1 (CH), 138.4 (qC), 140.7 (qC), 142.5 (qC), 146.8 (qC); HRMS (ESI) calcd. for C₁₉H₁₆O₂ (M+H⁺): 278.1183; found: 278.1181.

Preparation of **Napthalene-1-carboxylic acid methyl ester (4-85)** Yield: 65% (60 mg, 0.5 mmol); Rf = 0.48 (EtOAc–hexanes, 1:5); IR (CH2Cl2): 3054, 2987, 1715, 1511, 1436, 1265, 1203, 1138, 1037, 739 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 3.99 (s, 3H), 7.42-7.56 (m, 2H), 7.61 (dt, J = 6.8 & 1.4 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 8.18 (dd, J = 7.3 & 1.2 Hz, 1H), 8.91 (d, J = 8.7 Hz, 1H); ¹³C (APT) NMR (CDCl₃, 100 MHz): 52.1 (CH₃), 124.4 (CH), 125.8 (CH), 126.2 (CH), 127.0 (qC), 127.7 (CH), 128.5 (CH); 130.2 (CH); 131.3 (qC), 133.3 (CH), 133.8 (qC), 168.0 (qC); HRMS (ESI) calcd. for C₁₂H₁₀O₂Na (M+Na⁺): 209.0579; found: 209.0571.
Preparation of 3-(4-Methoxy-phenyl)-naphthalene-1-methylketone (4-101) Yield: 27% (37 mg, 0.5 mmol); \( R_f = 0.38 \) (EtOAc–hexanes, 1:5); IR (CH\(_2\)Cl\(_2\)); 3054, 2987, 1715, 1679, 1610, 1422, 1265, 896, 739 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz); \( \delta \) 2.78 (s, 3H), 3.87 (s, 3H), 7.04 (d, \( J = 8.7 \) Hz, 2H), 7.50-7.60 (m, 2H), 7.64 (d, \( J = 8.7 \) Hz, 2H), 7.89 (d, \( J = 7.6 \) Hz, 1H), 8.11 (d, \( J = 4.4 \) Hz, 2H), 8.67 (d, \( J = 8.1 \) Hz, 1H); \(^{13}\)C (APT) NMR (CDCl\(_3\), 100 MHz): 30.1 (CH\(_3\)), 55.4 (CH\(_3\)), 114.5 (CH), 125.8 (CH), 126.8 (CH), 127.7 (CH), 128.1 (CH), 128.4 (CH); 128.6 (CH); 128.9 (qC), 129.7 (CH), 132.6 (qC), 134.4 (qC), 136.2 (qC), 136.8 (qC), 159.6 (qC), 202.0 (qC); HRMS (ESI) calcd. for C\(_{19}\)H\(_{17}\)O\(_2\) (M+H\(^+\)): 277.1223; found: 277.1226.

Preparation of 4-Ethyl-1-naphthalenol (4-51) Yield: 61% (52 mg, 0.5 mmol); \( R_f = 0.34 \) (EtOAc–hexanes, 1:5); IR (CH\(_2\)Cl\(_2\)); 3576, 3054, 2987, 1688, 1626, 1422, 1265, 739 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz); \( \delta \) 1.34 (t, \( J = 7.5 \) Hz, 3H), 3.02 (q, \( J = 7.5 \) Hz, 2H), 5.24 (brs, 1H); 6.74 (d, 7.6 Hz, 1H), 7.14 (d, \( J = 7.6 \) Hz, 1H), 7.49-7.58 (m, 2H), 7.79 (d, \( J = 7.9 \) Hz, 1H), 8.21 (d, \( J = 7.9 \) Hz, 1H); \(^{13}\)C (APT) NMR (CDCl\(_3\), 100 MHz): 15.2 (CH\(_3\)), 25.4 (CH\(_2\)), 108.2 (CH), 122.2 (CH), 123.8 (CH); 124.5 (CH), 124.7 (qC), 124.8 (CH), 126.2 (CH); 132.7 (qC), 132.8 (qC), 149.8 (qC); HRMS (EI) calcd. for C\(_{12}\)H\(_{12}\)O\(_2\) (M\(^+\)): 172.0888; found: 172.0.892.
Biphenyl Derivatives

Preparation of **Dimethyl 4'-methoxy-1', 1'-biphenyl-5-methyl-3, 4-dicarboxylate (4-108)**
Yield: 72% (113 mg, 0.5 mmol); \( R_f = 0.25 \) (EtOAc–hexanes, 1:5); IR (CH\(_2\)Cl\(_2\)); 3055, 2987, 2954, 1731, 1609, 1517, 1438, 1333, 1266, 1106, 1069, 1033 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 2.37 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 6.95 (dd, \( J=6.7 \) & 2.1 Hz, 2H), 7.50 (dd, \( J = 6.7 \) & 2.1 Hz, 2H), 7.54 (d, \( J = 1.7 \) Hz, 1H), 7.97 (d, \( J=1.7 \) Hz, 1H) \(^{13}\)C (APT) NMR (CDCl\(_3\), 75 MHz): 19.2 (CH\(_3\)), 52.4 (CH\(_3\)), 55.2 (CH\(_3\)), 114.3 (CH), 125.5 (CH), 128.1 (CH); 128.5 (qC), 131.6 (qC), 132.2 (CH), 133.1 (qC); 136.0 (qC), 141.6 (qC), 159.7 (qC), 166.3 (qC), 169.7 (qC); HRMS (ESI) calcd. for C\(_{18}\)H\(_{19}\)O\(_5\) (M+H\(^+\)): 315.1232; found: 315.1236.

Preparation of **Dimethyl 4'-methoxy-1', 1'-biphenyl-5-ethyl-3, 4-dicarboxylate (4-117)**
Yield: 69% (113 mg, 0.5 mmol); \( R_f = 0.29 \) (EtOAc–hexanes, 1:5); IR (CH\(_2\)Cl\(_2\)); 3055, 2973, 2953, 1729, 1609, 1558, 1436, 1265, 1181, 1108, 1032 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 1.26 (t, \( J= 7.6 \) Hz, 3H), 2.69 (q, \( J=7.6 \) Hz, 2H), 3.83 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 6.97 (dd, \( J=6.7 \) & 2.1 Hz, 2H), 7.53 (dd, \( J = 6.7 \) & 2.1 Hz, 2H), 7.59 (d, \( J = 1.8 \) Hz, 1H), 8.00 (d, \( J=1.8 \) Hz, 1H) \(^{13}\)C (APT) NMR (CDCl\(_3\), 75 MHz): 15.6 (CH\(_3\)), 26.5
(CH₂), 52.40 (CH₃), 52.44 (CH₃), 55.3 (CH₃), 114.3 (CH), 125.8 (CH), 128.2 (CH); 128.5 (qC), 131.0 (CH), 131.9 (qC), 132.7 (qC); 141.9 (qC), 142.3 (qC), 159.8 (qC), 166.4 (qC), 169.8 (qC); HRMS (ESI) calcd. for C₁₉H₂₁O₅ (M+H⁺): 329.1389; found: 329.1392

Preparation of Dimethyl 4'-methoxy-1, 1'-biphenyl-5-trimethylsilyl-3, 4-dicarboxylate (4-119) Yield: 64% (119 mg, 0.5 mmol); Rf = 0.38 (EtOAc–hexanes, 1:5); IR (CH₂Cl₂): 3054, 2987, 1729, 1608, 1515, 1422, 1265, 1180, 1139, 896, 739 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.33 (s, 9H), 3.83 (s, 3H), 3.89 (s, 6H), 6.98 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 7.88 (d, J=1.9 Hz, 1H), 8.06 (d, J=1.9 Hz, 1H); ¹³C (APT) NMR (CDCl₃, 100 MHz): -0.4 (CH₃), 52.33 (CH₃), 52.51 (CH₃), 55.3 (CH₃), 114.4 (CH), 128.3 (CH), 128.4 (CH); 129.3 (qC), 132.0 (qC), 136.3 (CH), 137.8 (qC), 139.6 (qC); 141.2 (qC), 159.7 (qC), 167.1 (qC), 170.5 (qC); HRMS (ESI) calcd. for C₂₀H₂₅O₅Si (M+H⁺): 373.1471; found: 373.1468.

Preparation of Dimethyl 4'-methoxy-1, 1'-biphenyl-5-phenyl-3, 4-dicarboxylate (4-123) Yield: 33% (62 mg, 0.5 mmol); Rf = 0.16 (EtOAc–hexanes, 1:5); IR (CH₂Cl₂): 3054,
2987, 1731, 1609, 1438, 1422, 1265, 1180, 1032, 735 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 3.67 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 6.98 (d, \(J= 8.8\) Hz, 2H), 7.32-7.42 (m, 5H), 7.57 (d, \(J = 8.8\) Hz, 2H), 7.71 (d, \(J=1.9\) Hz, 1H), 8.16 (d, \(J=1.9\) Hz, 1H); \(^{13}\)C (APT) NMR (CDCl\(_3\), 100 MHz): 52.3 (CH\(_3\), 52.6 (CH\(_3\), 55.4 (CH\(_3\), 114.4 (CH), 126.9 (CH), 127.9 (CH); 128.3 (CH), 128.6 (CH), 128.8 (qC), 131.4 (qC), 132.1 (CH), 132.7 (qC), 139.4 (qC); 141.1 (qC), 141.8 (qC), 159.9 (qC), 166.3 (qC), 169.3 (qC); HRMS (ESI) calcd. for C\(_{23}\)H\(_{21}\)O\(_5\) (M+H\(^{+}\)): 377.1383; found: 377.1379.

4.8 References (Chapter 4)


Chapter 5

Nickel catalyzed ring opening reactions of C$^1$ substituted oxabenzonorbornadienes
5.1 Introduction

Nickel is a much cheaper catalyst than palladium and has been reported to catalyze many of the same reactions that palladium does. Oxabicyclic alkenes have been used as templates for developing several nickel catalyzed reactions for the preparation of a wide range of organic skeletons with multiple stereocentres. Organic iodides, aliphatic and aromatic terminal acetylenes, various propiolates, alkenyl zirconium reagents and alkyl zirconium reagents are used for opening oxabicyclic alkenes in the presence of Ni complexes to form 2-substituted 1,2-dihyronaphthalenols in excellent yields with high stereoselectivity (Scheme 5.1). The choice of solvent and nickel phosphine complex proved to be important for most of the conversions.

Scheme 5.1 Various Ni catalyzed ring opening reactions on 5-1.
Cheng’s group reported nickel catalyzed ring-opening reactions of 7-oxanorbornadienes and norbornenes with various organic halides. The reactions were done in the presence of NiCl$_2$(Ph$_3$P)$_2$ (5 mol%) and zinc (10 equivalents) in acetonitrile at 70 °C with organic halides (PhI, PhCH$_2$Br, PhCHCHBr, and PhCBrCH$_2$) to give the corresponding ring-opened products (Scheme 5.2). As previously states, the choice of solvent proved very crucial as among the several tested, including toluene, dichloromethane, methanol, DMF, DMSO, and THF, only acetonitrile appeared to be effective for the catalytic reaction.

Scheme 5.2 Ni Catalyzed ring opening reactions on 5-1 with organic halides.

Only one example of a reaction involving C$^1$ methyl substituted oxanorbornene is reported in the literature. It was found that the reaction of phenyl iodide with unsymmetrical oxanorbornene 5-14 gave a 2:1 mixture of regioisomers (Scheme 5.3). No rationalization was offered to account for formation of mixture of products. Moreover, to the best of our knowledge there are no reports on nickel catalyzed ring opening of bridgehead substituted benzoxyanorbornadienes in the literature.

Scheme 5.3 Regioselectivity in Ni catalyzed ring opening with 5-14.
Interestingly, a few examples were reported wherein the ring opening of C\textsuperscript{1} methyl substituted benzoanorbornadienes were found to be highly regioselective, affording a single regioisomer. Both palladium\textsuperscript{7} and rhodium\textsuperscript{8} catalyzed addition of a phenyl group on benzoanorbornadienes were found to be highly regioselective (Scheme 5.4).

Scheme 5.4 Regioselectivity in Pd and Rh catalyzed ring openings.

Similarly, the nickel catalyzed cyclization of 5-17, with alkyl propiolate 5-21 was found to be regioselective in forming benzocoumarin exclusively (Scheme 5.4).\textsuperscript{9} Interestingly, in each case the reaction occurred on the less hindered carbon of the olefin.

Scheme 5.5 Regioselective Ni catalyzed cyclization of 5-17

Since the nickel catalyzed ring opening of C\textsuperscript{1} substituted oxabicyclic is not regioselective, it appears that the mechanism may be different from that for palladium or rhodium catalyzed ring opening reactions of oxabicyclic alkenes. The nature of the
catalyst plays an important role in the regiochemical outcome of the reaction. Therefore it is important to understand the mechanism of reaction in detail.

5.1.1. Mechanism of Nickel Catalyzed Ring Opening Reactions

The mechanism for Ni catalyzed ring opening as proposed by Cheng begins from the reduction of Ni(II) to Ni(0) by zinc (Scheme 5.6). The Ni(0) species undergoes oxidative addition on R-I (5-2) to form Ni-(PPh₃)₂RI (5-24). Exo addition of Ni-R in Ni(PPh₃)₂RI to substrate 5-1 gives intermediate 5-25.

Scheme 5.6 Mechanism of Ni catalyzed ring opening reaction.

Cleavage of the β-oxygen-carbon bond results in the ring opening of 5-25 and is followed by reduction with zinc metal, giving the zinc salt of 5-27 and regenerating the
nickel (0) catalyst. The nickel (0) catalyst then reacts with RI to continue the catalytic cycle and hydrolysis of the zinc salt affords the final product 5-3.

For nickel catalyzed ring-opening reactions, Lautens et al. suggested the involvement of a π-allyl complex (Scheme 5.7). The mechanism involves oxidative addition of compound 5-1 to Ni(0), forming a π-allyl complex 5-28 which then reacts with the RZnX generated from the reaction of organic halide (RI, 5-2) and zinc metal. Hydrolysis of this complex gives compound 5-3.

![Scheme 5.7 Mechanism of Ni catalyzed ring opening reaction via π-allyl complex.](image)

To explore the possibility of this mechanism on nickel catalyzed ring opening of oxabicyclic alkenes, Cheng et al. carried out a few experiments and provided the following observations. First, it was found that the reaction of PhZnCl and 5-1 in the presence of Ni(PPh₃)₂Cl₂ in acetonitrile at 70 °C did not yield 5-3, but produced the biphenyl (5-29) in 78% yield (Figure 5.1).

![Figure 5.1 Structures of the by-products formed in Ni catalyzed reactions.](image)
Second, a control reaction indicated that there was no reaction of iodobenzene with the zinc metal powder in THF or acetonitrile at 60-70 °C. Third, for all reactions shown in Scheme 5.2, the products 5-30 and 5-31, which were expected for the ring-opening reaction involving a nickel π-allyl complex as intermediate, were not obtained. On the basis of the above observations, Cheng concluded that a nickel π-allyl mechanism is unlikely in ring opening reactions of oxabicyclic alkenes with aryl halides in the presence of Ni complexes.

5.2. Results and Discussion

In order to explore the nickel catalyzed ring opening reactions of unsymmetrical benzoaxanorbornadienes we selected two model compounds with electronically different types of substituents on the C1 carbon (Figure 5.2). As discussed in Chapter 3, generation of benzyne from 2-aminobenzoic acid and in situ Diels–Alder reaction with 2-substituted furans provided C1-substituted 7-oxanorbornadienes 5-32 and 5-33.

Figure 5.2 Structures of model compounds 5-32 and 5-33.

Compound 5-33 is substituted with an electron withdrawing methyl ester group whereas compound 5-32 has an electron donating ethyl substituent. It is important to note that the steric bulk of both substituents is similar. We were also interested in studying the effect of the nature of substituent on the electrophile (ArI) used for the ring opening
reactions. We selected aryl iodides possessing electron donating and an electron withdrawing functional groups for our study.

Based on the mechanisms proposed, the carbon-carbon bond formed in the reaction is a result of \textit{exo} addition of aryl nickel species, Ni(PPh$_3$)$_2$RI (5-49) onto the olefin carbons of the oxabicyclic alkenes. This is a key step for influencing the regiochemical outcome of the product (\textbf{Scheme 5.7}). Because of the presence of a substituent on allylic carbon results in the symmetry of olefin being lost, how this impacts the addition of aryl nickel species on the oxabicyclic alkene needs to be investigated (\textbf{Scheme 5.8}). We were curious to know how the electronic or steric bulk of a C$^1$ substituent affects the orientation of aryl nickel species.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_5.8.png}
\caption{Scheme 5.8 Possible transition intermediates during Ni catalyzed ring opening of C$^1$ substituted oxabicyclic alkenes.}
\end{figure}

Or does the nature of substituents on the aromatic ring of aryl iodides influence the alignment of aryl nickel species during the carbonickelation step? These, and many such unanswered questions form the basis for the current study.
5.2.1 Ring Opening of 1-Ethyl-7-oxabenzonorbornadiene with Different Aryl Iodides

Treatment of 1-ethyl-7-oxabenzonorbornadiene 5-32 containing an electron donating ethyl substituent on the bridgehead carbon with iodo benzene in the presence of Ni(Ph₃P)₂Cl₂ (5 mol%) and zinc powder (10 equivalents) in acetonitrile at 70 °C resulted in the formation of a mixture of two regioisomers 5-36a and 5-36b in approximately 67:33 ratio in 57% yield (Table 5.1). Both isomers co-elute during column chromatography as an inseparable mixture. In addition to the expected regiosomers, the nickel catalyzed reaction afforded some unidentified compounds. The major product 5-36a was a result of addition of phenyl group on the olefin carbon away from bridgehead ethyl group. When aryl group containing an electron donating group (4-iodoanisole) was reacted with 5-32, again the product obtained was mixture of isomers 5-37a and 5-37b in 65:35 in 53% yield.

Table 5.1 Ni catalyzed reactions of various aryl iodides on 1-ethyl oxabenzonorbornadiene.

<table>
<thead>
<tr>
<th>#</th>
<th>Substrate</th>
<th>Ar-I</th>
<th>Product A</th>
<th>Product B</th>
<th>a:b*</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-32</td>
<td></td>
<td><img src="image" alt="Product A" /></td>
<td><img src="image" alt="Product B" /></td>
<td>67:33</td>
<td>57%</td>
</tr>
</tbody>
</table>
When the benzene ring was substituted with an electron withdrawing group (4-nitroiodobenzene) and subjected to these reaction conditions, the expected products 5-38a and 5-38b were not obtained. This is not surprising, since it has been reported that the presence of an electron withdrawing substituent in the aromatic ring makes the dihydronaphthol ring susceptible for dehydration into the corresponding naphthalene derivatives.\textsuperscript{13} We observed similar results in Pd catalyzed ring opening reaction with an electron withdrawing \(-\text{NO}_2\) group in phenyl ring (iodonitrobenzenes).
Scheme 5.9 Ni catalyzed reactions of p-iodonitrobenzene on 1-ethyl oxabenzonorbornadiene.

Surprisingly, the product obtained from Ni catalyzed ring opening of reaction of 1-ethyl-7-oxabenzonorbornadiene 5-32 with 4-iodonitrobenzene did not match the dehydration products 5-41a and 5-41b but based on NMR and mass spectral data it appears to be the 1:1 mixture of aromatized naphthol derivatives of products 5-42a and 5-42b. Because the product is a mixture of two compounds, the NMR is complicated for structure confirmation. However a peak to peak comparison was performed with an authentic sample of 5-41a and the details are provided in the next section.

Even though oxidative transformations in organic synthesis are ubiquitous it is surprising that examples of the efficient oxidation of dihydronaphthols to 1-naphthol are rare. Martin and Chen studied the oxidation of 2-substituted-1,2-dihydronaphthol to 1-naphthol during their work directed towards synthesis of C-aryl glycosides. For conversion of 1,2-dihydronaphthols several oxidation procedures involving Dess-Martin periodinane, PCC, Swern reagent, Pd(OAc)$_2$/pyridine/O$_2$/toluene, Pd(OAc)$_2$/NaHCO$_3$/
O₂/DMSO, Pd(PPh₃)₄/PhBr/DMF/K₂CO₃ or NaH, TPAP, DMSO/NEt₃/py-SO₃, MnO₂, p-chloranil, Pd(nbd)Cl₂/sparteine/O₂, NCS/DMS/Et₃N etc were attempted with moderate success. The best results for conversion of 1, 2-dihyronaphthol to 1-naphthol derivatives were obtained by oxidation with IBX either in ethyl acetate, acetone or THF (Scheme 5.10).

Scheme 5.10 Oxidation of dihydronaphthols to 1-naphthol.

Based on this information, it appears the conversion of 1,2-dihyronaphthols (5-41a and 5-41b) to 1-naphthol derivatives (5-42a and 5-42b) may be possible in the conditions for nickel catalyzed ring opening, though it is rare.

5.2.2 Structure Confirmation by NMR

Since the nickel catalyzed ring opening of C₁ ethyl substituted bonzoxanorbonadiene 5-32 affords a regio isomeric mixture, the NMR spectral data of the products is complicated for analysis. The peak to peak comparison of C₁³ peaks of fully characterized authentic pure compounds 5-39 prepared by palladium chemistry with proposed structures 5-36a from nickel chemistry were done. The comparison shows that the C₁³ peaks of proposed structures matches perfectly with the secondary alcohol derivative. Please refer to table below for comparison of NMR data of pure authentic sample prepared using palladium chemistry.
Table 5.2 Comparison of $^{13}$C peaks of authentic 5-39 prepared by Pd catalyzed reaction with mixture of regioisomers obtained by Ni catalyzed reaction.

\[
\begin{align*}
5-32 & + 5-15 & \xrightarrow{\text{Ni}(\text{Ph}_3\text{P})_2\text{Cl}_2} \text{Zn, ACN, 70-72 °C, 12-16h}} & 5-36a & + 5-36b
\end{align*}
\]

<table>
<thead>
<tr>
<th>#</th>
<th>5-39</th>
<th>5-36a</th>
<th>5-36b</th>
<th>#</th>
<th>5-39</th>
<th>5-36a</th>
<th>5-36b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.9 (CH$_3$)</td>
<td>12.9 (CH$_3$)</td>
<td>15.2 (CH$_3$)</td>
<td>9</td>
<td>127.6 (CH)</td>
<td>127.6 (CH)</td>
<td>124.6 (CH)</td>
</tr>
<tr>
<td>2</td>
<td>25.1 (CH$_2$)</td>
<td>25.1 (CH$_2$)</td>
<td>25.4 (CH$_2$)</td>
<td>10</td>
<td>128.1 (CH)</td>
<td>128.1 (CH)</td>
<td>124.8 (qC)</td>
</tr>
<tr>
<td>3</td>
<td>47.0 (CH)</td>
<td>47.0 (CH)</td>
<td>47.0* (CH)</td>
<td>11</td>
<td>128.5 (CH)</td>
<td>128.5 (CH)</td>
<td>128.5 (CH)*</td>
</tr>
<tr>
<td>4</td>
<td>71.5 (CH)</td>
<td>71.6 (CH)</td>
<td>71.6 * (CH)</td>
<td>12</td>
<td>129.3 (CH)</td>
<td>129.3 (CH)</td>
<td>129.3 (CH)*</td>
</tr>
<tr>
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<td>122.9 CH</td>
<td>108.1 (CH)</td>
<td>13</td>
<td>133.6 (qC)</td>
<td>133.6 (qC)</td>
<td>126.0 (CH)</td>
</tr>
<tr>
<td>6</td>
<td>124.3 (CH)</td>
<td>124.3 (CH)</td>
<td>122.4 (CH)</td>
<td>14</td>
<td>136.9 (qC)</td>
<td>136.7 (qC)</td>
<td>132.3 (qC)</td>
</tr>
<tr>
<td>7</td>
<td>126.6 (CH)</td>
<td>126.6 (CH)</td>
<td>123.6 (CH)</td>
<td>15</td>
<td>138.2 (qC)</td>
<td>138.2 (qC)</td>
<td>132.6 (qC)</td>
</tr>
<tr>
<td>8</td>
<td>127.3 (CH)</td>
<td>127.3 (CH)</td>
<td>124.5 (CH)</td>
<td>16</td>
<td>138.5 (qC)</td>
<td>138.5 (qC)</td>
<td>150.1 (qC)</td>
</tr>
</tbody>
</table>

*(based on peak height)

Similarly, the peak to peak comparison of fully characterized authentic pure compounds, 5-40, prepared by palladium chemistry with proposed structures 5-37a from nickel chemistry showed perfect match, thus confirming the identity of 5-37a as a secondary alcohol derivative. The peaks corresponding to the tertiary alcohol derivatives
(5-37b) can be deduced from the remainder of the peaks in C\(^{13}\) spectra, shown in third column.

**Table 5.3 Comparison of C\(^{13}\) peaks of authentic 5-40 prepared by Pd catalyzed reaction with mixture of regioisomers obtained by Ni catalyzed reaction.**

![Chemical structure and reaction scheme]

<table>
<thead>
<tr>
<th>#</th>
<th>5-40</th>
<th>5-37a</th>
<th>5-37b</th>
<th>#</th>
<th>5-40</th>
<th>5-37a</th>
<th>5-37b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.9 (CH(_3))</td>
<td>12.9 (CH(_3))</td>
<td>12.8 (CH(_3))</td>
<td>10</td>
<td>127.6 (CH)</td>
<td>127.6 (CH)</td>
<td>128.2 (CH)</td>
</tr>
<tr>
<td>2</td>
<td>25.1 (CH(_2))</td>
<td>25.1 (CH(_2))</td>
<td>32.4 (CH(_2))</td>
<td>11</td>
<td>127.9 (CH)</td>
<td>127.9 (CH)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>46.0 (CH)</td>
<td>46.1 (CH)</td>
<td></td>
<td>12</td>
<td>129.6 (qC)</td>
<td>129.6 (qC)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>55.2 (CH(_3))</td>
<td>55.2 (CH(_3))</td>
<td>55.2 (CH(_3)) *</td>
<td>13</td>
<td>130.3 (CH)</td>
<td>130.3 (CH)</td>
<td>130.3 (CH)*</td>
</tr>
<tr>
<td>5</td>
<td>71.4 (CH)</td>
<td>71.5 (CH)</td>
<td>68.1 (CH)</td>
<td>14</td>
<td>133.6 (qC)</td>
<td>133.6 (qC)</td>
<td>133.5 (qC)</td>
</tr>
<tr>
<td>6</td>
<td>114.0 (CH)</td>
<td>114.0 (CH)</td>
<td>114.0 (CH)*</td>
<td>15</td>
<td>137.1 (qC)</td>
<td>137.1 (qC)</td>
<td>137.2 (qC)</td>
</tr>
<tr>
<td>7</td>
<td>122.8 (CH)</td>
<td>122.8 (CH)</td>
<td>123.1 (CH)</td>
<td>16</td>
<td>138.3 (qC)</td>
<td>138.3 (qC)</td>
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</tr>
<tr>
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<td>124.7 (CH)</td>
<td>124.7 (CH)</td>
<td>126.7 (CH)</td>
<td>17</td>
<td>158.8 (qC)</td>
<td>158.8 (qC)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>126.4 (CH)</td>
<td>126.4 (CH)</td>
<td>127.2 (CH)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*(based on peak height)*
Table 5.4 Comparison of C\textsuperscript{13} peaks of authentic 5-41 prepared by Pd catalyzed reaction with mixture of regio isomers obtained by Ni catalyzed reaction

The comparison between authentic sample of 5-41 and the product obtained from Ni catalyzed reaction of 5-iodonitrobenzene clearly shows that the majority of peaks do
not match. From this data it is clear that the product obtained from Ni catalyzed reaction is different from the one obtained from Pd catalyzed ring opening.

5.2.3 Ring Opening of C$^1$-CO$_2$Me-benzoxanorbornadine with Different Aryl Iodides

When 1-carbomethoxy-7-oxabenzonorbornadiene (5-33) was reacted with iodobenzene 5-15 in the presence of Ni(Ph$_3$P)$_2$Cl$_2$ (5 mol%) and zinc powder (10 equivalents) in acetonitrile at 70 °C, the expected dihydronaphthol was not obtained. It appears that the dihydronaphthols formed as result of ring opening with aryl iodide undergo rapid dehydration to form the naphthalene derivative.

![Scheme 5.11 Ni catalyzed regioselective ring opening of 5-33](image)

On the other hand, the nickel catalyzed reaction on 5-33 resulted in formation of a single regioisomer 5-45 exclusively in 63% yield. The regio isomer resulting from addition of aryl group at olefin carbon close to –CO$_2$Me was not formed. When an aryl group containing an electron donating group (4-iodoanisole) was reacted with 5-33, again a single regioisomer was obtained as result of attack on olefin carbon atom away from bridgehead substituted –CO$_2$Me in 68% yield (5-46). However, when a benzene ring substituted with an electron withdrawing group (4-nitroiodobenzene) was used, the expected product (5-47) was obtained in 25% yield along with some unreacted starting material.
Table 5.5 Ni catalyzed reactions of various aryl iodides on 1-carboxethoxy-7-oxa-benzonorbornadiene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate Ar-I</th>
<th>Product a</th>
<th>a:b</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-33</td>
<td>5-45</td>
<td>100:0</td>
<td>63%</td>
</tr>
<tr>
<td>2</td>
<td>5-33</td>
<td>5-46</td>
<td>100:0</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>5-33</td>
<td>5-47</td>
<td>100:0</td>
<td>25%</td>
</tr>
</tbody>
</table>
When an electron withdrawing substituent is found on C\textsuperscript{1} carbon the reaction was regioselective, affording one product exclusively as result of attack on the olefinic carbon away from C\textsuperscript{1} substituent. However, with an electron withdrawing substituent on the C\textsuperscript{1} carbon, the product appears to undergo spontaneous dehydration to form the aromatized naphthalene derivative irrespective of the substituent on the aromatic ring of the aryl iodides.

5.2.4 Proposed Mechanism to Explain the Regioselectivity in Ni Catalyzed Ring Opening Reactions

The regioselectivity of the nickel catalyzed ring opening reaction depends on the electronic nature of substituent at C\textsuperscript{1} carbon. When an electron donating ethyl substituent was present on the bridgehead carbon, a 2:1 regioisomeric mixture of ring opened products were obtained. However the presence of electron withdrawing methyl ester substituent on C\textsuperscript{1} carbon resulted in formation single regioisomer irrespective of electronic nature of substituent on the aromatic ring of newly added aryl group.

The mechanisms proposed by Cheng et al. for both Pd and Ni catalyzed ring opening reactions are similar but the regioselectivity in both cases is different.\textsuperscript{2} The reasons for the formation of mixtures of isomers in nickel catalyzed reaction could be explained only after detailed mechanistic study. However, Lautens et al. suggested the involvement of π-complex in Ni catalyzed ring opening reactions.\textsuperscript{12}

Based on the preliminary results obtained from ring opening reactions of electron deficient and electron rich C\textsuperscript{1} substituted benzooxanorbornadienes, the involvement of π-Ni complex mechanism could account for formation of mixture of isomers as shown in Scheme 5.12.
Scheme 5.12 Proposed mechanisms to explain formation of regioisomeric mixture in Ni catalyzed ring opening reactions.

When electron withdrawing methyl ester is present on the C1 carbon, the Ni-π-complex 5-51 is obtained exclusively, thus forming single product 5-52 as result of addition of aryl group on C3 to form arylative ring opening product. However, when ethyl group is present at C1 carbon, both electronic and steric factors come into play. The formation of major product is as result of addition of aryl group on the carbon (olefin carbon 3) away from sterically bulky ethyl group. The minor product is obtained as result addition of aryl group on the Ni-π-complex 5-49b to form 5-50b as the minor regioisomer.

5.3 Proposed Mechanism for Dehydration of 1, 2-Dihyronaphthols

It has been observed that ring opening reactions on oxabicyclic alkenes bearing an electron withdrawing substituent on the bridgehead carbon leads to spontaneous dehydration of 1,2-dihyronaphthol, resulting in the formation of the naphthalene derivative. This phenomenon was observed both in Pd and Ni catalyzed ring opening reactions and occurred with both electron donating and electron withdrawing substituents
on the aryl iodide. To explain this trend, the following mechanism as shown in **Scheme 5.13** is proposed for oxabicyclic alkenes containing electron withdrawing \(-\text{CO}_2\text{Me}\) substituent on C\(^1\) carbon. It is believed that due to the presence of the strong electron withdrawing \(-\text{CO}_2\text{Me}\) group in the intermediate 5-53, the proton on the allylic carbon (carbon 3) becomes acidic. In the presence of base, the allylic proton could be undergoing deprotonation. The negative charge on the molecule could be stabilized as result of resonance stabilization as depicted in the **Scheme 5.13**, to form the intermediate 5-55. The driving force for elimination of water is the subsequent aromatization resulting in the formation of stable naphthalene derivative 5-56.

**Scheme 5.13 Proposed mechanism for the dehydration of 1, 2-dihydronaphthol due to presence of an EWG at C\(^1\) carbon.**

In addition, the palladium catalyzed ring opening reactions of the oxabicyclic alkenes using aryl iodides containing an electron withdrawing substituent also resulted in dehydration irrespective of electronic nature of the substituent on the C\(^1\) carbon. The
presence of an electron withdrawing –CO\textsubscript{2}Me as well as an electron donating ethyl substituent on C\textsuperscript{1} carbon both led to facile dehydration.

The following mechanism as shown in Scheme 5.14 is proposed to account for the dehydration of 1,2-dihydronaphthols obtained by ring opening of oxabicyclic alkenes with aryl iodides containing electron withdrawing groups. Due to the presence of strong electron withdrawing –NO\textsubscript{2} group in the intermediate 5-57, the proton on the benzylic carbon (carbon 3) becomes acidic. The allylic proton could be undergoing deprotonation in the presence of base. The negative charge on the molecule could be stabilized as result of resonance stabilization as depicted in the Scheme 5.14, to form the intermediate 5-59. The driving force for the elimination of water is the subsequent aromatization resulting in the formation of stable naphthalene derivative 5-60.

![Scheme 5.14 Proposed mechanisms for the dehydration of 1,2-dihydronaphthols due to presence of an electron withdrawing substituent in newly added aryl ring.](image-url)
5.4 Experimental

All reactions were performed in septum-sealed, flame-dried flasks under nitrogen atmosphere. All commercial reagents were used as received from their respective suppliers. $^1$H NMR and $^{13}$C NMR spectra were recorded at 300/400 and 75/100 MHz, respectively. Chemical shifts are reported in parts per million (δ) using internal solvent signals as references and coupling constants are reported in hertz (Hz). Iodobenzene, 4-iodoanisole and 4-iodonitrobenzene were used as received from Aldrich. Other 1-substituted-7-oxa-benzonorbornadienes were synthesized according to the procedures reported in chapter 3.

**General procedure for the Ni catalyzed reaction between 1-substituted-7-oxabenzonorbornadiene and aryl iodides:**

NiCl$_2$(PPh$_3$)$_2$ (0.016 g, 0.05 mmol), zinc powder (0.315 g, 5 mmol) and a 1-substituted oxabenzonorbornadiene derivative (0.5 mmol) were weighed out in dry flask equipped with magnetic stirring bar. After the flask was sealed with a rubber septum, the system was evacuated and purged with nitrogen gas three times. A mixture of freshly distilled acetonitrile (3.0 mL) and aryl halide (0.55 mmol) was added via a syringe through the rubber septum into the flask. The mixture was heated with stirring at 70 °C until the 1-substituted-7-oxabenzonorbornadiene derivative was consumed as indicated by TLC analysis of the solution. During the reaction, the color of the mixture gradually changed from green to brown-green and remained the same color for the rest of reaction period.

The reaction mixture was then cooled and stirred under air for 15-20 minutes at room temperature. The reaction mixture was diluted with dichloromethane (10-15 mL)
and filtered through a pad of celite. The obtained filtrate was concentrated on a rotary evaporator to get brown oily residue. The crude residue was purified by flash chromatography, eluting with mixtures EtOAc/hexanes in the ratio given to provide the product.

Preparation of *cis*-1,2-Dihydro-4-ethyl-2-(phenyl)-1-naphthol (a) and *cis*-1,2-Dihydro-1-ethyl-2-(phenyl)-1-naphthol (b) Yield: 57% (143 mg, 1.0 mmol, light brown oil); Rf = 0.35 (EtOAc–hexanes, 1:5); 1H NMR (CDCl3, 400 MHz): δ 1.27 (t, J = 7.4 Hz, 3H of a), 1.37 (t, J = 7.5 Hz, 3H of b) 1.70 (d, J = 8.3 Hz, 1H of a), 2.62 (q, J = 7.3 Hz, 2H of a), 3.05 (q, J = 7.5 Hz, 2H of b), 3.86 (d, 4.5 Hz, 1H of a), 4.93 (dd, J = 7.5 & 6.4 Hz, 1H of a), 5.97 (d, J = 4.0 Hz, 1H of a), 6.02 (s, 1H of b), 6.62 (d, J = 7.5 Hz, 1H of b), 7.12 (d, J = 7.6 Hz, 1H of b), 7.20-7.35 (m, ~9H of a and b), 7.36-7.60 (m, ~7H of a and b), 8.02 (d, J = 8.1 Hz, 1H of b), 8.23-8.26 (m, 1H of b); 13C (APT) NMR (CDCl3, 75 MHz): 12.9 (CH3 of a), 15.2 (CH3 of b), 25.1 (CH2 of a), 25.4 (CH2 of b), 47.0 [CH of a and b (based on peak height)], 71.6 [CH of a and b (based on peak height)], 108.1 (CH); 122.4 (CH); 122.9 (CH of a); 123.6 (CH of b); 124.3 (CH of a); 124.5 (CH); 124.6 (CH); 124.8 (qC); 126.0 (CH); 126.6 (CH of a), 127.3 (CH of a), 127.6 (CH of a), 128.1 (CH of a), 128.5 [CH of a and b (based on peak height)], 129.3 [CH of a and b (based on peak height)]; 132.3 (qC of b); 132.6 (qC of b); 133.6 (qC of a), 136.7 (qC of a), 138.2 (qC of a), 138.5 (qC of a); 150.1 (qC of b);
Preparation of cis-1,2-Dihydro-4-ethyl-2-(4-methoxyphenyl)-1-naphthol and cis-1,2-Dihydro-1-ethyl-2-(4-methoxyphenyl)-1-naphthol

Yield: 53% (148 mg, 1.0 mmol, light brown oil); R<sub>f</sub> = 0.30 (EtOAc–hexanes, 1:5); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): \( \delta \) 1.10-1.30 (m, CH<sub>3</sub>, 3H of a and 3H of b), 1.49 (d, J = 8.6 Hz, 1H, OH of a); 1.70-1.82 (m, 1H, OH of b); 2.40-2.65 (m, CH<sub>2</sub>, 2H of a and 2H of b); 3.75 (s, OCH<sub>3</sub>, 3H of a and 3H of b); 4.71 (d, 1H of b) 4.87 (at, 1H of a); 5.28 (s, 1H of b); 5.77 (at, 1H of b); 5.91 (d, J = 4.3 Hz, 1H of a), 6.81 (d, J = 8.4 Hz, 2H of a), 7.11 (d, J = 8.5 Hz, 2H of a), 7.13-7.43 (m, H of a and b); <sup>13</sup>C (APT) NMR (CDCl<sub>3</sub>, 75 MHz): 12.8 (CH<sub>3</sub> of b); 12.9 (CH<sub>3</sub> of a); 25.1 (CH<sub>2</sub> of a); 32.4 (CH<sub>2</sub> of b); 46.1 (CH of a); 55.2 (CH of a and b); 68.1 (CH of b); 71.5 (CH of a); 114.0 [CH of a and b (based on peak height)]; 119.8 (CH of b); 122.8 (CH of a); 123.1 (CH of b); 124.7 (CH of a), 126.4 (CH of a), 126.7 (CH of b); 127.2 (CH of b); 127.6 (CH of a), 127.9 (CH of a), 128.2 (CH of b); 129.6 (qC of a), 130.3 [CH and B (based on peak height)], 133.5 (qC of b); 133.6 (qC of a), 137.1 (qC of a), 137.2 (qC of b); 138.3 (qC of a), 158.8 (qC of a);
Preparation of 4-Ethyl-2-(4-nitro-phenyl)-1-naphthol and 4-Ethyl-3-(4-nitro-phenyl)-1-naphthol Yield: 28% (82 mg, 1.0 mmol, dark yellow oil); $R_f = 0.30$ (EtOAc–hexanes, 1:5); $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 1.34 (t, J =7.5 Hz, 3H), 1.39 (t, J =7.5 Hz, 3H), 2.96-3.13 (m, 4H), 5.21 (brs, 1H, OH), 5.54 (brs, 1H, OH), 6.73 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H), 7.19 (s, 1H), 7.44-7.65 (m, 5H), 7.70-7.76 (m, 2H), 7.96-8.07 (m, 2H), 8.18-8.24 (m, 1H), 8.27-8.37 (m, 4H); $^{13}$C (APT) NMR (CDCl$_3$, 75 MHz): 15.1 (CH$_3$), 26.4 (CH$_2$), 108.2 (CH), 119.1 (qC), 122.2 (CH), 122.7 (CH), 123.9 (CH), 124.4 (CH), 124.8 (CH), 124.9 (qC), 125.5 (CH), 125.7 (CH); 126.2 (CH), 127.0 (CH) 130.2 (CH), 132.8 (qC), 133.4 (qC), 145.0 (qC), 146.4 (qC), 147.0 (qC), 149.8 (qC); HRMS (EI) calcd. for C$_{18}$H$_{15}$NO$_3$ (M$^+$): 293.1052 Found: 293.1058

\[
\begin{array}{c}
\text{MeO} & \text{CO}_2\text{Me} \\
\text{Ni(Ph}_3\text{P})_2\text{Cl}_2 & \text{Zn, ACN} & \text{Ni(Ph}_3\text{P})_2\text{Cl}_2 \\
\text{70-72 °C, 12-16h} & \text{MeO} & \text{CO}_2\text{Me}
\end{array}
\]

Preparation of 3-Phenynaphthalene-1-carboxylic acid methyl ester. Yield: 63% (83 mg, 0.5 mmol, pale yellow oil); $R_f = 0.50$ (EtOAc–hexanes, 1:5); IR (CH$_2$Cl$_2$); 3054, 2987, 1716, 1436, 1265, 1197, 1152, 897 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 4.03 (s, 3H), 7.40 (t, J =7.3 Hz, 1H), 7.43 (t, 1.1 Hz, 1H), 7.50 (t, J = 7.3 Hz, 1H), 7.45-7.58 (m, 3H), 7.62 (at, 1H), 7.74(m, 2H), 7.92(d, J = 8.1 Hz, 1H), 8.20 (d, J= 1.6 Hz, 1H), 8.48 (d, 1.9 Hz, 1H), 8.93(d, 8.7 Hz, 1H); $^{13}$C (APT) NMR (CDCl$_3$, 75 MHz): 52.2 (CH$_3$), 125.7(CH), 126.5 (CH), 127.3 (CH), 127.6 (qC), 127.7 (CH), 128.8 (CH); 128.9 (CH); 129.8(CH), 130.4 (qC), 130.8 (CH), 134.2 (qC), 137.2 (CH), 139.9 (qC), 167.9 (qC); HRMS (EI) calcd. for C$_{18}$H$_{14}$O$_2$ (M$^+$): 262.0994; found: 262.0998
Preparation of 3-(4-Methoxy-phenyl)-naphthalene-1-carboxylic acid methyl ester.

Yield: 68% (99 mg, 0.5 mmol, light brown solid); $R_f = 0.38$ (EtOAc–hexanes, 1:5); IR (CH$_2$Cl$_2$): 3054, 2987, 1716, 1610, 1517, 1437, 1422, 1265, 1181, 739 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): CDCl$_3$ δ 3.85 (s, 3H), 4.02 (s, 3H), 7.02 (d, $J = 8.8$ Hz, 2H), 7.53 (m, 1H), 7.59 (dt, $J = 8.4$ & 1.3 Hz, 1H), 7.66 (d, $J = 8.7$ Hz, 2H), 7.89 (d, $J = 8.0$ Hz, 1H), 8.13(d, $J = 1.1$ Hz, 1H), 8.44(d, $J = 1.9$ Hz, 1H); 8.91(d, $J = 8.5$ Hz, 1H); $^{13}$C (APT) NMR (CDCl$_3$, 100 MHz): 52.1 (CH$_3$), 55.3 (CH$_3$), 114.3(CH), 125.6 (CH), 126.5 (CH), 127.4(CH), 127.5 (qC), 128.3 (CH); 128.6 (CH); 129.6(CH), 129.9 (CH), 130.0 (qC), 132.3 (qC), 134.3(qC) 136.8 (qC), 159.4 (qC), 167.9 (qC); HRMS (ESI) calcd. for $C_{19}H_{16}O_3$ (M+H$^+$): 293.1177; found: 293.1176

Preparation of 3-(4-Nitro-phenyl)-naphthalene-1-carboxylic acid methyl ester

Yield: 25% (38 mg, 0.5 mmol, yellow solid); $R_f = 0.50$ (EtOAc–hexanes, 1:4); IR (CH$_2$Cl$_2$): 3080, 1715, 1597, 1519, 1434, 1350, 1250, 1193 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz):δ 4.03 (s, 3H), 7.55-7.70 (m, 2H), 7.85 (d, $J = 8.9$ Hz, 2H), 7.95 (d, $J = 8.6$ Hz, 1H), 8.23 (d, $J = 1.6$ Hz, 1H), 8.32 (d, $J = 8.9$ Hz, 2H), 8.42(d, $J = 2.0$ Hz, 1H), 8.91 (d, $J = 8.6$ Hz, 1H); $^{13}$C (APT) NMR (CDCl$_3$, 100 MHz): 52.4 (CH$_3$), 124.2(CH), 125.8 (CH), 240
127.1(CH), 127.9(CH), 128.3 (qC), 128.7 (CH); 129.0 (CH); 131.0(qC), 131.6 (CH), 134.1 (qC), 134.7 (qC), 146.2 (qC), 147.3 (qC), 167.5 (qC); HRMS (ESI) calcd. for C$_{18}$H$_{13}$NO$_4$ (M+H$^+$): 308.0922 Found; 308.0936

5.5 References (Chapter 5)


Chapter 6

Epilogue
6.1 Synopsis

In order to broaden the substrate scope of transition metal catalyzed ring opening reactions of unsymmetrical oxabicyclic alkenes, an understanding of the regiochemical outcome of the reaction is of utmost importance. To study this, a large number of unsymmetrical C\textsuperscript{1} substituted oxabicyclic alkenes needed to be synthesized. According to literature procedures, the most efficient method of accessing these structures was through a Diels-Alder reaction between dimethyl acetylenedicarboxylate (DMAD) or an \textit{in situ} generated benzyne and 2-substituted furan. Although the DMAD and benzyne reagents were easily accessible, obtaining a wide array of 2-subsituted furans proved much more difficult.

Only a few examples of 2-substituted furans are commercially available and thus many had to be synthesized by hand. We identified 2-bromofuran as a key starting material for this task; however like many of the 2-substituted furans, 2-bromofuran was not readily available from catalog reagent suppliers like Aldrich. Complicating matters, the synthetic procedures available from the literature involved cumbersome procedures and poor yields for the isolation of 2-bromofuran. Because of this we developed a simple, and scalable process for production of up to 50-60 grams of pure 2-bromofuran. This newly developed procedure would serve as a our starting point, allowing us to access a variety of differently substituted oxabicyclic alkenes from which regiochemical information could then be collected.

Starting from 2-bromofuran, a number of transformations were theoretically possible to obtain the desired 2-substituted furans. For the preparation of 2-aryl furans, we optimized a palladium catalyzed Suzuki cross-coupling reaction of 2-bromofuran with
a wide range of aryl boronic acids in good to excellent yields (Scheme 6.1). Unfortunately, the protocol was not successful in accessing 2-alkyl substituted furans and thus another procedure was sought. We were successful in preparing a series of 2-alkyl furans through an optimized iron catalyzed cross coupling reactions of 2-bromofuran with wide range of alkyl Grignard reagents using Fe(acac)$_3$ in DMPU in moderate yields (Scheme 6.1).

Scheme 6.1 Preparation of 2-aryl furans by Suzuki cross-coupling protocol (top) and preparation of 2-alkyl furans by iron cross-coupling protocol (bottom).

Interestingly, iron catalyzed cross-coupling reactions with aryl Grignard reagents gave very poor yields. Thus, the palladium catalyzed cross-coupling reactions and iron catalyzed cross-coupling reactions are complementary to each other, wherein the former is suitable for preparing 2-aryl furans while the later is useful for the preparation of 2-alkyl furans.

With the 2-substituted furans in hand, we set out to synthesize our primary substrates with which the ring opening reaction would be carried out, the C$_1$ substituted oxabicyclic alkenes. The easiest access to C$_1$ substituted oxanorbornadienes was through
Diels-Alder cycloaddition of 2-substituted furans with commercially available DMAD as shown in **Scheme 6.2**. The series of C¹ substituted benzoxanorbornadienes was prepared by Diels-Alder cycloaddition of 2-substituted furans with *in situ* generated benzyne. For our work, benzyne was prepared by treatment of anthranilic acid with isoamyl nitrite (**Scheme 6.2**).

**Scheme 6.2** Preparation of C¹-substituted-oxanorbornadiene (top), and preparation of C¹-substituted-oxabenzonorbornadiene.

The ring opening reactions on these newly synthesized substrates were optimized by varying palladium catalyst, solvent and Lewis acids using two model compounds. The ring opening reactions have proven to be, for the most part, high yielding under favourable conditions. The Pd catalyzed ring opening reactions of C¹ substituted benzoxanorbornadienes have been shown to be highly regioselective, demonstrating an exclusive preference for the double bond carbon distal to that of the C¹ substituted carbon as shown in **Scheme 6.3**. The presence of an electron withdrawing group at the C¹ carbon of benzoxanorbornadiene resulted in spontaneous dehydration of 1,2-dihydronaphthol.
derivative. The dehydration occurred with either electron donating substituents or electron withdrawing substituents on the aryl iodide. The presence of electron withdrawing substituent in aryl iodide triggers the dehydration in the oxabenzonorbonadiene substituted with electron donating ethyl substituent at C\(^1\) carbon as well. The ring opening reactions of C\(^1\) substituted oxanorbornadienes provided easy access to highly functionalized biphenyl derivatives in very regioselective fashion in good to moderate yields (Scheme 6.3).

\[
\begin{align*}
\text{Scheme 6.3 Preparation of highly functionalized cis-1,2-dihydronaphthols (top),}
\end{align*}
\]
preparation of functionalized naphthalenes (middle), and preparation of highly
functionalized biphenyls by Pd catalyzed ring opening reactions (bottom).

The ring opening reactions were further explored using a nickel catalyst. It was
found that the nickel catalyzed ring opening reaction with carboxymethyl substituent
occurred regioselectively to form a single regio isomer as result of addition of the aryl
group on the olefin carbon away from the C1 substituent. However, the nickel catalyzed
ring opening of an oxabenzonorbornadiene with an electron donating ethyl substituent
resulted in the inseparable regioisomeric mixture of ring opened products (Scheme 6.4).

![Scheme 6.4 Ni catalyzed regioselective ring opening reactions (top) and Ni catalyzed
non-regioselective ring opening reactions (bottom).](image)

Building on the pioneering work by Lautens and Cheng groups, the substrate
scope of transition metal catalyzed ring opening reactions have been successfully
expanded to a variety of C1 substituted oxabenzonorbornadienes and oxanorbornadiene
systems. The information contained within this thesis will play a significant role in the application of this methodology to the construction of biologically relevant molecules.

### 6.2.0 Future Perspective

The tetrahydronaphthalene ring is a core structure in many medicinally useful compounds as shown in Figure 6.1. The development of synthetic strategies for easy access to these molecules will attract the attention of industrial chemists. Many of these molecules can be prepared using ring opening reactions involving oxabicyclic alkenes. Therefore, further development of ring opening reactions will have significant impact in the pharmaceutical industry which is always looking at ways of preparing the complex molecules in shortest possible routes.

![Figure 6.1 Medicinally useful molecules with tetrahydronaphthalene core.](image-url)
6.2.1 Intramolecular Ring Opening Reactions

From the studies we conducted using a variety of substituents on bridgehead carbon it is clear that a wide range of groups are tolerated during ring opening reactions. The bulky TMS, t-Bu, biphenyl as well as the electron withdrawing acetyl and carboxymethyl groups are shown to undergo the ring opening reaction efficiently. The hydroxymethyl group containing a free OH group was also tolerated at C\(^1\) carbon of oxabicyclic alkene during ring opening reactions. The next extension of this methodology would be to introduce substituents containing aryl iodides or alkenyl iodides that can participate in an intramolecular ring opening to form highly functionalized polycyclic templates as proposed in Scheme 6.5.

![Scheme 6.5 Proposed intramolecular ring opening reactions.](image)

6.2.2 Kinetic Resolution

The palladium catalyzed ring opening reactions of C\(^1\) substituted oxabicyclic alkenes are highly regioselective. A single regioisomer is obtained as a result of addition of aryl group on the olefin carbon away from bridgehead carbon. Several enantioselective ring opening reactions have been developed using different types of chiral ligands. These chiral ligands can be utilized for the ring opening reaction of racemic C\(^1\) substituted
oxabicyclic alkenes to form optically enriched cis-dihyronaphthols as proposed in Scheme 6.6. The unreacted C₁ substituted benzoxanorbornadiene will also be obtained as enantio enriched product.

Scheme 6.6 Proposed kinetic resolution of recemic benzoxanorbornadienes.

7.0 Appendix (Page 252-276)
\textbf{H NMR of cis-1,2-Dihydro-4-ethyl-2-(4-methoxyphenyl)-1-naphthol}

\textbf{MAR-II-48-1 in CDCl$_3$ (400Mhz) 32 scans}

\textbf{Proton 32 scans}

\textbf{OH}

\textbf{OMe}

\textbf{4-46a}

\textbf{10.0} \textbf{9.5} \textbf{9.0} \textbf{8.5} \textbf{8.0} \textbf{7.5} \textbf{7.0} \textbf{6.5} \textbf{6.0} \textbf{5.5} \textbf{5.0} \textbf{4.5} \textbf{4.0} \textbf{3.5} \textbf{3.0} \textbf{2.5} \textbf{2.0} \textbf{1.5} \textbf{1.0} \textbf{0.5} \textbf{ppm}
$^1$C NMR of cis-1,2-Di Hydro-4-ethyl-2-(4-methoxyphenyl)-1-naphthol
$^1$H NMR of cis-1,2-Dihydro-4-methyl-2-(4-methoxyphenyl)-1-naphthol
C NMR of cis-1,2-Dihydro-4-methyl-2-(4-methoxyphenyl)-1-naphthol
Molecular Structure of cis-1,2-Dihydro-4-methyl-2-(4-methoxyphenyl)-1-naphthol from X-Ray Diffraction analysis
\[^{1}\text{H} \text{NMR of cis-1,2-Dihydro-4-cyclobutyl-2-(4-methoxyphenyl)-1-naphthol}\]
C NMR of cis-1,2-Dihydro-4-cyclobutyl-2-(4-methoxyphenyl)-1-naphthol
$^1$H NMR of 3-(4-Methoxyphenyl)-naphthalene-1-carboxylic acid methyl ester
$^{13}$C NMR of 3-(4-Methoxyphenyl)-naphthalene-1-carboxylic acid methyl ester
H NMR of 3-Phenyl-naphthalene-1-carboxylic acid methyl ester

MAR-II-77-1 In CDCl₃
Ring opening of Ethyl BND with Iodobenzene
(repeat NMR)
Proton 4 scans

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**NS**
MAR-II-77-1 (400MHz)H
**ECD**
**PROC**
1
**DATA**
20110626
**TIME**
17:11
**INSTRUM**
spect
**PROC**
5 mm PABBO BB-
**PROD**
ep370
**TD**
32768
**SOLVENT**
CDCl₃
**NS**
4
**DS**
0
**SW**
5597.015 Hz
**FID**
0.172027 Hz
**AQ**
2.9273246 msec
**TA**
134
**DF**
89.333 us
**DS**
6.65 us
**TE**
294.9 K
**DI**
1.00000000
**TOO**
1

---------- CHANNEL e1 ----------
**NUCL**
1H
**EI**
14.60 us
**EL**
-1.20 dB
**PGN**
13.41083047 W
**SPOL**
400.1324730 MHz
**ST**
32768
**SF**
400.1300447 MHz
**WDM**
1M
**SIEB**
0
**LAM**
0.30 Hz
**GB**
0
**PC**
1.00
$^{13}$C NMR of 3-Phenyl-naphthalene-1-carboxylic acid methyl ester

MAR-II-77-1 in CDCl₃
Ring opening of Ethyl BND with Iodobenzene (repeat NMR)
Quaternary and $^{13}$C down CH₃ and CH down
$^1$H NMR of 3-(4-Methoxy-phenyl)-naphthalene-1-carboxylic acid methyl ester

MAR-II-60-1 in CDCl$_3$(400MHz)
Repeat NMR
Proton 4 scans
$^{13}$C NMR of 3-(4-Methoxy-phenyl)-naphthalene-1-carboxylic acid methyl ester
$^1$H NMR of 3-(4-Nitro-phenyl)-1-ethyl-naphthalene
$^{13}$C NMR of 3-(4-Nitro-phenyl)-1-ethyl-naphthalene
$^1$H NMR of Dimethyl 4'-methoxy-1, 1'-biphenyl-5-ethyl-3, 4-dicarboxylate
C NMR of Dimethyl 4-′-methoxy-1, 1-′-biphenyl-5-ethyl-3, 4-dicarboxylate

NAME  MAR-II-27-1
EXPNO  2
PROCNO  1
Date  28/10/94
Time  18.80
INSTRUM  400
PROBDD  5 mm FABBO BB-
FULPROG  nmed
TD  655/6
SOLVENT  CDC3
NS  200
DS  0
SWH  17985.61 Hz
FIDRES  0.274439 Hz
AQ  1.829968 sec
RG  23178.5
DW  27.800 usec
DE  6.00 usec
TE  301.5 K
CNST2  145.000000
CNST11  1.000000
DI  6.0000000 sec
D20  0.00069655 sec
TD0  1

CHANNEL f1

NUCI  13C
P1  9.00 usec
E2  13.00 usec
PL  2.00 dB
PLW  48.9671216 W
SFO1  75.4753953 MHz

CHANNEL f2

CPDPRG2  waitz16
NUCI  1H
PCPD2  70.00 usec
PL  0.00 dB
PLW  14.30 dB
PL2W  10.29873466 W
PL2W  0.38363425 W
SFO2  306.1312655 MHz
SI  32768
SB  75.4757523 MHz
WDW  2 EM
SSB  0
LB  3.00 Hz
GE  9
PC  0.50
$^1$H NMR of Dimethyl 4-methoxy-1,1'-biphenyl-5-phenyl-3,4-dicarboxylate

MAR-III-5-2 in CDCl$_3$(400Mhz)
Ring opening of Phenyl BND with 4-iodoanisole
Proton 4 scans

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$^{13}$C NMR of Dimethyl 4'-methoxy-1', 1'-biphenyl-5-phenyl-3, 4-dicarboxylate
H NMR of cis-1,2-Dihydro-4-ethyl-2-(4-methoxyphenyl)-1-naphthol and cis-1,2-Dihydro-1-ethyl-2-(4-methoxyphenyl)-1-naphthol
$^{13}$C NMR cis-1,2-Dihydro-4-ethyl-2-(4-methoxyphenyl)-1-napthol and cis-1,2-Dihydro-1-ethyl-2-(4-methoxyphenyl)-1-naphthol
$^1$H NMR of 3-(4-Methoxy-phenyl)-naphthalene-1-methylketone
13C NMR of 3-(4-Methoxy-phenyl)-naphthalene-1-methylketone
$^1$H NMR of cis-1,2-Dihydro-4-ethyl-2-(phenyl)-1-naphthol (a) and cis-1,2-Dihydro-1-ethyl-2-(phenyl)-1-naphthol (b)
$^{13}$C NMR of cis-1,2-Dihydro-4-ethyl-2-(phenyl)-1-naphthol (a) and cis-1,2-Dihydro-1-ethyl-2-(phenyl)-1-naphthol (b)