Contemporary Organic Transformations Enabled by Novel Cationic Processes

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CONTEMPORARY ORGANIC TRANSFORMATIONS ENABLED BY NOVEL CATIONIC PROCESSES

A Dissertation
Submitted to the Graduate Faculty of the
Louisiana State University
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Chemistry

by
Caitlan Ayala
B.S., Northern Illinois University, 2011
May 2016
This work is dedicated to my family: my parents, Karen and Tony Ayala,
siblings, Meagann and AJ Ayala, and Rachel Mynier,
I wouldn’t be here without you.
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LIST OF ABBREVIATIONS

[α]^{20}_D .............................................................. absolute optical rotation

^{1}H ..................................................................... proton NMR

^{13}C ..................................................................... carbon NMR

Å .......................................................................... angstrom

Ac ................................................................. acetate

b ........................................................................... broad

Bn ....................................................................... benzyl

Boc .................................................................... tert-butoxycarbonyl

Bu ......................................................................... butyl

CDCl\textsubscript{3} .................................................................. deuterated chloroform

cm .......................................................................... centimeter

COSY ..................................................................... correlation spectroscopy

CSA ..................................................................... camphorsulfonic acid

\delta ................................................................. chemical shift

d ........................................................................... doublet

DCM ...................................................................... dichloromethane

DEPT .................................................................... distortionless enhancement by polarization transfer

DIBAL .................................................................... diisobutylaluminium hydride

DIPEA ................................................................... N,N-diisopropylethylamine

DMAP ..................................................................... 4-dimethylaminopyridine

DMF ...................................................................... dimethylformamide

DMP ..................................................................... Dess-Martin periodinane
DMSO ................................................................. dimethylsulfoxide
dr ................................................................. diastereomeric ratio
ee ........................................................................... enantiomeric excess
er ............................................................................ enantiomeric ratio
Et ................................................................. ethyl
FT-IR .......................................................... Fourier-transform infrared
g ............................................................ gram
GCMS .............................................................. gas chromatography mass spectrometry
HPLC .............................................................. high-performance liquid chromatography
HRMS .............................................................. high resolution mass spectrometry
Hz ..................................................................... Hertz
iPr ................................................................ isopropyl
iPrOH ................................................................ isopropanol
$J$ ................................................................ coupling constant
LAH .............................................................. lithium aluminium hydride
LDA .............................................................. lithium diisopropylamide
m ................................................................. multiplet
mCPBA .......................................................... meta-chloroperoxybenzoic acid
Me ................................................................. methyl
MeOH ........................................................... methanol
mg ............................................................... milligram
$\mu$g ................................................................ microgram
mL ................................................................... milliliter
mM .............................................................................................................. millimolar
mmol ............................................................................................................. millimol
NBS .............................................................................................................. N-bromosuccinimide
NMO ........................................................................................................... N-methylmorpholine N-oxide
NMR .............................................................................................................. nuclear magnetic resonance
NOE .............................................................................................................. nuclear Overhauser effect
NOESY ......................................................................................................... nuclear Overhauser effect spectroscopy
p-Tol .......................................................................................................... para-toluoyl
Ph ................................................................................................................ phenyl
PMB ............................................................................................................. para-methoxybenzyl
ppm ................................................................................................................. part per million
PPTS .............................................................................................................. pyridinium para-toluenesulfonate
Py ............................................................................................................... pyridine
Py·TfOH .................................................................................................... pyridinium triflate
Rf .................................................................................................................. retention factor
s ..................................................................................................................... singlet
t ..................................................................................................................... triplet
TBAF .............................................................................................................. tetra-N-butylammonium fluoride
TBS ............................................................................................................. tert-butylidimethylsilyl
t-Bu ............................................................................................................. tert-butyl
TEA .............................................................................................................. triethylamine
TEMPO ...................................................................................................... 2,2,6,6-tetramethylpiperidine-1-oxyl
Tf ................................................................................................................... triflate

xiv
TFA .......................................................................................................................... trifluoroacetic acid
THF .......................................................................................................................... tetrahydrofuran
TLC .......................................................................................................................... thin layer chromatography
TRIP ......................................................................................................................... 3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
Ts ................................................................................................................................. tosyl
UV ............................................................................................................................. ultraviolet
ABSTRACT

This dissertation focuses on the development of synthetic methodologies in organic synthesis in two different areas. Chapter 1 discusses the more recent examples of transforming alcohols to their corresponding alkyl chlorides. The first area of our group’s research interest is the development of a mild chlorination method from unactivated alcohols, detailed in Chapter 2.

Chapter 3 provides an insight into the history of oxyallyl cations, the basis of the second methodology development project in our laboratory. This chapter focuses on the traditional reactions that utilize these reactive intermediates, and it also showcases the concept of direct nucleophilic addition and the applications of the α-indole ketones. Chapters 4 through 7 detail the discovery and development of a novel method involving the use of “protected” oxyallyl cation intermediates. In these chapters, the reactivity of starting materials, nucleophilic additives, solvents, and catalysts are described in regards to the formation of a variety of distinctive small molecules.
CHAPTER 1: CHLORINE IN ORGANIC SYNTHESIS AND ITS BROADER APPLICATIONS

1.1 Purpose

The purpose of this chapter is to provide a review of the role of organochlorines, from agricultural, material, and pharmaceutical perspectives, and to discuss synthetic methods of these compounds. Recent developments of organic and organometallic methodologies to transform hydroxy groups to carbon-chlorine bonds will also be presented.

1.2 Organochlorines in Society

Organohalogenes have been extensively explored in the scientific community. There is a countless amount of chlorine-containing compounds in the world, both natural and man-made. Historically, organochlorines were used in agricultural industries as potent pesticides.\textsuperscript{1-2} Organochlorines can also be found in everyday life due to their physical properties in materials products.\textsuperscript{3} Pharmaceutical drugs containing chlorine in their synthesis or as a part of the final biologically relevant product are increasingly utilized in the treatment of diseases.\textsuperscript{4}

Dating back to the 1950’s and 1960’s, organochlorine pesticides (OCP’s) remain a controversial topic of discussion. Previously, compounds such as dichlorodiphenyltrichloroethane (DDT), hexachlorocyclohexanes (HCH’s), and Drins, Figure 1.1, were commonly used in the agricultural industry as pesticides. Today, they have all been flagged as environmentally and biologically toxic, and many countries have issued bans on the compounds’ uses. The hydrophobic character of these compounds allows for fast cellular uptake in plants, which indirectly cause animal and human health issues due to the ingestion of these chemicals.
They are stored in the lipophilic tissues of animals and humans, and most of these compounds exhibit carcinogenic and mutagenic activities. There is also a possibility for chemical transfer, as countries that continue to utilize these pesticides have climates that facilitate long-range atmospheric transport.\textsuperscript{1-2} While controversy continues to rise over pesticides and their health concerns, there have been medically beneficial findings in regards to chlorine in material applications.

The most famous use of covalent chlorine linkages in materials was the development of polyvinyl chloride (PVC). The material was first discovered in the 19\textsuperscript{th} century, and was produced on an industrial scale for a variety of applications.\textsuperscript{5} Today PVC’s are made in chemical plants that use thermal cracking of ethylene and chlorine gas to form ethylene dichloride as a precursor to the monovinyl chloride monomer.\textsuperscript{5} With plasticizers, PVC’s can be made into flexible tubing found in the medical community and many other materials.\textsuperscript{6} Everyday household items including backpacks, aprons, packaging, clothing racks, and more are made from PVC’s.\textsuperscript{6}
Along with PVC, there are a wide variety of health applications for carbon-chlorine bonds in the synthesis of small organic molecules and natural products. There are over 4,700 known naturally occurring chlorine-containing molecules in the world.\(^7\) Many, although isolated and characterized, lack the volume necessary to carry out a significant range of biological testing.\(^8\)-\(^10\) One of the most widely used natural product antimicrobial compounds is triclosan 1.6, a sterilizing agent (Figure 1.2).\(^11\) This compound is commonly found in hand soap, detergent, and other household cleaners.\(^11\) Other small molecules such as Nexium®, Crestor®, and Advair® all utilize carbon-chlorine intermediates in their pharmaceutical scale syntheses (Figure 1.2; 1.6, 1.7 and 1.9). The sales of which led the industry’s top 100 drug sales in 2012 to provide a financial gain of approximately $16 billion.\(^12\)

One of the more understudied classes of natural product compounds, which drives our group’s interests, are the chlorosulfolipids. Elovson and Vagelos first discovered this class of lipids in 1969 in their chemical biology studies.\(^8\),\(^13\) These compounds are produced by marine mollusks, and researchers Ciminiello and Fattorusso later discovered that these lipids are thought to be the causative agents of diarrhetic shellfish poisoning.\(^13\)-\(^18\) In few cases, they are the primary component found in cell membranes of these organisms aside from phospholipids.\(^8\),\(^19\) Chlorosulfolipids are relatively small, intricate, and stereoenriched polychlorinated compounds with intermittent sulfate groups along a hydrocarbon backbone (Figure 1.3).\(^8\)

Due to their stereochemical complexity, this class of compounds has only recently been attempted as targets for organic synthesis. In 2009, Carreira and coworkers were successful in completing the first total synthesis of the simplest compound, hexachlorosulfolipid 1.10, Figure 1.3.\(^20\) Since then, several other chlorosulfolipid natural products have been achieved, but the
paths to get to the target compounds along the synthetic routes employed either harsh chemical reagents, or saw loss of stereocontrol (Figure 1.3).\textsuperscript{8, 21}

![Nexium](image1.png) Nexium (esomeprazole) 1.6

![Crestor](image2.png) Crestor (rosuvastatin calcium) 1.7

![Triclosan](image3.png) Triclosan 1.8

![Advair](image4.png) Advair (fluticasone propionate/salmeterol xinafoate) 1.9

Figure 1.2 Pharmaceuticals Commonly Made via Chlorination

### 1.3 Synthetic Methods for Organochlorine Synthesis

Few methods have been developed to take on the synthesis of the highly desired chlorosulfolipids,\textsuperscript{21-22} but of those that have, many involve the use of challenging chemicals and have limited substrate compatibility, particularly when the desired functionality undergoing transformation are alcohols.\textsuperscript{8, 20} Commonly used reactions that synthetic chemists perform to
transform alcohols to chlorides are the more classical approaches (i.e. phosphorus pentachloride, thionyl chloride, the Appel reaction etc.), chlorinating reagents in conjunction with transition metal catalysts, and halogenation of alkenes. While these have the ability to produce alkyl chlorides in decent yields, the tedious removal of byproducts by column purification are likely to make isolation of the desired product much more time intensive than necessary.

Traditional chemical transformations of alcohols have limitations in their scope of substrates. For example, SOCl$_2$ and (COCl)$_2$ are not compatible with acid sensitive
functionalities due to their production of HCl that may degrade important reaction components. Scheme 1.1 shows the reaction involving SOCl₂ transforming a primary alcohol, and after release of desired alkyl, HCl becomes a potentially reactive species in the mixture. At this point, any unmasked sensitivities become a liability for the desired transformation to proceed successfully. The Appel reaction was one such method that was developed to produce a milder pathway to desired alkyl chlorides. While the byproduct of this reaction is not reactive, separation of the target-chlorinated products can be difficult due to the stoichiometric production of phosphine oxides (Scheme 1.1).

\[ \text{Thionyl Chloride Transformation:} \]

\[ \text{Appel Reaction:} \]

Wagener and coworkers have reported an example of these reactions in a study published in 2004. Production of their halogenated synthons was carried out using traditional halogenation methods, however, the procedural data shows the amount of work each reaction necessitated to obtain pure material. For the case of desired alkyl bromide chains, the group utilized the well-studied Appel reaction (Scheme 1.1). While the reaction was completed quickly, the acidic byproduct was initially concerning as to the effect it would have had on the final product.
desired compound was isolated using fractional distillation, a most often tedious procedure. Similarly, the alkyl chlorides were also prepared using a traditional route.\textsuperscript{28-30} Researchers needed to use distilled, and extremely reactive, thionyl chloride as a reagent, which required careful addition over an hour. After the reaction was complete, and using excess heat, the final product was then distilled to provide desired chlorinated compound.\textsuperscript{27} While these experiments have been proven to work, their lengthy operations leave something to be desired in an ever-increasing field that relies on time and cost-efficiency. In an effort to provide a more mild and diverse method to obtain alkyl chlorides, several groups have undertaken the use of organic and transition metal methods to install these necessary functionalities.

\textbf{1.3.1 Giacomelli’s TCT Promoted Chlorination Method}

In 2002, Giacomelli and coworkers published a new discovery from their Italian laboratory. They found that conversion of primary, secondary, and tertiary hydroxy groups was readily promoted with the use of 2,4,6-trichloro-[1,3,5] triazine (TCT, 1.18) in DMF. These researchers utilized their methodology to expand the scope of substrates compatible to halogenation of alcohols and reduce the amount of byproducts in the crude mixture.\textsuperscript{31-34} Where a previous report used ionic liquids as mild a source of halogenation in conjunction with strong Bronsted acids to moderate reaction yields,\textsuperscript{31} Giacomelli’s group found an earlier precedence utilizing TCT as a chlorinating agent that transformed simple aliphatic alcohols to corresponding alkyl chlorides in the presence of a base (Scheme 1.2).\textsuperscript{32,35}
Giacomelli’s researchers found that reaction times were as little as ten minutes and as long as four hours under their optimized reaction conditions.\textsuperscript{35} A universal procedure was found for functionalized primary, secondary, and tertiary alcohols, where a 1.0M solution of alcohol was added to a TCT/DMF reaction mixture. Upon reaction completion determined by the disappearance of TCT through TLC-analysis, simple aqueous work-up removed unwanted byproducts and provided desired alkyl chlorides in excellent yields without the need for further purification. Table 1.1 shows a representative sample of the simple aliphatic alcohols that were utilized in their study.

Entries 1 and 2 show the conversion of simple 3-phenyl-1-propanol, and 2-thiophenylethanol to the corresponding alkyl chlorides in quantitative yields, although reactivity of entry 2 was significantly decreased. The use of secondary alcohols, entries 3 and 4, showed fast reaction times and high turnover to alkyl halides. Entry 3 showed that the alkyl bromide
could be achieved with the addition of sodium bromide to the reaction mixture but alkyl chloride was formed as a byproduct, which could be separated out through vacuum distillation. Tertiary alcohols also proved suitable for their chemistry, where entry 5 showed robust production of desired alkyl chloride in high yield.\textsuperscript{32}

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Entry} & \textbf{Alcohol} & \textbf{Product} & \textbf{Time} & \textbf{\% Yield} \\
\hline
1 & \begin{diagram}
\text{Ph} & \text{OH} \\
1.24a & & & & \\
\end{diagram} & \begin{diagram}
\text{Ph} & \text{Cl} \\
1.25a & & & & \\
\end{diagram} & 15 min & 99 \\
\hline
2 & \begin{diagram}
\text{Ph} & \text{Me} & \text{OH} \\
1.24b & & & & \\
\end{diagram} & \begin{diagram}
\text{Ph} & \text{Br} & \text{Me} \\
1.25b & & & & \\
\end{diagram} & 30 min & 70\textsuperscript{a} \\
\hline
3 & \begin{diagram}
\text{Ph} & \text{OH} \\
1.24c & & & & \\
\end{diagram} & \begin{diagram}
\text{Ph} & \text{Cl} \\
1.25c & & & & \\
\end{diagram} & 1 hr & 98 \\
\hline
4 & \begin{diagram}
\text{cyclohexyl} & \text{Me} & \text{OH} \\
1.24d & & & & \\
\end{diagram} & \begin{diagram}
\text{cyclohexyl} & \text{Cl} \\
1.25d & & & & \\
\end{diagram} & 4 hrs & 98 \\
\hline
5 & \begin{diagram}
\text{OH} \\
1.24e & & & & \\
\end{diagram} & \begin{diagram}
\text{OH} & \text{Cl} \\
1.25e & & & & \\
\end{diagram} & 15 min & 98 \\
\hline
6 & \begin{diagram}
\text{BzC} & \text{N} & \text{COOMe} & \text{OH} \\
1.24f & & & & \\
\end{diagram} & \begin{diagram}
\text{BzC} & \text{N} & \text{COOMe} & \text{Cl} \\
1.25f & & & & \\
\end{diagram} & 4 hrs & 94 \\
\hline
\end{tabular}
\caption{Giacomelli’s Substrate Compatibility Studies}
\end{table}

\textsuperscript{a}Alkyl chloride can be produced as byproduct
To continue their investigation of substrate compatibility, Giacomelli’s group also subjected diols, and enantiopure alcohols to their methodology. In doing so, they were able to determine that common amine protecting groups withstood reaction conditions and retained enantiopurity (entries 7 and 8), albeit with slightly longer reaction times. Due to the stereochemical outcome of entry 4, researchers proposed that the reaction proceeded through an $S_{N}2$-pathway, similar to that of the Vilsmeier-Haack reaction mechanism as seen in Scheme 1.3.  

![Scheme 1.3 TCT Reaction Activation Mechanism](image)

The mixture of TCT and DMF forms more reactive intermediate 1.28, and the hydroxy group attacks at the activated formaldehyde carbon to displace a TCT byproduct. Once the iminium intermediate 1.29 is formed, a free chlorine ion attacks the electrophilic carbon in an $S_{N}2$ fashion to form inverted alkyl chloride 1.30.

### 1.3.2 Cahiez and Coworker’s Preparation of Secondary Alkyl Chlorides

Out of necessity to achieve large-scale secondary chlorides, the Cahiez group took on the challenge of optimizing reaction conditions for a more mild method to produce stable alkyl chlorides.  

Previously, the group had published a study that utilized lithium halide salts in THF
to obtain alkyl halides (R-Br, R-I, and attempt R-Cl isolation) after converting the hydroxy groups to sulfonates; however, they found that alkyl chlorides were difficult to form. The addition of MnCl₂ succeeded in producing the desired chloride, but reaction conditions still necessitated excess heat and time.³⁶ Using the idea that S_N₂ reactions are more readily accessed in polar aprotic solvents, investigators then looked to other halide sources, such as ammonium chloride salts.³⁶, ³⁷ Researchers ultimately found that benzyltributyl ammonium chloride (1.1 equiv) in acetone at reflux provided desired product in excellent yields (Table 1.2).

Table 1.2 Cahiez’s Substrate Compatibility Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="1.32a" /></td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="1.32b" /></td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="1.32c" /></td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="1.32d" /></td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="1.32e" /></td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="1.32f" /></td>
<td>92</td>
</tr>
</tbody>
</table>
Scientists then conducted a substrate scope where they found several functional groups withstood reaction conditions. Entry 1 in Table 1.2 shows the alkyl chloride production of highly ionizable 2-chloro-3-phenyl propane in high yield. Sensitive nitrile and N-Boc functionalities also withstood reaction conditions (entries 2 and 3). Similarly, carbonyl groups also proved compatible with the standard procedure (entries 4 and 5). Entry 6 supported the assumed S_N2 mechanism of the reaction, where the starting carbon-sulfonate bond was completely inverted upon chlorination in excellent yield.

Once completing this substrate study, authors also applied their strategy to address a complex issue. The synthesis of 3α-chlorocholesterol-5-ene 1.34 had been known to be challenging from its 3β-analog 1.33, given that a previously established method using an S_N2 reaction pathway had only led to a moderate yield (Scheme 1.4). Known S_N1 pathways led to the alkyl chloride product in high yields but resulted in the epimerization of the desired stereocenter.

![Scheme 1.4 Cahiez’s Method Application](image)

After slight optimization of the sulfonate-leaving group in an appropriate media, scientists discovered they were able to obtain an excellent yield of their desired product in only two hours. Finally, the researchers proved that a one-pot conversion of their secondary alcohols to corresponding chlorides could be obtained by combining pyridine and sulfonyl chloride, along
with their ammonium chloride salt at reflux (Scheme 1.5). Overall, the authors were able to produce a method leading to secondary aliphatic alkyl chlorides in near quantitative yields. An attempt to improve upon a previous strategy using metal catalysis led to a robust organic method to obtain these sensitive functionalities without byproducts.

**Scheme 1.5 One-Pot Chlorination Method**

\[
\begin{align*}
\text{OH} & \quad \text{PhSO}_2\text{Cl (1.5 equiv), BnBu}_3\text{NCl (1.1 equiv)} \\
& \quad \text{pyridine, reflux, 1hr} \\
& \quad \text{97% yield} \\
\rightarrow & \quad \text{Cl}
\end{align*}
\]

1.3.3 **Nguyen and Bekensir’s Chlorination Method**

Similar to Cahiez’s method of secondary alcohol chlorination, Nguyen and Bekensir investigated the activation of alcohols and carboxylic acids using a tropylium-chloride salt. At the time, investigators wanted to initiate studies for the synthetic applications of tropylium cations, as these stable compounds were underrepresented in organic synthesis. Inspired by the Lambert’s contribution on nucleophilic substitution activation using dearomatization-aromatization driving forces of cyclopropenium cations, Nguyen and Bekensir envisioned a similar mode of activation using 1,1-dichloroheptatriene (DHT).

Scheme 1.6 shows the proposed mechanism of action for activation of alcohols and carboxylic acids to their alkyl chlorides and acyl chlorides, respectively. Once the tropylium cation is formed, hydroxy group from either carboxylic acid or alcohol attacks to form more reactive chloroheptatriene intermediates 1.40a or 1.41a, which reionizes to release a chloride ion. This chloride ion then attacks at the electrophilic carbon center, releasing tropone 1.42 and the respective alkyl or acyl chloride, 1.43 or 1.44.
Scheme 1.6 Tropone Activation Mechanism
Because isolation of acyl chlorides is increasingly difficult, the authors chose to trap these intermediates through esterification to provide a series of products containing 1.45 structure. Researchers found this strategy to be compatible with a number of different activated and unactivated primary and secondary alcohols. Table 1.3 entries 1 through 4 show several instances of successful chlorination with primary aliphatic alcohols, where entry 4 shows dichlorination with excess DHT.

Entries 5 and 6 detail bromination with the addition of bromide salt, and activated primary and secondary alcohols also gave the desired product in high yields (entries 7-9). Investigators also conducted an interesting experiment where a mixture of activated and aliphatic alcohols were subjected to these conditions, and they found predominantly selective chlorination of the activated alcohol to the aliphatic chain (entry 10) to form 1.47. One question the researchers had, however, was to determine which functionality would react faster or if both would provide equal reactivity. This was a challenge they hoped to solve using Scheme 1.7.

![Scheme 1.7 Enantiomerically Pure Substrate Application](image)

Once completing a scope of carboxylic acid compatibility study and trapping the acyl chloride with a variety of alcohols and amines, the authors combined functionalities in \((R)-(\cdots)-\)mandelic acid 1.48. Subjection of this material to the reaction conditions with one equivalent of DHT produced \(\alpha\)-hydroxy ester 1.49 in 66% yield and 1.51 in 5% yield (Scheme 1.7). This
finding showed that preferential acyl chloride formation took precedence over chlorination of the hydroxy moiety. Three equivalents of 1.38, however, gave trace 1.49 with 77% of 1.51 in 94% ee, pushing full conversion to chlorination of both functional groups.

Table 1.3 Nguyen and Bekensir’s Substrate Compatibility

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.47a</td>
<td>81</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.47b</td>
<td>84</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.47c</td>
<td>88</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.47d</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>1.47e</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>1.47f</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>1.47g</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>1.47h</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>1.47i</td>
<td>89</td>
</tr>
<tr>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.47j</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>1.47k</td>
<td>&lt;3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions were heated to 75°C; <sup>b</sup>Alcohols were in a 1:1 mixture
Investigators also noticed that they were able to isolate tropone in significant yields. Their interests then turned to generating a catalytic system with tropone by regenerating 1.37b with slow addition of oxallyl chloride. Table 1.4 shows careful optimization of the addition times for oxallyl chloride addition with 10 mol% of tropone catalyst. Both alkyl and unactivated alcohols generated their chlorinated products (entries 1-4), as well as bromination when bromide salts were included (entries 5 and 6). This chemistry effectively communicated the activation of hydroxy groups using a tropylium cation to generate a reactive intermediate that prompts nucleophilic addition through an $S_N2$-type mechanism.\(^{39}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>% Yield</th>
<th>(COCl)$_2$ Addn TIme</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph\xrightarrow{Cl} 1.52a</td>
<td>68</td>
<td>1 hr</td>
</tr>
<tr>
<td>2</td>
<td>Ph\xrightarrow{Cl} 1.52b</td>
<td>80</td>
<td>3 hr</td>
</tr>
<tr>
<td>3</td>
<td>Ph\xrightarrow{Cl} 1.52c</td>
<td>72</td>
<td>5 hr</td>
</tr>
<tr>
<td>4</td>
<td>Ph\xrightarrow{Cl} 1.52d</td>
<td>78</td>
<td>3 hr</td>
</tr>
<tr>
<td>5(^a)</td>
<td>Ph\xrightarrow{Br} 1.52e</td>
<td>71</td>
<td>18 hr</td>
</tr>
<tr>
<td>6(^a)</td>
<td>Ph\xrightarrow{Br} 1.52f</td>
<td>74</td>
<td>18 hr</td>
</tr>
</tbody>
</table>

\(^a\)2.5 equiv of Br salt was added
1.3.4 Baba’s Indium (III) Catalyzed Deoxygenative Halogenation

The transformation of carbonyl functionalities to alkyl chlorides had not been widely studied when Akio Baba and coworkers first became interested in this chemistry.\textsuperscript{47} Previously, Baba and investigators had expanded on a methodology that incorporated the carbonyl substrate, a silicon-bound nucleophile, and functional group-silicon compounds. Using this strategy, investigators were able to reduce carbonyl functionalities to tertiary and secondary all-carbon centers.\textsuperscript{48-51} The three-component methodology was reduced to a two-component system when optimizing reaction conditions for their desired chlorination strategy detailed in Table 1.5.\textsuperscript{47}

<table>
<thead>
<tr>
<th>Table 1.5 Baba’s Ketone Compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>
Indium (III) hydroxide was found to be the optimal catalyst with HSiMeCl and chloroform as the reaction solvent, and a number of different ketones were subjected to reaction conditions (see Table 1.5). Sensitive functional groups, such as halides, esters and alkynes all survived optimized reaction conditions (Table 1.5, entries 1-3). Entries 1-4, which also contain highly reactive ionizable positions, gave desired alkyl chlorides in moderate yields. Additional successful attempts were made to incorporate a different halide and a tertiary center from these reactions (Scheme 1.8).⁴⁷

![Scheme 1.8 Indium Catalized Halogenations](image)

In addition to this study, Baba and coworkers also contributed a communication transforming hydroxy groups to their corresponding alkyl halides.⁵² Revisiting a three-component system, authors found that HSiMe₂Cl along with benzil (PhCOCOPh) and indium (III) chloride gave desired alkyl chlorides. With a scope of substrate compatibility study, investigators were able to provide a variety of tertiary carbon centers (Table 1.6, entries 1-3).
Activated secondary alkyl chlorides were also obtained in high yields (entries 4 and 5), but an unactivated primary hydroxy group remained unaffected by reaction conditions (entry 6). Scheme 1.9 shows a comparative study between tertiary and primary alcohols, where tertiary alcohol of 1.62 is successfully transformed while primary alcohol remains unaffected. These results, accompanied by the findings in the substrate scope, indicate an S$_{N}$1 pathway to form the alkyl chlorides.$^{52}$

Table 1.6 Baba’s Alcohol Compatibility

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="1.61a" alt="diagram" /></td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td><img src="1.61b" alt="diagram" /></td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td><img src="1.61c" alt="diagram" /></td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td><img src="1.61d" alt="diagram" /></td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td><img src="1.61e" alt="diagram" /></td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td><img src="1.61f" alt="diagram" /></td>
<td>0</td>
</tr>
</tbody>
</table>
Overall, Baba and coworkers found effective ways to catalyze the deoxygenative halogenation of both activated and unactivated ketones and alcohols using a transition metal reagent. Their explorations into indium activation have opened another method to obtaining more complex alkyl chlorides that would not have previously been possible under classical conditions.

Scheme 1.9 Chemoselectivity of In(II) Chloride Activation

1.3.5 Li’s Silver Decarboxylative Chlorination

To expand on the Hunsdiecker reaction, Li and coworkers produced a report detailing the decarboxylative chlorination of a variety of different alcohols. Unlike previous conditions, which require anhydrous catalysts or a lengthier synthesis of a leaving group (i.e. Barton decarboxylation),\textsuperscript{53-54} Li’s reported pathway utilized an easily accessible halide source and less care intensive conditions.\textsuperscript{55} After completing optimization studies, appropriate ligands for the metal complex were chosen, and the reaction was found to proceed in acetonitrile and \( t\)-BuOCl.

This reaction was found to give a wide variety of alkyl chlorides from the corresponding carboxylic acids in excellent yields. Both aliphatic and aromatic carboxylic acids were treated with optimized conditions with catalytic amounts of the silver catalysts. Interestingly, investigators designed several experiments to examine the mechanism, and unlike previous reports, a proposed mechanism details the use of single electron transfer catalysis.
In the first exploration of the mechanism, investigators treated both cis and trans starting materials 1.64 and 1.66 to the catalytic conditions (Scheme 1.10). Alkyl chlorides were surprisingly obtained in a 1:2 dr for both starting materials. Researchers also saw 1.68 undergo cyclization to give pyrrolidine before chlorination, and generated a mixture of stereoisomers 18:14:38:30.

![Scheme 1.10 Chlorination of Various Carboxilic Acid Substrates](image-url)

Substituted cyclopropene was finally subjected to reaction conditions, and researchers saw ring opening to give only benzylic alkyl chloride 1.71. The formation of primary alkyl
chloride was not observed. All of these results provide support for a single electron transfer mechanism as described below.\textsuperscript{55}

Silver (I) is oxidized to silver(II) upon addition of t-BuOCl and forms a dimetallic complex. This complex then reacts with carboxylic acid to release t-BuOH (Scheme 1.11). Single electron transfer then generates an oxyradical that collapses to release carbon dioxide and generate a carbon radical. This species then reacts with the remaining chlorine in the dimetallic complex to release alkyl chloride.\textsuperscript{55} This novel method effectively generates an excellent variety of alkyl chlorides using an interesting single electron transfer path.

![Scheme 1.11 Silver Activation Mechanism](image)

**Scheme 1.11 Silver Activation Mechanism**

### 1.4 Conclusion

A few classic chlorination conditions were discussed involving the transformation of alcohols to their corresponding alkyl chlorides. A variety of chlorination strategies were discussed as well as their respective substrate scopes and various applications. While most relied
on activation of starting materials through the use of organic or inorganic reagents to undergo
either an $S_N$1 or $S_N$2 pathway, one pathway also showed single electron transfer to achieve
radical formation of alkyl chlorides. While many procedures showed generation of the desired
alkyl chlorides, some involved the use of expensive reagents to force the reaction to progress.
CHAPTER 2: MILD AMINE BASE/TRIPHOSGENE ACTIVATION OF ALIPHATIC PRIMARY AND SECONDARY ALCOHOLS

2.1 Purpose

The goals of these chlorination projects were to develop a mild method of converting aliphatic alcohols to their respective alkyl chlorides. The reactions utilized an amine base promoter and triphosgene to activate the otherwise unreactive alcohols. Primary dehydroxychlorination was first developed and suited a variety of substrates for transformation in high yields. Mechanistic studies were conducted by GC-MS to improve the visualization of a reaction mechanism in order to provide insight to the intermediates involved in the reaction.

Incompatibilities were discovered, which, ultimately, led to investigation to obtain a secondary dehydroxychlorination method. We conducted a survey of secondary and α-branched primary alcohols under the optimized conditions, and when subjected to this method, we confirmed compatible transformation to corresponding alkyl chlorides. We also proposed a mechanism similar to the primary chlorination of the transformation of the secondary alcohol substrates.

2.2 Primary Alcohol Activation with Triethylamine and Triphosgene

The methodologies described in this document outline alternative strategies that are both mild and clean, and install carbon-chlorine bonds in an SN2-like manner.\(^{56,57-60}\) Probing the efficiency of this reaction required synthesis of model substrate 2.1b. Our sequence began with allylmagnesium bromide addition to acetophenone 2.1a in 85% yield (Scheme 2.1). Reductive ozonolysis with sodium borohydride in methanol then provided 2.1b in 97% yield.
Scheme 2.1 Synthesizing Model Starting Material 2.1b

Table 2.1 depicts the use of model substrate 2.1b used in this group’s primary chlorination as it was subjected to previously existing chlorination conditions. While all entries resulted in their respective primary chlorination products, $^1$H NMR proved entry 4 a much cleaner reaction and its yield was significantly higher.\textsuperscript{56} Triphosgene (TP) was chosen over the notorious phosgene due to its stability, making it a safer substitute for this chemistry.\textsuperscript{56,61-63, 64}

**Table 2.1 Primary Chlorination Methods Comparison**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chlorinating Agents</th>
<th>% Yield 2.2$^a$</th>
<th>% Yield 2.3$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SOCl\textsubscript{2}</td>
<td>complex mixture</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>CCl\textsubscript{4}, PPh\textsubscript{3}</td>
<td>30</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>Triphosgene, PPh\textsubscript{3}</td>
<td>78</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>Triphosgene, TEA</td>
<td>98</td>
<td>--</td>
</tr>
</tbody>
</table>

$^a$Yield based on isolation by flash chromatography

Our group initially probed for an optimized set of chlorination conditions. A series of GC-MS studies was conducted to investigate the amount of TEA required to maintain reaction rate, but reduce the amount of byproduct 2.5 formed (Scheme 2.2). Without TEA, our investigations showed no formation of product, confirming its role as an amine base promoter.
Conversely, increasing equivalents of our amine base, showed steadily greater productions of our product in decreasing reaction times. After this analysis, it was determined that the optimal reaction conditions called for the dilution of starting material to a 2.0 mM solution in dry DCM, which was then cooled to 0°C. TP (0.5 equiv.) was then added in one portion, followed by the addition of 2.5 equivalents of TEA. The reaction was stirred for five minutes at 0°C, then warmed to room temperature and stirred for three hours.

Along with our optimized conditions, a mechanism of action was proposed as a result of GC-MS studies, as shown in Scheme 2.2. This involves the use of two possible pathways for chlorination. The first is through a path to the formation of chloroformate 2.6a, followed by nucleophilic attack of chlorine ion in solution.

![Scheme 2.2 Proposed Chlorination Mechanism](image)

The second path involves the attack of TEA to chloroformate intermediate 2.6a, which activates the primary carbon center for nucleophilic attack of chlorine, but also, with increased
steric congestion, is the cause for de-ethylation leading to diethyl carbamate 2.6c. The positively charged pyridinium ion intermediate went undetected in GC-MS.

While several substrates for this study were conveniently commercially available, others required a simple synthesis. Scheme 2.3 shows syntheses of starting alcohols 2.4c-2.4f. Alcohol 2.4c was produced from reduction of carboxylic acid 2.1c, followed by epoxidation with *m*CPBA. Synthesis of 2.4d was easily formed through monoprotection of its propanediol precursor 2.1d. Treatment of 2.1e with phenyllithium provided 2.4e in good yields, and enantiopure cyclopropane was also treated with phenyllithium to give 2.4f.

![Scheme 2.3 Synthesizing Primary and Secondary Alcohols](image)

Simple primary alcohols 2.4a and 2.4b proved robust under our optimized conditions (Table 2.2). Additional studies included determining the stability of substrates during the
reaction, in which acid and base sensitive functionalities, as well as easily ionizable functional groups, such as 2.4c and 2.4e, withstood reaction conditions. Two substrates produced crystalline structures of their respective chlorides, one of which is shown in Figure 2.1, which is further proof of the mildness of the reaction in the maintenance of the ionizable tertiary alcohol 2.4e.\textsuperscript{56,68}

Table 2.2 Primary Chlorination Substrate Compatibility

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material\textsuperscript{a}</th>
<th>Product</th>
<th>Yield\textsuperscript{b,c,d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph\textsuperscript{-}OH 2.4a</td>
<td>Ph\textsuperscript{-}Cl 2.7a</td>
<td>82%</td>
</tr>
<tr>
<td>2</td>
<td>Me\textsuperscript{-}OH 2.4b</td>
<td>Me\textsuperscript{-}Cl 2.7b</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>Ph\textsuperscript{-}O\textsuperscript{-}OH 2.4c</td>
<td>Ph\textsuperscript{-}O\textsuperscript{-}Cl 2.7c</td>
<td>87%</td>
</tr>
<tr>
<td>4</td>
<td>TBSO\textsuperscript{-}OH 2.4d</td>
<td>TBSO\textsuperscript{-}Cl 2.7d</td>
<td>78%</td>
</tr>
<tr>
<td>5</td>
<td>Ph\textsuperscript{-}OH 2.4e</td>
<td>Ph\textsuperscript{-}OH 2.7e</td>
<td>92%</td>
</tr>
<tr>
<td>6</td>
<td>Ph\textsuperscript{-}Me\textsuperscript{-}OH 2.4f</td>
<td>Ph\textsuperscript{-}Me\textsuperscript{-}Cl 2.7f (45%)</td>
<td>2.6c (27%)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Alcohols 2.4b and 2.4c are racemic; \textsuperscript{b}Yield based on product isolated by flash chromatography; \textsuperscript{c}Lower yields attributed to the volatility of the alkyl chloride; \textsuperscript{d}Minor (<10%) diethylcarbamate byproduct was detected by GC-MS or crude NMR in some cases.
An investigation into the use of an enantioenriched alcohol 2.4f in this study by yielded a mixture of alkyl chloride and diethyl carbamate products 2.4f and 2.7f, respectively. The optical rotation of the purified chloride 2.7f confirmed the inversion of stereochemistry of the stereocenter from the alcohol.\textsuperscript{56} Investigation into the diethyl carbamate product also supported the proposed mechanism, as the stereocenter remained intact for this product.\textsuperscript{56} In order to deter the formation of diethylcarbamates from sterically hindered $\alpha$-branched alcohols, as well as secondary alcohols, a continuation study needed to be carried out.\textsuperscript{69}

![X-ray Crystal Structure of 2.7c](image)

**Figure 2.1** X-ray Crystal Structure of 2.7c

### 2.3 Secondary Alcohol Transformation to Alkyl Chlorides

Strategies involving various amine base mixtures were tested in a variety of solvent mixtures and temperatures.\textsuperscript{69} Multiple screening studies of amine base mixtures were conducted, and our finding was that the use of only 2.0 equivalents of pyridine with 0.5 equivalent of TP
was needed in order to eliminate the possibility of generating diethyl carbamate adduct 2.7.\textsuperscript{69,70} Substrate scopes were also carried out, as seen in Table 2.3. As was the case with primary chlorination, easily ionizable functionalities, such as entry 2, were readily tolerated. Their respective chlorides were produced in relatively high yields. Lower yields were assumed to be the result of high volatility of the alkyl chloride compounds.\textsuperscript{56}

Similar to the primary chlorination study, the proposed mechanism was designated to be one of an S\textsubscript{N}2-type mechanism (Scheme 2.4).\textsuperscript{56,71-74} An inversion of stereochemistry was again shown from the reaction with chiral starting material and confirmed with an optical rotation study; thereby supporting the theory of nucleophilic back-side attack of chlorine from the N-acylpyridinium ion 2.10. The formation of intermediate 2.10 further activates the carbonyl center, simultaneously promoting the chloride ion attack and promoting the release of carbon dioxide.\textsuperscript{71-74}

![Scheme 2.4 Proposed Secondary Chlorination Mechanism](image)

Starting material syntheses for compounds 2.8b-2.8e are listed in Scheme 2.5. For these substrates, a few more steps were involved compared to starting materials in our primary chlorination. Compound 2.8b was synthesized from Aldol condensation to phenylacetaldehyde.
2.8b.1. Alcohol 2.8c was formed through Grignard addition to aldehyde 2.8b.1. Alcohol 2.8d resulted from treatment of 2.8d.1 to form Weinreb’s amide, which was then reacted with allylmagnesium bromide. This intermediate was then reduced using lithium aluminum halide (LAH) in THF at cooled temperature. Starting material 2.8e was formed through selective protection of the primary alcohol in 24% yield.

Scheme 2.5 Preparation of Secondary Alcohol Substrates

This methodology proved useful upon transformation of a number of different secondary alcohols. Highly ionizable positions, such as those in 2.8b-2.8d in Table 2.3, maintained their structure, as elimination was thought to be a potential problem for our desired compounds. Protecting groups also maintained their structural integrity during this transformation, as 2.11a and 2.11e were isolated in high yields.
The next avenue for this chemistry will be transitioned into a form of “global” activation and chlorination. In the secondary chlorination study, aliphatic diols were subjected to dichlorination as well, and we found that these conditions needed to be suitably optimized to yield the dichloride product. The goal for future work is to continue utilizing a sub-stoichiometric amount of TP with a reasonable amount of pyridine to carry out simultaneous activation of polyhydroxylated species. In addition, chloride ion is expected to routinely attack the activated site in a stereospecific fashion.

---

**Table 2.3 Secondary Chlorination Substrate Compatibility**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HO-&lt;br&gt;2.8a</td>
<td>Cl-&lt;br&gt;2.11a</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>EtO-&lt;br&gt;2.8b</td>
<td>Cl-&lt;br&gt;2.11b</td>
<td>82%</td>
</tr>
<tr>
<td>3</td>
<td>Ph-&lt;br&gt;2.8c</td>
<td>Ph-&lt;br&gt;2.11c</td>
<td>94%</td>
</tr>
<tr>
<td>4</td>
<td>Ph-&lt;br&gt;2.8d</td>
<td>Ph-&lt;br&gt;2.11d</td>
<td>82%</td>
</tr>
<tr>
<td>5</td>
<td>BnO-&lt;br&gt;2.8e</td>
<td>BnO-&lt;br&gt;2.11e</td>
<td>84%</td>
</tr>
</tbody>
</table>

<sup>a</sup>All substrates are racemic; <sup>b</sup>yields based on flash-column chromatography.
2.4 Conclusion

A general, mild strategy was discovered to cleanly transform unactivated and some activated aliphatic alcohols. Primary chlorination conditions involved the use of triethylamine as the base and reaction promoter. Using GC-MS studies, our group was able to propose a mechanism of action. While TEA worked well for the sterically free aliphatic alcohols, steric congestion caused production of diethyl carbamate adducts. This finding promoted investigation to the use of other amine bases that could promote alkyl chloride formation. Optimized conditions showed pyridine could effectively generate desired products in high yields and eliminate the possibility of diethyl carbamate formation.
CHAPTER 3: OXYALLYL CATIONS: TRADITIONAL SYNTHETIC UTILITY AND DIRECT NUCLEOPHILIC TRAPPING

3.1 Purpose

The purpose of this chapter is to describe a brief history of the generation of oxyallyl cations from both unsubstituted and α-substituted ketones and their capture to form a variety of cyclic synthons. In addition to this small review, three more recent examples of the direct nucleophilic capture of oxyallyl cations with indole will be discussed, along with the potential synthetic applicability to large molecule synthesis.

3.2 Capturing Oxyallyl Cation Intermediates: Favorskii Rearrangement

Organic chemists have extensively explored oxyallyl cations and their utility in synthetic methods. Historically, the Favorskii Rearrangement has been extensively explored. First reported in 1864, this method involves formation of a putative oxyallyl cation 3.2, which is in equilibrium with a more stable cyclopropanone 3.3 (Scheme 3.1). A nucleophile then attacks at the carbonyl carbon of 3.3, resulting in a ring contraction with a pendant carboxylic acid 3.4.

\[
\text{3.1} \quad \begin{array}{c}
\text{Cl} \\
\text{NaOCH}_3 \\
\text{Et}_2\text{O}, 35^\circ\text{C}, 2\text{hrs}
\end{array} \quad \begin{array}{c}
\text{3.2} \\
\text{3.3} \\
\text{3.4}
\end{array}
\]

Scheme 3.1 Favorskii Reaction

This mechanism is also compatible with larger and more complex structures, such as those shown in Scheme 3.2. A chiral example from Yoon’s group in 1994 showcases the
diastereoselectivity of this reaction in high yields leading to ester compound 3.6. Further investigations found that the loss of the 3-oxo group on 3.5 resulted in diminished selectivity, implying the importance of this functional group. A similarly challenging system, such as that of cubane, was also achieved using the Favorskii rearrangement, this time using potassium hydroxide as the nucleophile to yield the dicarboxylic acid 3.10.

\[
\begin{align*}
\text{Yoon (1994)} & \\
\text{3.5} & \xrightarrow{\text{NaOMe, MeOH}} 80\% & \text{THPO, CO}_2\text{Me} \\
\text{3.6} & \\
\text{3.7} & \xrightarrow{\text{NaOMe, MeOH}} 80\% & \text{MeO, OH} \\
\text{3.8} & \\
\end{align*}
\]

\[
\text{Eaton (1964)} & \\
\text{3.9} & \xrightarrow{\text{KOH}} & \text{3.10}
\]

Scheme 3.2 Applications of the Favorskii Reaction

3.3 Capturing Oxyallyl Cation Intermediates: Cycloadditions

Cycloadditions to oxyallyl cations have been integral in creating more complex structures, such as five- and seven-membered rings. Seven-membered rings are especially difficult to form due to opposing effects from entropy and ring strain. Many experiments have been conducted to test various ionization conditions and achieve the goal of both [4+3] and [3+2]
cycloadditions, where the oxyallyl cation intermediate plays the role of the 3-carbon cationic system. Metal complexes such as Fe\(_2\)(CO\(_2\))\(_9\), Zn/Cu, and Zn/Ag have all been studied and proven useful in the generation of the oxyallyl cations.\(^{81-83}\) In early cases, the reactions to generate the oxyallyl cations necessary to undergo cycloadditions require the use of \(\alpha\) or \(\alpha, \alpha'\)-haloketone starting materials (Table 3.1).\(^{80,84-85}\) Interestingly, some cases detail the use of basic conditions to successfully form the reactive intermediate.\(^{80,86}\)

Table 3.1 Lewis Acid Influence of Bicycle Conformational Outcome

<table>
<thead>
<tr>
<th>Entry</th>
<th>Activation Conditions</th>
<th>3.12 : 3.13 : 3.14</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaI/Cu</td>
<td>90.9 : 3.0 : 6.1</td>
</tr>
<tr>
<td>2(^a)</td>
<td>Zn/Cu</td>
<td>73.9 : 8.7 : 17.4</td>
</tr>
<tr>
<td>3(^b)</td>
<td>Zn/Cu</td>
<td>74.5 : 10.3 : 15.2</td>
</tr>
<tr>
<td>4</td>
<td>Fe(_2)(CO(_2))(_9)</td>
<td>44 : 0 : 56</td>
</tr>
</tbody>
</table>

\(^{a}\)DME was used as solvent; \(^{b}\)MeCN was used as solvent

Many natural products contain these large ring structures easily accessed through this methodology. There are, however, considerations to take into account when predicting regio- and stereoselectivity. Because of the predominantly endo products, which show striking resemblance to the Diels-Alder reaction due to secondary orbital interactions, it is assumed that the oxyallyl cation takes “\(W\)”-shape preference over the possible “\(U\)” or “sickle” forms (Scheme 3.3).\(^{80,87-88}\) These pathways produce either diequatorial or diaxial species 3.12 and 3.13 with varying selectivities dependant upon reaction conditions (Table 3.1).
Changing the electronic properties of the oxyallyl cation can promote selectivity of the \textit{exo}-extended stereoisomer 3.13 formation and other isomeric forms. \cite{80} Increasing the electrophilicity of the intermediate via use of iron catalyst (Table 3.1, entry 4), for example, investigators were able to achieve a slight selectivity for \textit{endo}-compact product 3.12 as well as an axial-equatorial substituted product 3.14. Metal coordination can also interfere with orbital interactions with the changing of the electronic properties of the oxo-species destabilizing these secondary interactions. The production of 3.13 and 3.14 is also thought to be due to the larger steric interactions on the metal center. \cite{80} Another aspect of mechanism alteration shows that it is possible to modify the method to become stepwise. \cite{88}

Interestingly, if the reaction is stepwise, then the intermediate cationic species can undergo [3+2] addition. A concerted pathway is not thermally allowed for this type of [2\(\pi\)+2\(\pi\)] process, but the stepwise mechanism allows for the appropriate orbital configuration. \cite{89} Scheme
3.4 shows the alignment of this process, as well as the possibility of C- or O-addition in the second step of cyclization to give ketone 3.17a or heterocycles 3.17b or 3.17c.

Scheme 3.4 Concerted vs. Stepwise Cycloadditions Involving Oxyallyl Cations

Unlike the [4+3] additions, five membered ring formations involving oxyallyl cations have shown to have differing reactive properties. While the former [4+3] reactions required relatively electron rich $4\pi$ partners for the electrophilic $3\pi$ oxyallyl species, more electron deficient $2\pi$ systems are reportedly compatible with oxyallyl intermediates. Alkynes can also react with the cationic $2\pi$ system to yield a variety of more complex all carbon or heteroatom structures.
3.4 Capturing Oxyallyl Cation Intermediates: Nazarov Cyclization

The Nazarov process is widely known to be a concerted electrocyclic ring closure. It is well documented that this 4π process is distributed through an oxypentadienyl cationic system, a five carbon – one oxygen system. This key cyclization step is promoted by activation of divinyl ketone 3.18 with a Lewis acid, which promotes pentadienylic cation formation. This system then undergoes conrotatory ring closure after establishing a trans-relationship between the two alkene groups. Once this cyclization occurs, the system then becomes an oxyallyl cation, at which point, neighboring hydrogen is eliminated (3.20) forming an α, β-unsaturated ketone system 3.21 (Scheme 3.5). In order for the necessary electrocyclic conrotary ring closure to occur, compound 3.18 must take on the form of s-trans.

The electronic effects of α-substituents have been explored in this reaction. Electron donating groups have been known to lower the activation energy of ring closure with only catalytic amounts of acid activation. In contrast, electron-withdrawing groups were known to
give predominantly polymerization products. The first particular instance of regioselective deprotonation was detailed in Reagan and Andrew’s report (Scheme 3.6), which also showed excellent selectivity of the protonation step, which is normally uncontrollable.\(^{32,35}\)

![Nonselective Deprotonation](image)

**Regan & Andrews:**

![Scheme 3.6 Overcoming Nonselective Deprotonation](image)

Many variants of this reaction have been identified, including chirality induced transformations, intramolecular reactions, and nitrogen containing Nazarov cyclizations.\(^{27-28,33-34,75}\) One of the more interesting, however, is the direct trapping of the oxyallyl cation intermediate with neighboring alkenes and heteroatoms. West and coworkers have termed this particular transformation the “interrupted” Nazarov cyclization.\(^{29-30,75,96}\) Initial reports detail ring closure, and the intermediate is then prone to cyclization, such as the transformation shown in Scheme 3.7.\(^{30}\) With only BF\(_3\)-OEt\(_2\), the alkene of intermediate 3.27a attacks the oxyallyl cation, which is further trapped as the hemiacetal upon addition of water.\(^{30}\) More recently, West and coworkers have investigated experimental and theoretical aspects of the direct intermolecular capture of the
oxyallyl cations with indole (Scheme 3.7). The direct nucleophilic capture of oxyallyl cations from ketones has been elusive to investigators, and to our knowledge only three other groups have been able to produce these types of results with indole as the nucleophile.

**Scheme 3.7 Interrupted Nazarov Cyclizations**

*West (1998)*

```
Et

BF₃·OEt₂

Me

3.27

Me

Me

Me

Me

Me

3.27a

3.27b

Et

HO

O

3.28

H

H

H

H

3.27c
```

*West (2014)*

```
Me

Me

Ph

Ph

3.29

\(\text{TMSOTf} \quad \text{1-Benzindole} \quad \text{CH}_2\text{Cl}_2 \quad -78^\circ\text{C} \quad 92\% \text{ yield}\)

Me

Me

Ph

Ph

\(\text{N}^\text{Bn}\)

3.30
```

Scheme 3.7 Interrupted Nazarov Cyclizations

### 3.5 Applications of Direct Nucleophilic Coupling to Ketones: Total Synthesis

The advancements of directly coupling indoles to ketones are highlighted by the introduction of \(\text{sp}^2-\text{sp}^3\) carbon-carbon bonds at the \(\alpha\)-position, which have been used in the concise syntheses of various indole-containing alkaloids.\(^{97-102}\) Indole alkaloids, such as hapalindoles, fischerindoles, welwitindolinones, ambiguines, hapalindolinones, hapaloxindoles,
and fontronamides, are synthetically challenging due to their structural complexity (Scheme 3.8).\textsuperscript{102-103} Several antifungal, insecticidal, and biological studies have been conducted on these compounds, and many have been found useful.\textsuperscript{103} These families of compounds share similar traits, where indole and terpene units are found in most if not all of the natural products. Many of them also contain an isonitrile or isothiocyanate moiety in their structures.\textsuperscript{103}

When first developing their direct coupling strategy, Phil Baran and coworkers, were able to achieve (+)-hapalindole and (-)-12-\textit{epi}-fischerindole U isothiocyanate in five synthetic steps from their \(\alpha\)-indole ketone 3.36 (Scheme 3.9).\textsuperscript{104-106,107} Their optimized conditions were found to be oxidative agents LHMDS and Cu(II)\textsubscript{2}-ethylhexanoate in THF. After deprotonation of both ketone and indole, the copper agent presumably oxidizes both anions, which can then couple to form the singular product in high diastereoselectivity.
Scheme 3.9 Baran’s Strategy to Introduce Indoles

From this point, total syntheses of two natural products were achieved in just five steps from a common precursor. Scheme 3.10 details routes to achieve both natural products, where α-indole ketone 3.36 was treated with LHMDS/L-selectride and oxidized with Martin’s sulfurane to achieve product 3.37 in 75% overall yield calculated from the direct oxidative coupling step. (+)-Hapalindole Q was formed after treatment of NH$_4$OAc and NaBH$_3$CN, and this synthon was then treated with CS(imid)$_2$. α-Indole ketone 3.37 was treated with TMSOTf, and then the same NH$_4$OAC/NaBH$_3$CN conditions. The amine group was then treated with CS(imid)$_2$ to achieve natural product 3.38 (Scheme 3.10).$^{107}$
3.5.1 Direct Nucleophilic Capture with Indole: Chi’s Method

Examples of the direct trapping of oxyallyl cations with carbon nucleophiles, especially indole, are few and far between.\textsuperscript{108-114} To our knowledge, there have only been three reports detailing this phenomenon.\textsuperscript{115,116} The first report of this type of strategy of generation of oxyallyl formation then nucleophilic attack to form $\alpha$-substituted ketones was reported in 1978 by Freter and coworkers.\textsuperscript{116}
This early example of nucleophilic inclusion had some drawbacks, however. Oxyallyl cation formation was driven through extremely strong acid activation of α-hydroxy ketone. This drawback was not addressed until over thirty years later, in 2012,\textsuperscript{117} when Chi and co-workers, discovered mild basic conditions to activate their system and trap their intermediates with indole at the α-position of a ketone (Scheme 3.11, eqn. 1). In these conditions, Na$_2$CO$_3$ is employed with non-nucleophilic TFE as a solvent to activate 3.39. After optimization trials, reactions were completed in 24 hours at room temperature to achieve variations of 3.41. Their attempts produced α-indole ketones in near robust yields for a variety of different ketones and indoles.

Table 3.2 showcases several examples of the types of indoles employed in Chi’s method. Entries 1 and 2 show compatibilities of both protected and electron donating indoles with symmetrical α-chloroketone 3.39. Weaker nucleophilic indoles, such as the electron withdrawing series also showcases a variety of compatible functional groups that could be altered in downstream syntheses.\textsuperscript{117} Deactivating systems, such as 5-cyanindole, had and excellent isolated yield with this reaction to give 3.40c. 6-Chloroindole also reacted well to give its adduct 3.40d in 94% yield.

When expanding the scope of ketone substrates, investigators activated a diverse range of α-haloketones. Scheme 3.11, equation 2 details the mechanistic theory of dihaloketone activations, where ionization of both α, α’-dichlorosystem 3.39b and α-dichlorosystem 3.39c lead to identical oxyallyl cation intermediates, such as 3.40b. Both bromo and chloro-systems (Table 3.3 entries 1 and 2, respectively) fit ionization conditions to yield desired indole adduct 3.43a. Entries 3 and 4 of Table 3.3 show ionization of secondary and tertiary α-chlorohexanones, and gave the same product 3.43b in 10:1 diastereomeric ratio.
Table 3.2 Chi’s Direct Indole Addition: Indole Compatibility

While this report largely employed symmetrical systems, however, the use of an unsymmetrical oxyallyl cation proved to be rather problematic, as addition of indole to the intermediate of an unsymmetrical intermediate seemed to occur competitively at both α and α’ positions, producing a mixture of regioisomers. Nonetheless, researchers indicated the possibility to regulate regioselectivity in their study. Entry 5 illustrates the ionization of 0.5 mmol 3.31 : 0.5 mmol indole : 0.6 mmol Na₂CO₃.
dibromoketone 3.42e. The resultant diindole adduct 3.43c, was found as a single regioisomer, and it was thought that the benzilic stabilization after the first indole addition helped stabilize the intermediate produced upon second oxyallyl cation 3.40d formation (Scheme 3.11, eqn. 3).

Scheme 3.11 Chi’s Employment of Direct Indole Addition to Oxyallyl Cations

3.5.2 Direct Nucleophilic Capture with Indole: Macmillan’s Approach

Shortly after Chi’s report was published, Macmillan and several of his researchers published a similarly mild method of trapping an oxyallyl cation with indoles. With the intention of generating a mild method for softer nucleophilic trapping, researchers went about producing conditions for their technique. Optimized conditions were those shown in Scheme 3.12 (eqn. 1). α-Tosylketone 3.44 is activated using TEA at room temperature with TFE as the nonnucleophilic
solvent, and the ensuing oxyallyl cation was trapped with 1-methylindole to generate 3.45 in 91% yield. A variety of ketones showed significant reactivity (Table 3.4).\(^\text{118}\)

### Table 3.3 Chi’s Direct Indole Addition: Substrate Compatibility

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me_O_Me_Br</td>
<td>3.42a</td>
<td>3.43a</td>
</tr>
<tr>
<td>2</td>
<td>Me_O_Cl</td>
<td>3.42b(^a) (syn or anti)</td>
<td>3.43b</td>
</tr>
<tr>
<td>3</td>
<td>Me_O_Cl_Me</td>
<td>3.42c</td>
<td>3.43b</td>
</tr>
<tr>
<td>4</td>
<td>Br_O_Br</td>
<td>3.42d</td>
<td>3.43c</td>
</tr>
</tbody>
</table>

\(^a\) 0.6 mmol 3.42a, 0.7 mmol Na\(_2\)CO\(_3\); \(^b\) 10:1 dr

Symmetrical ketones readily generated their \(\alpha\)-indole products, and five- and ten-membered rings reacted well to give desired products in good yields (entries 1 and 2, Table 3.4).
Open chain ketone 3.49c produced a mixture of regioisomers, a similar finding as those published in Chi’s study. However, β-substituted cyclohexanone 3.49e gave indole adduct 3.50e as a single regiosomer, which suggests steric repulsion as a factor of regioselectivity.

Table 3.4 MacMillan’s Direct Trapping: Substrate Compatibility

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.49a</td>
<td>3.50a</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>3.49b</td>
<td>3.50b</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>3.49c</td>
<td>3.50c</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>3.49d</td>
<td>3.50d</td>
<td>87</td>
</tr>
</tbody>
</table>

An exciting feature to this report showcased the inclusion of a variety of different heteroatom nucleophiles that could be incorporated to this study. α-Carbon-nitrogen bonds could
be achieved, as shown in entries 1-3 of Table 3.5 in good yields. Oxygen nucleophiles, such as 4-cyanophenol and isopropanol also trapped the oxyallyl cation intermediates to give compounds 3.52d and 3.52e (entries 4 and 5, respectively). In addition, the use of cesium-halide salts generated α-haloproducts 3.52f and 3.52g.

Table 3.5 MacMillan’s Expansion to Nucleophiles Beyond Indole

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>H₂N</td>
<td>O</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>Nucleophile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>TEA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>TFE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NH₂</td>
<td>O</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Product</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>HO</td>
<td>O</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>Nucleophile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>TEA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>TFE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CsF</td>
<td>O</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>Nucleophile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>TEA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>TFE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CsCl</td>
<td>O</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Me</td>
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</tr>
<tr>
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<td>Me</td>
<td>TEA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>TFE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Reactions utilized 3 equiv Nuc and 1 equiv of TEA in HFIP as solvent
Investigators also made efforts to induce enantioselectivity into their reaction. Modification of optimized conditions to those shown in Scheme 3.12 (eqn. 2) detail slight formation of one isomer using prolinol catalyst 3.48. They also found that a base, such as dipotassium phosphate, that was insoluble in organic solvents was necessary for catalysis to occur.

![Scheme 3.12 MacMillan’s Activation Method and Enantioselective Variant](image)

**3.6 Conclusion**

Traditional generation of oxyallyl cations and trapping strategies to form a multitude of different products were discussed. Extensive reviews and reports continue to be investigated in the classic Favorskii rearrangement, the Nazarov reaction, [4+3] cycloadditions, and the more recent [3+2] cycloadditions. Direct trapping of an oxyallyl cation, however, is severely limited in literature, especially with indole, where α-indole ketones have proven useful in a number of complex indole containing alkaloid syntheses.
CHAPTER 4: DIRECT NUCLEOPHILIC TRAPPING OF SILOXYALLYL CATIONS WITH INDOLE VIA MILD BRØNSTED ACID CATALYSIS

4.1 Purpose

The purpose of this chapter is to communicate the synthetic methodology development strategy our laboratory has undertaken in the expansion of direct nucleophilic trapping of oxyallyl cations. Our strategy involves the protection of an oxyallyl cation in the form of silylenol ether to selectively install α-indole ketone derivatives.

4.2 Silylenol Ether Formation: Strategic Expansion of Classical Methods

Of the many functionalities in organic synthesis, silylenol ethers are one of the most widely used in important transformations. Their stability provides for easy handling, and they have many applications as nucleophiles to install differing groups to the α-position of a ketone.\textsuperscript{119-125, 115} Traditional methods to prepare silylenol ethers show selectivity with different conditions for single α-substituted ketone precursors such as 4.1, as shown in Scheme 4.1. From this point, a researcher may choose to obtain the kinetic, less substituted 4.2 with a strong base, such as LDA in cryogenic temperatures to deprotonate the less hindered α-proton.\textsuperscript{126-127} Thermodynamic, or more substituted silylenol ether 4.3 may be produced with a weaker base at warmer temperatures to deprotonate the more hindered proton at equilibration conditions.

These classical conditions, however, are not useful in obtaining regioselectivity of α,α’-disubstituted ketones, such as 4.4, where the α-protons have similar pKa’s. Without any differentiation of the α,α’-hydrogens from the R-group side chains, either thermodynamic or kinetic conditions are predicted to yield a mixture of regioisomers.\textsuperscript{126-135} Methods to access selection of 4.5a over 4.5b or vice versa are severely limited.\textsuperscript{136-140}
Our group predicted that a structural motif, such as $\alpha'$-hydroxy protected silylenol ether 4.6 could provide selection of one regioisomer. This objective would be achieved through activation of the starting material to form intermediate 4.7 through mild acid activation. Indole would then directly trap the oxyallyl cation-type intermediate at the less sterically hindered $\alpha'$-position to provide 4.5a as a single regioisomer. This step not only solves the regiochemical production of a disubstituted silylenol ether, but also would solve regioselectivity issues of indole addition to unsymmetrical ketones (Scheme 4.2).

As previously discussed in Chapter 3, both Chi and Macmillan’s reports indicated lack of selectivity upon ionization of their unsymmetrical ketones. Scheme 4.2 showcases moderate regioselectivity, but good yields of their indole adducts. Where ionization of 4.8 and 4.10 produces putative oxyallyl cations 4.8a and 4.10a, respectively; isolated yields showed mixtures of no greater than 3 : 1 regiomeric ratios. With our study, we predicted that trapping of our
intermediate from secondary \( \alpha \)\( \square \)-hydroxy compound 4.6 could be achieved with a number of indole-derived nucleophiles. We expanded our strategies to include a tertiary \( \alpha \)-hydroxy series 4.12 that also may be ionized to form identical intermediate 4.7 from ionization of 4.6. The trapping of this intermediate would produce a single regioisomer with total selectivity due to steric interactions.

Scheme 4.2 Previous Issues with Regioselectivity

Our strategy is dependant on several factors: First, the hydroxy groups must be able to depart from the system in the presence of a mild Brønsted acid. We are also presuming that interaction with hydroxy groups of both 4.6 and 4.12 with a mild Brønsted acid will kinetically outcompete interactions of the silylenol ether functionality in a nonpolar solvent to prevent
protodesilylation.\textsuperscript{141-145} Finally, we needed to establish that a conjugate base was acting as a spectator species rather than promoting an S\textsubscript{N}2’ reaction.

4.2.1 Initial Strategy Design

Because we had successfully introduced novel S\textsubscript{N}2 pathways that lead through activation of an alcohol in our primary and secondary chlorination papers, we were inspired to expand this type of activation.\textsuperscript{56, 69} A general reaction mechanism for the two types of pathways is detailed in Scheme 4.3. Our proposed solution for the generation of a regioselective oxyallyl cation strategy, essentially an S\textsubscript{N}1 mechanism, would provide a better strategy for addition versus an S\textsubscript{N}2 path, due to the planarity of the carbocation intermediate.

\textit{S}_{\text{N}1}

\begin{equation}
\begin{aligned}
\text{Scheme 4.3 Activation Inspiration}
\end{aligned}
\end{equation}

\textit{S}_{\text{N}2}

\begin{equation}
\begin{aligned}
\text{Scheme 4.3 Activation Inspiration}
\end{aligned}
\end{equation}

Analogous to our previous chlorination studies, we envisioned a leaving group similar to the positively charged ammonium intermediates from the chlorination pathways. We thought we
could achieve this goal through the use of a CDI derived alcohol 4.15. Activation of this compound would generate a positively charged species, which, in an $S_N1$ pathway, we presumed would leave through neighboring stabilization of the R-groups, releasing carbon dioxide and imidazole. Such stabilization would occur through oxyallylic resonance in our case. This planar intermediate would then make more sterically congested centers more accessible through its open geometry, allowing for nucleophilic attack from either side of the carbocation. Another mechanism could also occur through an $S_N2$ pathway, but more sterically congested centers would be more difficult to achieve.

4.3 Optimization Studies on Regioselective Indole Addition

Surveying the appropriate Brønsted acid for our transformation began, and trials with pyridinium salts are detailed in Table 4.1. Molecular sieves were added into the reaction mixture as a precaution against interactions with water to prevent protodesilylation. Entries 1 and 3 show successful production of desired product 4.19 as a single regioisomer. Entry 2, however, involved the use of pyridinium sulfate, which failed to yield a significant amount of compound 4.20. Because pyridinium triflate (entry 3) gave a higher yield than that of PPTS (entry 1), we began molar equivalent optimizations of both the acid and indole.

Reduction of the equivalents of indole to 1.1 led to a loss of yield (entry 5), so we held the equivalents at 2.0 for the remainder of the study, although the reaction time did increase slightly. Further reduction of the amount of acid necessary to proceed surprisingly led us to find that a catalytic amount could turnover starting material in excellent yields, as shown in entry 8. This experiment yielded compound 4.20 in 91% yield, although the reaction was a lengthier 66 hours with no hint of protodesilylation.
Table 4.1 Optimization Studies for Indole Addition

![Chemical structure](image)

| Entry | Brønsted Acid | Equiv | Equiv of Indole | Time (hr) | Yield  

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Py·TsOH</td>
<td>2.0</td>
<td>4.0</td>
<td>0.7</td>
<td>58%</td>
</tr>
<tr>
<td>2</td>
<td>Py₂H₂SO₄</td>
<td>2.0</td>
<td>4.0</td>
<td>48</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>Py·TfOH</td>
<td>2.0</td>
<td>4.0</td>
<td>9</td>
<td>86%</td>
</tr>
<tr>
<td>4</td>
<td>Py·TfOH</td>
<td>2.0</td>
<td>2.0</td>
<td>32</td>
<td>84%</td>
</tr>
<tr>
<td>5</td>
<td>Py·TfOH</td>
<td>2.0</td>
<td>1.1</td>
<td>32</td>
<td>69%</td>
</tr>
<tr>
<td>6</td>
<td>Py·TfOH</td>
<td>1.5</td>
<td>2.0</td>
<td>32</td>
<td>84%</td>
</tr>
<tr>
<td>7</td>
<td>Py·TfOH</td>
<td>1.0</td>
<td>2.0</td>
<td>36</td>
<td>75%</td>
</tr>
<tr>
<td>8</td>
<td>Py·TfOH</td>
<td>0.1</td>
<td>2.0</td>
<td>66</td>
<td>91%</td>
</tr>
<tr>
<td>9</td>
<td>TfOH⁺</td>
<td>0.1</td>
<td>2.0</td>
<td>6</td>
<td>67%</td>
</tr>
</tbody>
</table>

* Isolated yield after flash column chromatography.

To rule out any effect that pyridine may have on the reaction, we also utilized triflic acid in our conditions and found indole addition in moderate yield, along with 8% of protodesilylation of compound 4.20. This result did suggest that pyridine remains a spectator base throughout the reaction. Throughout all of these reaction conditions, protodesilylation of the starting material did not occur. We were easily able to monitor the reaction through TLC analyses, and begin investigations into the scope of indole compatibility with our conditions.115

### 4.4 Scope of Indole Additions to α’-Hydroxysilylenol Ethers

As our optimization studies led us to find catalytic conditions, we then sought to functionalize our starting material with a variety of different indoles (Table 4.2). 1-Methylindole generated indole adduct 4.20a in 72% yield. Surprisingly 2-phenylindole 4.20b also reacted well with our conditions. We had initially assumed the phenyl group might have hindered reaction progress, but it showed no effect on the efficiency of the reaction.
Table 4.2 Additions to Siloxyallyl Cations: Indole Compatibility Study

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Product</th>
<th>Yield$^a$</th>
<th>Entry</th>
<th>Indole</th>
<th>Product</th>
<th>Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N-Me 4.21a</td>
<td>![Image]</td>
<td>72% 41 hrs</td>
<td>5</td>
<td>5-CO$_2$CH$_3$ 4.21e</td>
<td>![Image]</td>
<td>67% $^b$ 74 hrs</td>
</tr>
<tr>
<td>2</td>
<td>2-Ph 4.21b</td>
<td>![Image]</td>
<td>83% 41 hrs</td>
<td>6</td>
<td>4-CN 4.21f</td>
<td>![Image]</td>
<td>60% $^b$ 147 hrs</td>
</tr>
<tr>
<td>3</td>
<td>5-Br 4.21c</td>
<td>![Image]</td>
<td>84% 53 hrs</td>
<td>7</td>
<td>Azaindole 4.21g</td>
<td>![Image]</td>
<td>53% $^c$ 21 hrs</td>
</tr>
<tr>
<td>4</td>
<td>5-OMe 4.21d</td>
<td>![Image]</td>
<td>76% 40 hrs</td>
<td>8</td>
<td>5-OMe-Benzindole 4.21h</td>
<td>![Image]</td>
<td>57% 47 hrs</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield after flash chromatography; $^b$ Starting material was not fully consumed; $^c$ Reactions were performed at 40°C; $^d$ No reactions at room temp or 40°C; $^e$ No reaction with 2 equiv of pyridinium triflate
5-Bromoindole 4.21c showed excellent reactivity with ionization conditions, generating 4.20c in 84% yield. Electron rich and poor indoles were also studied on their capacity to generate desired indole adducts (entries 4-6). 5-Methoxyindole readily afforded product 4.20d in good yield. While reaction times increased for the electron withdrawing indoles, 5-methylcarboxylate indole did generate compound 4.20e in 67% at room temperature and 57% at 40°C. Similarly, 4-cyanoindole did require a significant amount of time for the reaction to progress, but some starting material remained unreacted. Fortunately, compound 4.20f formed crystals upon purification and X-ray analysis showed unambiguous regiochemistry of the silylenol ether, where the double bond lies between the α-methyl and the O-TBS groups (Figure 4.1). Overall, the indole adducts 4.20a-h afforded the less-favorable indole addition.

Figure 4.1 X-ray Crystal Structure of 4.20f

Azaindole 4.20g was also utilized in the study, but remained unreactive toward nucleophilic addition. We hypothesize that the nucleophilicity is quenched due to the basicity of the pyridine ring of the azaindole as we also attempted this reaction with 2.0 equivalents of pyridinium triflate. Larger benzindole 4.21h also suitably provided compound 4.20h in 57% yield as a single regioisomer.
4.5 Synthesis of Tertiary Alcohol Substrates

Once we had established indole compatibility studies, we then turned our focus to vary the alkyl side chains of our starting material to include a more diverse array of alkyl and aryl groups. It was a goal to utilize the bare cyclopentanedione 4.23, Scheme 4.4, protect it in its α,β-unsaturated form, and subject compound 4.28 to a variety of organometallic additions to build our series. Although the bare 1,2-cyclopentanedione was not commercially available, there was a report that we had found to generate this desired system detailed in Scheme 4.4.149, 150

![Scheme 4.4 Route to Tertiary Alcohol Series](image)

Unfortunately, this report failed to yield a suitable amount of product to carry out our studies, so we turned to more classic organic methods to achieve desired compound 4.23.115 First, we oxidized cyclopentene to 1,2-cyclopentanediol using OsO₄ and NMO. At this point, we oxidized diol 4.25 using Swern oxidation conditions to obtain the tautomer of compound 4.23,
concluded through NMR studies. From there, we protected this product with TBSCl and imidazole, and began a series of Grignard additions (Table 4.3, compounds 4.29a-h).

Alcohol 4.29c included a lengthier synthesis, which is shown in Scheme 4.5. Initial Grignard addition was carried out with allylmagnesium bromide. This compound was then subjected to Grubb’s double bond cross metathesis with ethyl acrylate then reduced with DIBAL. The primary alcohol of structure was then protected with TBSCl and imidazole to give tertiary alcohol 4.29c.

![Scheme 4.5 Synthesis of Tertiary Alcohol 4.29c](image)

**4.6 Indole Addition to Tertiary Alcohol Series**

Table 4.3 shows an extensive range of both aryl and alkyl side chains incorporated into our starting materials. Entry 1 showcases a control example, where tertiary methyl alcohol 4.29a was exposed to our reaction protocol, which gave the desired compound in 75% yield.
**Table 4.3 Substrate Compatibility Screening**

![Chemical structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Time (hrs)</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>OTBS</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>TBSO&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>138</td>
</tr>
<tr>
<td>3</td>
<td>OTBS</td>
<td></td>
<td></td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>OTBS</td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>OTBS</td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>OTBS</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td></td>
<td>46</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after flash chromatography; <sup>b</sup> Reaction was performed on gram scale
Alkyl chains shown entries 2 and 3 demonstrated lengthier reaction times but good yields of our desired products. Surprisingly, the primary silyl ether of compound 4.29c proved robust under our conditions, exemplifying the extreme mildness of our procedure. Installing hydrogen as the side chain in alcohol 4.29d showed no reaction under our activation methods, implying the necessity of an α-substituent to stabilize the putative intermediate.

Aromatic rings, shown in entries 5-8, all proved successful in our conditions. Compound 4.29e cleanly generated its indole addition derivative in 86% yield, an accomplishment that previously established reaction conditions would have been difficult if not impossible to achieve. Similarly, toyl side chain exhibited by compound 4.29f achieved its corresponding α-aryl-α’-indole adducts in 92% yield. Compound 4.33f was also easily achieved on gram scale synthesis in 91% yield. Heteroatom aryl group 3-methyl thiophene also promoted α’-indole addition in high yield. All products obtained were isolated as single regioisomers.

4.7 Applications of α-phenyl-α’indole Silylenol Ethers

The ability to achieve such novel and complex architectures led us to investigate other synthetically useful moieties we could achieve through transformation of these silylenol ethers (Scheme 4.6). Using diaryl compound 4.33g, we carried out a number of these alterations. First, we removed the silylenol ether with TBAF in THF to achieve moderate diastereoselectivity of trans-diaryl ketone 4.34 in 3:1 ratio. We then protected the nitrogen of compound 4.35 using LDA and acetic anhydride in order to carry out other reaction conditions.

Using hydroboration, we were able to install three contiguous stereocenters with excellent diastereoselectivity in compound 4.36. Surprisingly, attempts to brominate at the α-phenyl carbon produced α, β-unsaturated ketone 4.37 as a single product.
4.8 Conclusion

With the development of this study, we were able to produce a novel report of a regioselective disubstituted silylenol ether synthesis through the use of silyl protected oxyallyl cation intermediates. A variety of indoles were screened with our mild activating conditions, utilizing pyridinium triflate as a catalyst. The use of classical conditions to enolize the corresponding ketones would have been difficult as the $\alpha$-hydrogens would have been comparatively sterically hindered and similarly acidic. Our strategy also solves the challenging issue of regiocontrol of unsymmetrical oxyallyl cations. All examples supplied in this report have differing stereo and electronic effects in their system, but they routinely produced similar $\alpha,\alpha'$-disubstituted systems as single regiosomeric products.
CHAPTER 5: DIRECT TRAPPING OF COOPERATIVE BENZYLIC-OXYALLYLIC CATIONS TO FORM QUATERNARY CENTERS

5.1 Purpose

The purpose of this chapter is to describe investigations into the regioselectivity of a previously discovered activation method to generate quaternary centers on silylenol ethers as single isomers. Conceptual and optimization procedures will be discussed along with an established set of conditions that our group utilized to obtain a wide variety of complex enol ether structures. An in-depth profile of all-carbon quaternary centers that can be obtained through our newly established study will be mentioned. Our focus for this study also included the use of nucleophiles beyond indole to achieve a variety of all-carbon and carbon-heteroatom centers.

5.2 Attempts at Switching Regioselectivity

\[ \text{Differentiation Goal} \]

\[ \begin{array}{c}
\text{5.1} \\
\text{R} \\
\text{X} \\
\text{O} \\
\text{C} \\
\text{5.2} \\
\text{R} \\
\alpha \\
\alpha' \\
\text{Nu-H} \\
\text{5.3} \\
\text{R} \\
\text{Nu} \\
\alpha \\
\alpha' \\
\end{array} \]

\[ \text{Previously} \]

\[ \begin{array}{c}
\text{5.4} \\
\text{R} \\
\text{OTBS} \\
\text{OH} \\
\text{Py-TfOH} \\
\text{(10 mol %)} \\
\text{toluene, 4Å MS} \\
\text{5.5} \\
\text{R} \\
\alpha \\
\alpha' \\
\text{5.6} \\
\text{R} \\
\alpha \\
\alpha' \\
\text{indoles} \\
\end{array} \]

\[ \text{R = alkyl, aromatic} \]

Scheme 5.1 Differentiation of $\alpha$ vs $\alpha'$ positions

With the report of our previous findings,\textsuperscript{115} our group wanted to explore the full capacity of our methodology.\textsuperscript{151} It was our goal to expand to quaternary center formation to obtain
compound 5.3, Scheme 5.1, as a single product. This would require differentiation of the α-protons in the system, however, which is not feasible through classic routes. Formations of quaternary centers are traditionally accessed through the $S_N1$ path both due to the more accessible bond geometries of intermediates and their high electrophilicity.\textsuperscript{152-155} Due to the presumed planar geometry of our intermediate, we thought sterically congested centers could be more conveniently and easily obtained (Scheme 5.1, eqn. 1).\textsuperscript{156-161} Previous methods, however, have established harsh conditions, such as highly acidic media,\textsuperscript{162} in which sensitive functional groups may not be retained. An opportunistic feature of our ionization is its proven mildness in retaining sensitive functionalities, such as enol ethers.\textsuperscript{151, 163-167}

### Table 5.1 Quaternary Center Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate R\textsubscript{1}</th>
<th>Substrate R\textsubscript{2}</th>
<th>Catalyst (mol%)</th>
<th>Conc. (M)\textsuperscript{[a]}</th>
<th>Time (h)</th>
<th>Yield\textsuperscript{b}</th>
<th>5.8 : 5.9\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.7a -TBS</td>
<td>-H</td>
<td>10</td>
<td>0.05</td>
<td>66</td>
<td>91%</td>
<td>99 : 1</td>
</tr>
<tr>
<td>2</td>
<td>5.7a -TBS</td>
<td>-H</td>
<td>50</td>
<td>0.2</td>
<td>3</td>
<td>70%</td>
<td>99 : 1</td>
</tr>
<tr>
<td>3</td>
<td>5.7b -Me</td>
<td>-H</td>
<td>50</td>
<td>0.2</td>
<td>1</td>
<td>71%\textsuperscript{d}</td>
<td>56 : 44\textsuperscript{e}</td>
</tr>
<tr>
<td>4</td>
<td>5.7c -Me</td>
<td>-Ph</td>
<td>50</td>
<td>0.2</td>
<td>1</td>
<td>86%</td>
<td>1 : 99</td>
</tr>
<tr>
<td>5</td>
<td>5.7c -Me</td>
<td>-Ph</td>
<td>10</td>
<td>0.2</td>
<td>2</td>
<td>81%</td>
<td>1 : 99</td>
</tr>
<tr>
<td>6</td>
<td>5.7c -Me</td>
<td>-Ph</td>
<td>10\textsuperscript{f}</td>
<td>0.2</td>
<td>1</td>
<td>14%\textsuperscript{g}</td>
<td>1 : 99</td>
</tr>
<tr>
<td>7</td>
<td>5.7d -TBS</td>
<td>-Ph</td>
<td>10</td>
<td>0.2</td>
<td>110</td>
<td>38%\textsuperscript{h}</td>
<td>1 : 99</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]}Concentration of starting material; \textsuperscript{[b]}Isolated yields after flash chromatography; \textsuperscript{[c]}Regioisomers determined by $^1$H NMR of crude mixture; Combined yield; \textsuperscript{[d]}Corresponding ketones were isolated; \textsuperscript{[e]}Starting material never fully consumed
Initial investigations are listed in Table 5.1, where quaternary center formation was attempted first with our silylenol ether starting material 5.7.\textsuperscript{115} We thought by increasing the catalyst equivalents along with concentration, reaction speed would lead to a mixture of isomers (entry 2). While reaction times did decrease dramatically, our regioisomeric mixture hypothesis was disproven, however, which led us to attempt alternative paths. Thinking that the large silyl group was the cause for slower rates and steric drive towards preference for the less hindered carbon,\textsuperscript{168-169} we thought we could alter the protecting group of the enol ether. By replacing the protection of the diketone 5.10 with MeI and K$_2$CO$_3$ in acetone, we were able to achieve a general intermediate (eqn 1, Scheme 5.2). Switching to a methyl enol ether led to a near 50 : 50 mixture of tertiary and quaternary center products, a promising result for our study.\textsuperscript{151}

When looking for possible alterations to our starting materials, we had remembered that Chi’s studies involved the use of $\alpha$-dibromoketone, shown in Scheme 3.11 equation 2. Upon ionization of their dihalo-compound, they predicted single indole addition occurred (See Chapter 3, Scheme 3.11).\textsuperscript{117} When this resultant compound underwent a second ionization, however, researchers witnessed another indole addition, this time at the benzylic carbon, suggesting some electronic stability of the oxyallyl intermediate due to the benzylic group placement, the synthesis of which is shown in Scheme 5.2. Borrowing from their findings, we introduced a phenyl ring into our studies, to produce compound 5.7c.

Expecting indole addition to occur similar to Chi’s findings, it was predicted that indole addition would take place at the $\alpha$-phenyl carbon. The resultant indole addition occurred at the $\alpha'$-methyl center, however, implying that the benzylic system stabilizes the oxyallyl cation intermediate to drive carbon-carbon bond formation at the $\alpha'$-center. Another fortuitous aspect of this reaction is its speed, as entry 5 was completed in one hour, where the O-TBS variant 5.7d
took over 100 hours without reaction completion. Pyridine was also ruled out of the reaction mechanism as the use of triflic acid showed 14% yield with degradation of starting materials. Once some further optimization was completed, we carried out a large number of compatibility studies between differing starting materials and indoles.

Scheme 5.2 Synthesis of Various Starting Materials

5.3 Five and Six-Membered Ring Compatibilities with Indoles

As with the previous study, a variety of indoles bearing different electronic and sterically dissimilar properties were utilized to determine compatibilities. Both five and six-membered ring starting materials 5.12 and 5.13 were tested. Both were proven compatible with regular indole
(Table 5.2, entry 1), but six-membered 5.13 proceeded with a longer reaction time. Reaction times increased, and yields decreased, with only 1.1 equiv. of indole. Protected 1-methylindole also readily provided indole adducts 5.14b and 5.15b in moderate yields, but the reaction time significantly increased for the formation of compound 5.15b. Electron donating 5-methoxyindole also readily provided adducts 5.14c and 5.15c in 74% and 69% yields, respectively. 5-Bromoindole also gave high yields of its respective quaternary center (entry 4). A stronger deactivating group methyl-5-carboxylate indole provided desired products, albeit with a slight increase in reaction times. Surprisingly, entry 6 details 4-cyanoindole showing no reactivity toward capturing our putative oxyallyl cation intermediate of 5.12.

5.4 Varying the R-Group of Substrates

An exploration into the ability to achieve alkyl and aryl variation was also conducted. Using aryl-organometallic reagents, we introduced a variety of different aryl groups into compound 5.10b (eqn. 2 Scheme 5.2), and we were able to obtain tertiary alcohols of differing electronic values (Table 5.3). The use of aryl groups with electron donating or withdrawing groups were utilized (entries 1 and 2, respectively), and the reaction saw no loss in time for starting material consumption. In fact, reactions proceeded more quickly with these substituents with 90% yields in each case. Similarly, heteroatom aryl group 3-thiophenyl compound 5.16c also proceeded to generate the desired quaternary center product 5.18c in excellent yield.

Varying the R-groups of our α’-position proved a more lengthy synthesis. Scheme 5.2 equation 3 shows the addition of a variety of organometallic alkylating agents to α-phenyl ketone 5.11a, which was synthesized according to literature procedures.171 Upon extension of the methyl group to the octyl chain starting material 5.17d, shown in entry 4, the reaction time dramatically increased but managed to generate indole adduct 5.18d in 80% yield. Alcohol 5.17e
also had a lengthier reaction time and lower yield. A mixture of regioisomers for compound 5.18e was isolated in 3 : 2 regiomeric ratio. Table 5.4 showcases our following attempts for

Table 5.2 Indole Additions to 5- and 6-Membered Rings

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Product</th>
<th>Time (hrs)</th>
<th>Yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="indole.png" alt="Indole" /></td>
<td><img src="product.png" alt="Product" /></td>
<td>5.14a = 2; 8(^b)</td>
<td>81%; 79%</td>
</tr>
<tr>
<td>2</td>
<td><img src="indole.png" alt="Indole" /></td>
<td><img src="product.png" alt="Product" /></td>
<td>5.14b = 2</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td><img src="indole.png" alt="Indole" /></td>
<td><img src="product.png" alt="Product" /></td>
<td>5.14c = 2</td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td><img src="indole.png" alt="Indole" /></td>
<td><img src="product.png" alt="Product" /></td>
<td>5.14d = 6</td>
<td>68%</td>
</tr>
<tr>
<td>5</td>
<td><img src="indole.png" alt="Indole" /></td>
<td><img src="product.png" alt="Product" /></td>
<td>5.15e</td>
<td>NR</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yields after flash chromatography; \(^b\)1.1 equiv of Indole was used in the reaction

![Indole](indole.png)

![Product](product.png)
Table 5.3 Substrate Compatibility Screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="5.16a" alt="Image" /></td>
<td><img src="5.18a" alt="Image" /></td>
<td>90% (1 h)</td>
</tr>
<tr>
<td>2</td>
<td><img src="5.16b" alt="Image" /></td>
<td><img src="5.18b" alt="Image" /></td>
<td>90% (1 h)</td>
</tr>
<tr>
<td>3</td>
<td><img src="5.16c" alt="Image" /></td>
<td><img src="5.18c" alt="Image" /></td>
<td>93% (1 h)</td>
</tr>
<tr>
<td>4</td>
<td><img src="5.17d" alt="Image" /></td>
<td><img src="5.18d" alt="Image" /></td>
<td>80% (18 h)</td>
</tr>
<tr>
<td>5</td>
<td><img src="5.17e" alt="Image" /></td>
<td><img src="5.18e" alt="Image" /></td>
<td>46%[c] 3:2 rr[d] (26 h)</td>
</tr>
<tr>
<td>6</td>
<td><img src="5.17f" alt="Image" /></td>
<td><img src="5.18f" alt="Image" /></td>
<td>99% (3 h)</td>
</tr>
</tbody>
</table>

[a] Isolated yields after flash chromatography; [b] Lower yields attributed to poor solubility; [c] Combined yield for both regioisomers; [d] Ratio determined by 1H NMR, where major isomer was unassigned.
Table 5.4 Expansion to Alternative Nucleophilic Addition

Where Tables 5.2 and 5.4, show the regiomeric maintenance of nucleophilic addition, this finding suggested that the “benzylc-oxyallylic push” could be overcome with the use of sterically bulky groups at the $\alpha'$-position. In comparison, the less bulky hydrogen of compound
5.17f in entry 6 provided regioisomer 5.18f in 99% yield. While removal of the aryl group, and replacement with an isobutyl side, such as entry 7 compound 5.17g also led to a mixture of regioisomers, supporting the theory that the electronics of the aromatic side chain drive regioselectivity of indole addition.

5.5 Introducing Different Nucleophiles into the System

While several groups have extensively studied a variety of indoles as nucleophiles for the direct trapping of intermediates,\textsuperscript{115,117-118} few have yet to establish other carbon and heteroatom nucleophile uses in their reactions.\textsuperscript{118, 172} Initially, it was my goal to establish a catalog of different nucleophiles to apply to quaternary center formations. I began an intensive and unsuccessful attempt at including a random number of nucleophiles from our laboratory stock. After a significant amount of time spent on this inefficient strategy, we turned to literature to propose an alternative, and smarter, approach to this issue.

Mayr’s nucleophilicity parameters was luckily found and applied to our chemistry, as his group composed a tabulated list of compounds, including carbon and heteroatom nucleophiles, according to their reactivity ($N$).\textsuperscript{173-175} Noting that indoles we had attempted, such as regular indole (81% yield), which has a catalogued $N$ value of 5.6, and 4-cyanoindole, where 5-cyanoindole has an $N$ value of 2.8, we began to select carbon nucleophiles within a range of these calculated values.

Sterically bulky benzindole, entry 1 of Table 5.4, generated 94% of its corresponding adduct in the five-membered ring 5.22a. Pyrrole, which has a similar nucleophilicity value to that of indole, successfully added to the intermediates of both five- and six-membered ring starting materials (entry 2). 2,4-Dimethyl pyrrole, a much more reactive pyrrole derivative ($N = 10.6$), gave its quaternary center 5.22c in 83% in less than an hour. Predictably, 3-methyl thiophene
failed to give any isolable amount of product, as its nucleophilicity is predicted to be around 1.4. Nucleophiles within our range, such as azulene (N = 6.7) and 2-trimethylsiloxyfuran (N = 7.2), entries 5 and 6, respectively, were also compatible with our reaction conditions. X-ray crystallographic analysis of 5.22f showed greater than 20:1 diastereomeric ratio of the α,β-unsaturated quaternary center product.

Heteroatom nucleophiles present a particular challenge in when using Brønsted acid catalyzed generation of oxyallyl cations. The potential kinetic deprotonation from the nucleophile is thought to be competitive with the starting material ionization. The first explorations we attempted with heteroatom nucleophiles are described in entries 7-9 of Table 5.4. Oxygen-centered heteroatoms, such as primary alcohols methanol and 3-phenyl-1-propanol, readily added to our ionized intermediate from starting material 5.19 to produce desired products 5.22g and 5.22h in 69% and 39% yield. When 3-phenyl-1-propanol was utilized in place for the six-membered enol ether 5.20, we saw nearly quantitative production of diether product 5.23h. However, cyclohexanol (entry 9) failed to generate any trace of alcohol adduct, suggesting there may be steric hinderance in the ensuing interactions to prevent addition. Mercaptan products 5.22j and 5.23j were generated in 78% and 91% yields, respectively. Attempts at generating carbon-nitrogen bonds of both five- and six-membered materials 5.19 and 5.20 routinely failed to produce any viable amount of product to both five and six-membered rings. A variety of anilines, amines, azides, succinimides all showed no reactivity with our methodology, presumptively due to the inherent basicity of nitrogen, which captures the proton of the Brønsted acid, preventing reactions from occurring.
5.6 Synthetic Applications of Quaternary Centers

Because we had established a method to synthesize a variety of indole-bearing quaternary centers within enol ethers regioselectively, we were interested in creatively exploiting these functionalities toward further synthetic variation. Scheme 5.3 details the directions we attempted in these studies. Compound 5.25 was generated upon exposure to toluenesulfonic acid at -20°C in 5.5:1 diastereoselectivity in 73% yield of cis to trans-diaryl ketone. Our method clearly demonstrates the easy accessibility to these α-indole compounds, an achievement previously established enolization conditions would not have been able to attain. Notably, the newly found uses for these types of α-indole ketones have proven useful in ongoing natural product syntheses.97-101 Another transformation 5.24 could undergo was hydrogenation with palladium to achieve compound 5.26, which bears three contiguous stereocenters in 80% yield and 2.3:1 dr.

Scheme 5.3 Applications of Indole Adducts
Further protection of the nitrogen of the indole of compound 5.24 allowed for more complex oxidative processes toward the enol double bond. For example, oxidation of the internal alkene of compound 5.27 was possible using \( m \)-CPBA in dichloromethane at -30°C in 80% yield and 5 : 1 diastereoselectivity.\(^{185}\) Stereochemical properties of this reaction were also confirmed through X-ray crystallography.\(^{70}\) Oxidative ring opening of the alkene in compound 5.27 led to \( \alpha \)-indole ketoester 5.29 in 73% yield.\(^{186-187}\) Traditional \( \alpha \)-addition of indole to this ester functionality of ketoester 5.29 precursor could also be difficult, as \( \alpha \)-hydrogens of ketones and esters are quite similar.\(^{188}\)

5.7 Conclusion

Our previously established method was expanded to switch the regioselectivity of the indole addition to an oxyallyl cation.\(^{115, 151}\) With the aid of a neighboring benzylic system, the oxyallyl cation was stabilized in such a way that allowed indole, and other nucleophiles, addition to the \( \alpha \)-methyl carbon of the cationic intermediate. A wide range of indoles and starting materials were investigated. An important key to these reactions is the accessibility to compounds that would not otherwise have been possible under classical enolization chemistries. After strategic planning of carbon nucleophiles, we were also able to achieve a variety of nucleophilic addition to our methoxyenol ether starting materials. We also were able to install C-O and C-S bonds at the \( \alpha \)-methyl position.\(^{151}\)
CHAPTER 6: 2-SILYLOXYPENTADIENYL CATIONS AND THEIR REACTIVITY TOWARDS NUCLEOPHILIC ADDITION

6.1 Purpose

This chapter describes the method development to form a single regioisomer of silyl dienol ethers. In this project, we extend our cationic intermediates to span 5-carbon atoms in the form of 2-siloxypentadienyl cations, an intermediate relatively underexplored. Starting material ionization was carried out with a mild Bronsted acid catalyst, and direct trapping with indole and other nucleophiles provided desired products in excellent yields and good stereocontrol.

6.2 Importance and Reaction Design

Silyldienol ethers are isolable synthetic intermediates that have found significant applications in the construction of complex molecules, including natural products. These compounds commonly serve as a convenient source of four carbon atoms in versatile carbon-carbon bond forming processes, such as [4+2] cycloaddition reactions and vinylogous Mukaiyama aldol reactions. Silyldienol ethers are generally prepared via deprotonation of α,β-unsaturated ketones, viz 6.1, in the presence of a base, followed by capture of the forming dienolate anions with trialkysilyl chloride. Nevertheless, due to the comparable acidity of hydrogen atoms at the α’- and γ-positions in ketones 6.1, this classical enolization strategy could potentially produce a mixture of isomeric products 2a and 6.2b. Hypothetically, this regioselectivity issue could be further convoluted by the lack of control in the stereochemistry of the forming alkenes (Scheme 6.1).

Our group recently reported a new tactic that successfully introduced rapid functionalization of silylenol ethers at the α-position via an intermediacy of unsymmetrical silyloxyallyl cations, viz 6.4, which were generated upon ionization of □-
hydroxy silylenol ether precursors 6.3 in the presence of a Brønsted acid. We discovered that these reactive species readily underwent direct nucleophilic addition, regioselectively at the less substituted \( \alpha \)-carbon, to produce the corresponding \( \alpha \)-functionalized silylenol ethers 6.5 as a single constitutional isomer.

**CONCERNING REGIO- AND OLEFIN SELECTIVITY**

![Scheme 6.1 Conceptual Reaction Hypothesis]

**PREVIOUS WORK**

![Previous Reaction Steps]

**HYPOTHESIS**

![Potential Conformational Equilibrium]

Scheme 6.1 Conceptual Reaction Hypothesis
We envisioned that the regioselective synthesis of silyldienol ethers with an opportunity to control the double bond stereochemistry could be accomplished via an analogous cationic approach, more specifically, through an intermediacy of 2-silyloxypentadienyl cations.\textsuperscript{109, 117-118, 209-214} We hypothesized that ionization of $\alpha$-hydroxy silylenol ether derived starting materials 6.6, promoted by a Brønsted acid catalyst, should readily generate the corresponding 2-silyloxypentadienyl cations, \textit{viz.} 6.7a. Based upon our previous findings,\textsuperscript{206-208} the ensuing attack by nucleophiles to these reactive intermediates is expected to occur at the less substituted electrophilic carbon, which is in this case, the $\gamma$-position. This process would accordingly produce the intended $\gamma$-functionalized silyldienol ether 6.8a in a regioselective manner. Nonetheless, we must also consider the possibility that 2-silyloxypentadienyl cations 6.7a could participate in a conformational equilibrium from the \textit{s-trans} to the \textit{s-cis} form 6.7b. This alternative conformation, upon nucleophilic addition, would generate silyldienol ether adduct 6.8b, bearing the opposite olefin geometry.

In addition to developing a \textit{de novo} synthesis of highly functionalized silyldienol ethers, the significance of our work would be further emphasized by the reveal of chemical behavior of 2-silyloxypentadienyl cations. As opposed to 3-oxypentadienyl cations, of which there are extensive studies reported towards their applications in the Nazarov cyclization,\textsuperscript{94, 215-218} synthetic utilities of 2-oxypentadienyl cations and their structurally related species are essentially underexplored. There are only a few literature precedents that describe the participation of these reactive intermediates in ring annulations via [4+3] cycloaddition.\textsuperscript{219-222} Nonetheless, to the best of our knowledge,
there are yet any accounts on the reactivity of 2-oxypentadienyl cations towards direct addition by nucleophiles.

6.3 Indole Additions to Putative Cationic Intermediates

Figure 6.1 describes our initial study, in which divinyl alcohol derived compound 6.11 was employed as a model substrate with a reason that the cyclic nature of this material would help simplify the formation of different products. Model compound 6.11 was easily synthesized in two steps from commercially available 1,2-dione 6.9, which was subjected to regioselective silylation, followed by addition of 2-propenylmagnesium bromide to the resulting ketone 6.10. We initially screened several Lewis and Brønsted acids to ionize 6.11 in the presence of indole in toluene at room temperature.

![Chemical structure and reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>La(OTf)3</td>
<td>22</td>
<td>20%</td>
</tr>
<tr>
<td>2</td>
<td>AcOH</td>
<td>18</td>
<td>42%</td>
</tr>
<tr>
<td>3</td>
<td>Py-TsOH</td>
<td>22</td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td>Py-TrOH</td>
<td>2.5</td>
<td>99%</td>
</tr>
<tr>
<td>5</td>
<td>TfOH</td>
<td>10 min</td>
<td>45%b</td>
</tr>
</tbody>
</table>

a The double bond geometry was determined by NOE.
b Protodesilylation product 6.12 was isolated in 48%.

Figure 6.1 Catalyst Screening and Optimization Studies
As indicated in entry 4, we discovered that the use of catalytic pyridinium triflate (10 mol%) and indole (1.1 equiv) at room temperature cleanly produced the corresponding \( \gamma \)-functionalized silyldienol ether 6.12 in a quantitative yield. There were two notable observations from these experiments: 1) As hypothesized, the addition of indole occurred solely at the less substituted electrophilic carbon, \( i.e. \) the \( \gamma \)-position. 2) The newly formed fully substituted double bond in silyldienol ether 6.12 was produced exclusively as the \( Z \) isomer. This result is particularly intriguing as the construction of tetrasubstituted alkenes in stereoselective manner is a formidable synthetic challenge.\(^{223-229}\) The exquisite control of the stereo- and regioselectivity in this reaction did not appear to originate from the free pyridine liberated upon proton transfer. As indicated in entry 5, a control experiment using catalytic triflic acid afforded silyldienol ether 6.12 also as a single isomer, along with the protodesilylated \( \alpha,\beta \)-unsaturated ketone byproduct 6.13, presumably generated due to the strongly acidic reaction conditions.

As shown in Table 6.1, the high selectivity in the \( \gamma \)-functionalization of divinyl alcohol 11 with catalytic pyridinium triflate appeared to be universal across various substituted indoles that were subjected to our studies. For example, sterically encumbered 2-phenylindole, halogen-containing 5-bromoindole, and electron-rich 5-methoxyindole, generated silyldienol ethers 6.14a-6.14c in excellent yields. Interestingly, electron-deficient indoles were also tolerated in this reaction. Indoles containing methyl-5-carboxylate, 4-carbonitrile, and 4-carboxaldehyde groups cleanly produced the corresponding adducts 6.14d-6.14f in excellent yields. Some of these reactions were completed as rapidly as in 15 minutes, thus signifying the high reactivity of the putative 2-silyloxypentadienyl cations towards indole addition. More importantly, the
tetrasubstituted alkenes in all of these silyldienol ether products were produced exclusively with a $Z$ geometry.\textsuperscript{230}

Table 6.1 Indole Compatibility with Starting Material 6.11

\begin{table}
\centering
\begin{tabular}{c c c}
\hline
\textbf{TBSO} & \textbf{Py-TfOH (10 mol\%)} & \textbf{TBSO} \\
\textbf{Me} & \textbf{indoles (1.1 equiv)} & \textbf{Me} \\
\textbf{6.11} & \textbf{toluene (0.2 M), rt} & \textbf{6.14}\textsuperscript{a} \\
& \textbf{(15 min to 4 hrs)} & \\
\hline
\textbf{TBSO} & \textbf{Ph} & \textbf{TBSO} \\
\textbf{Me} & \textbf{NH} & \textbf{Me} \\
\textbf{6.14a} (91\%) & \textbf{6.14b} (91\%) & \\
\hline
\textbf{TBSO} & \textbf{NH} & \textbf{TBSO} \\
\textbf{Me} & \textbf{OMe} & \textbf{Br} \\
\textbf{6.14c} (97\%)\textsuperscript{b} & \textbf{6.14d} (74\%) & \\
\hline
\textbf{TBSO} & \textbf{NH} & \textbf{TBSO} \\
\textbf{Me} & \textbf{NC} & \textbf{Me} \\
\textbf{6.14e} (95\%)\textsuperscript{b} & \textbf{6.14f} (89\%) & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}The double bond geometry was determined by NOE; \textsuperscript{b}The structural assignment of these products was confirmed by X-ray crystallography.

6.4 Reactivity Studies: Substituent Effects on Stereoselective Outcome

We then investigated the effect of substituents inherent to starting materials 6.15.

To focus on the substitution pattern at the $\beta$-position, we initially prepared a series of
substituted divinyl alcohols 6.15a-6.15c and subjected these compounds to our reaction conditions (Table 6.2, entries 1-3). Interestingly, replacement of the β-methyl substituent with a sterically more demanding phenyl group in substrate 6.15a afforded γ-indole adduct 6.16a in 75% yield; however, we observed a significant erosion in the double bond selectivity (up to 3:1 when the reaction was carried out at -15°C). Surprisingly, removal of the α'substituent in starting materials 6.15b and 6.15c fully reversed the resulting olefin geometry, as these compounds produced their respective adducts 6.16b and 6.16c as the E isomer.

We also probed the role of α'-substituents to identify the controlling elements for the observed regioselectivity pattern at the γ-position. As shown in Table 6.2, entries 4-6, treatment of α'-phenyl and α’-thiophene substituted starting materials 6.15d and 6.15e with catalytic pyridinium triflate and indole produced their respective γ-functionalized silyldienol ethers 6.16d and 6.16e in good yields as a single regioisomer. These results supported our original hypothesis, in which nucleophilic additions to the putative 2-silyloxypentaldienyl cations would preferably occur at the least substituted electrophilic carbon. These results supported our original hypothesis, in which nucleophilic additions to the putative 2-silyloxypentaldienyl cations would preferably occur at the least substituted electrophilic carbon.

Nevertheless, we discovered that nucleophilic addition at the α’-position, leading to formation of a presumed thermodynamically more favorable silyldienol ether isomer, became considerably much more competitive when the degree of substitution at both α’- and γ-positions was identical. For example, activation of substrate 6.15f with our standard reaction conditions afforded α’-indole product 6.16f in 57% yield.
Table 6.2 Substrate Effects on Olefin Geometry

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield a</th>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBSO Ph</td>
<td>6.15a</td>
<td>75% b</td>
<td>4</td>
<td>TBSO Me</td>
<td>6.15d</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>6.16a</td>
<td>E/Z = 3:1 (48 h, -15°C)</td>
<td></td>
<td>Me</td>
<td>6.16d</td>
<td>(22 h)</td>
</tr>
<tr>
<td>2</td>
<td>TBSO Me</td>
<td>6.15b</td>
<td>64%</td>
<td>5</td>
<td>S TBSO Me</td>
<td>6.15e</td>
<td>52%</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>6.16b</td>
<td>(1 h)</td>
<td></td>
<td>Me</td>
<td>6.16e</td>
<td>(14.5 h)</td>
</tr>
<tr>
<td>3</td>
<td>TBSO Me</td>
<td>6.15c</td>
<td>64%</td>
<td>6</td>
<td>TBSO Me</td>
<td>6.15f</td>
<td>57% c</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>6.16c</td>
<td>(14 h)</td>
<td></td>
<td>Me</td>
<td>6.16f</td>
<td>E/Z = 3:1 (24 h)</td>
</tr>
</tbody>
</table>

a The double bond geometry was determined by NOE; b Product 6.16a was isolated in 67% with E/Z ratio = 1.7:1 when the reaction was performed at room temperature; c The product of indole addition at γ-position was isolated in 7% yield.
6.5 Reactivity Studies: Nucleophile Variations on Stereoselective Outcome

Table 6.3 depicts our exploration in the compatibility of various nucleophiles in this methodology beyond substituted indoles. We commenced by employing heteroatom-centered nucleophiles (entries 1-4). Interestingly, attempts to functionalize starting material 6.11 with tert-butylaniline and thiophenol under catalytic pyridinium triflate afforded the corresponding silyldienol ethers 6.17a and 6.17b in good yields, however as a 1:1 mixture of double bond isomers. More surprisingly, the use of methanol and 3-phenyl-1-propanol produced the respective products 6.17c and 6.17d with a complete reversal of selectivity, in which the tetrasubstituted alkene geometry was observed exclusively as the $E$ isomer. The utility of other aromatic nucleophiles was also investigated. For instance, 1,3,5-trimethoxybenzene and pyrrole afforded the corresponding $\gamma$-functionalized silyldienol ethers 6.17e and 6.17f in high yields. As anticipated, these products were isolated as the $Z$ isomer (entries 5-6).

The exact origin on how these heteroatom nucleophiles eroded or even altered the double bond selectivity from $Z$ to $E$ geometry is currently under investigation. Nevertheless, the above experimental results suggested that $s$-cis 6.7b appeared to readily undergo equilibrium with $s$-trans 6.7a, which we believed to have occurred during the approach of heteroatom nucleophiles to the putative 2-silyloxypentadienyl cations. We also propose that this origin could be due to the propensity for reionization to occur from the heteroatom adducts, leading to an inversion in the double bond geometry as well. To test this hypothesis, we subjected 6.17c to optimized ionization conditions using indole as a nucleophile as shown in Scheme 6.2. Interestingly, we isolated compound 6.12 as a single $Z$-isomer in just 3 hours.
Table 6.3 Alternative Nucleophile Screening

\[
\begin{array}{cccc}
\text{Entry} & \text{Nucleophile} & \text{Product} & \text{Yield} \\
1 & t-\text{Bu}-\text{Ph}-\text{NH}_2 & \text{TBSO} \begin{array}{c}
\begin{array}{c}
\text{Me} \\
\text{H}
\end{array}
\end{array} \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} \begin{array}{c}
\text{Nuc}
\end{array} & 73\% \\
& & & E/Z = 1:1 \\
& & & (0.75 \text{ h}) \\
2 & \text{Ph-SH} & \text{TBSO} \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} \begin{array}{c}
\text{S}
\end{array} \begin{array}{c}
\text{Ph}
\end{array} & 62\% \\
& & & E/Z = 1:1 \\
& & & (5 \text{ h}) \\
3 & \text{MeOH} & \text{TBSO} \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} \begin{array}{c}
\text{OMe}
\end{array} & 59\% \\
& & & (0.25 \text{ h}) \\
4 & \text{Ph-CH(OH)} & \text{TBSO} \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} \begin{array}{c}
\text{O}
\end{array} \begin{array}{c}
\text{Ph}
\end{array} \begin{array}{c}
\text{Me}
\end{array} & 97\% \\
& & & (0.75 \text{ h}) \\
5 & \text{MeO-Ph} & \text{TBSO} \begin{array}{c}
\begin{array}{c}
\text{MeO}
\end{array}
\end{array} \begin{array}{c}
\begin{array}{c}
\text{MeO}
\end{array}
\end{array} & 60\% \\
& & & (0.75 \text{ h}) \\
6 & \text{Py} & \text{TBSO} \begin{array}{c}
\begin{array}{c}
\text{Me}
\end{array}
\end{array} & 89\% \\
& & & (0.25 \text{ h}) \\
\end{array}
\]

\text{a}\text{The double bond geometry was determined by NOE.}
6.6 Conclusion

In summary, we have developed a procedure to generate 2-silyloxypentadienyl cations under mild Brønsted acid catalysis, and uncovered their unprecedented reactivity towards direct nucleophilic additions. Furthermore, our ability to modulate conformations in these cationic intermediates and control their reactivity between the $\alpha'$- and the $\gamma$-positions has enabled us to exploit their useful synthetic utility towards the construction of highly functionalized silyldienol ethers bearing tetrasubstituted alkenes, which were accomplished in a regio- and stereoselective manner. We are currently pursuing detailed mechanistic studies and further applications of these chemistries in the construction of other high value, synthetically challenging compounds.
CHAPTER 7: A NEW APPROACH TO CARBAZOLE ANNULATION VIA CASCADE NUCLEOPHILIC ADDITION-CYCLIZATION INVOLVING 2-SILOXYPENTADIENYL CATION INTERMEDIATES

7.1 Purpose

With this chapter, the discovery of a route to access a series of new, never before isolated carbazoles is described. These compounds were accessed with Brønsted acid catalysis from vinyl substituted α-hydroxy silylenol ether starting materials in conjunction with indole, which then underwent intramolecular annulation in a one-pot process. The details of this chapter describe and showcase this operationally simple procedure through the isolation of over 20 different compounds in good yields.

7.2 Utilities of Carbazoles

The carbazole core is an aromatic, tricyclic system that has been extensively explored in both chemistry and biology. These polyaromatic structures were first reported by Graebe and Glaser over 100 years ago in 1872. Since then, further investigations into the inherent electronics of its tricyclic system made this structure a useful compound in material chemistry with practical development of several organic optoelectronics. Many carbazoles and related tricyclic derivatives, both synthetic and naturally occurring compounds, have significant impacts in pharmaceutical applications. Figure 7.1 showcases just a few of these compounds, where these assorted carbazole derivatives range in therapeutic activity. The series of derivatives listed showcase the diversity of these compounds, where treatments span psychosis, cancer, nausea, malaria, and hypertension. Due to this functionality’s widespread impact, continued investigations into synthetic methodologies for carbazole formations remain a significant task.
7.3 Hypothesis and Reaction Development

Our group recently discovered the γ-addition of indoles to 2-siloxypentadienyl cations in a stereoselective manner.249 The mild acid utilized in this study, pyridinium triflate, allowed us to isolate the silyl dienol ether products in high yields and tunable stereocontrol through the use of different starting materials, such as compound 7.4, Scheme 7.1. We determined that the ionized intermediate could exist in two equilibrating forms (7.5 and 7.7). Depending upon the substituents at the β-position, we could isolate either only E- or only Z-isomer. Interestingly, we noted that the Z-isomers could be utilized for a broader synthetic use.
We believed that the continued activation of compound 7.8 to 7.9 in the presence of a slightly stronger Brønsted acid, would provide an opportunity for intramolecular cyclization. This would occur through protodesilylation of compound 7.8, and activation with a stronger acid, such as camphorsulfonic acid (CSA), would activate the carbonyl group of 7.9, promoting annulation and reinstalling aromatization to provide our desired carbazole series.
In attempting to access carbazole formation, our group studied a variety of reaction conditions. Our studies began with the use of a pyridinium triflate as our acid catalyst with our 5-membered ring starting material 7.11, which remained halted at intermediate 7.12 (Table 7.1). Our direction then shifted to using CSA, where we were happy to see reaction progression to 66% isolated yield of carbazole 7.14 and ketone 7.13 in 30% yield. We then attempted a reaction using dichloromethane as solvent to improve catalyst solubility, resulting in 29% carbazole isolation (entry 3). We also reduced indole ratio to 1.0 from 1.1 to decrease chromatographic separation difficulty, and upon subsequent screenings of CSA ratios, we found that 50 mol % of CSA, with 1.0 equivalent of indole provided only our desired carbazole in 99% yield in just five hours.

![Table 7.1 Reaction Optimization]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid</th>
<th>Equiv of Acid</th>
<th>Equiv of Indole</th>
<th>Time (h)</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt; 7.12 : 7.13 : 7.14</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>Py·TfOH</td>
<td>0.1</td>
<td>1.1</td>
<td>3</td>
<td>99 : -- : --</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>CSA</td>
<td>0.1</td>
<td>1.1</td>
<td>78</td>
<td>-- : 30 : 66</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>CSA</td>
<td>0.1</td>
<td>1.1</td>
<td>78</td>
<td>-- : 52 : 29</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>CSA</td>
<td>0.1</td>
<td>1.0</td>
<td>24</td>
<td>-- : -- : 56</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂</td>
<td>CSA</td>
<td>0.2</td>
<td>1.0</td>
<td>24</td>
<td>-- : -- : 85</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>CSA</td>
<td>0.5</td>
<td>1.0</td>
<td>5</td>
<td>-- : -- : 99</td>
</tr>
</tbody>
</table>
7.4 Carbazole Formation

With these optimized conditions in hand, we then explored the applicability of our carbazole annulation methodology towards various substituted indoles (Table 7.2). As shown in entries 2-5, indoles containing both electron-donating groups and halogen atoms were well tolerated by starting material 7.11. Such nucleophiles readily generated the corresponding substituted carbazoles 7.16b-7.16e in excellent yields. Electron-deficient indoles, such as those containing 4-cyano and methyl 5-carboxylate substituents, also afforded the carbazole adducts 7.16f and 7.16g in 99% and 51% yields, respectively (entries 6 and 7). Nonetheless, these reactions required a slightly elevated temperature to promote the key carbazole annulation; otherwise, a considerable amount of the corresponding γ-indolyl α,β-unsaturated ketone adducts would remain uncyclized. As indicated in entry 8, we also subjected 5-methoxy-1H-benzo[g]indole as a coupling partner, and this reaction furnished a highly conjugated polycyclic carbazole product 7.16h in respectable 48% yield.

The compatibility of 6-membered vinyl substituted α’-hydroxy silylenol ethers variant, viz. 7.15, towards our carbazole methodology was also examined. Consistent with our previous findings, this substrate proved to be less reactive than the 5-membered counterpart, thus requiring more stringent reaction conditions. Upon a short campaign in reaction optimization (see Supporting Information), we identified that the intended tetrahydrobenzocarbazole core 7.17 could be prepared in one synthetic operation from starting material 7.15 in good yields using a stoichiometric amount of CSA under gentle reflux. These alternate conditions appeared to be tolerated by both electron-rich and halogenated indoles, as well as 5-methoxy-1H-benzo[g]indole (entries 1-5, 8), affording the respective functionalized carbazoles 7.17a-7.17e and 7.17h in good yields. Unfortunately, applications of electron-poor indoles with the six-membered starting
material only led to significant decomposition of the materials (entries 6-7). Despite these complications, our chemistry still managed to generate ester-containing carbazole product 7.17f albeit in 29% isolated yield.

When examining 6-membered ring compatibility in our carbazole formation studies, we knew that γ-indole addition would be more difficult. This was thought to be due to bond geometries in the forming 2-siloxypentadienyl cation intermediate. Ionization of a 6-membered ring is expected to be slower due to the bond strain of less than 120° angle. A 5-membered ring’s ionization is proposed to be faster due to the bond angles being closer to the ensuing sp² angles of 120°. With this in mind, we also screened optimization conditions for this system, and we found that heating 6-membered ring material 7.15 to 40°C in dichloromethane with 1.0 equivalent of CSA and 1.0 equivalents of indole provided desired adducts in good yields.

7.5 Reaction Compatibility with Side Chain Variants

Table 7.3 depicts our subsequent investigation on the scope of substrates by using a series of starting materials 7.18. In particular, we were interested in identifying the substituent effects at the α’, α, and α-positions towards the carbazole annulation. For instance, substrates 7.18a-7.18d possessing allyl, n-nonyl, phenyl, and indolyl groups at the α’-position, respectively, were found to be compatible under the optimized annulation conditions, as these starting materials readily furnished the corresponding substituted carbazoles 7.19a-7.19d in respectable yields (entries 1-4). We then continued our study by introducing a different substitution patterns at the β- and γ-positions. As exemplified in entries 6 and 7, the use of substrates bearing β-phenyl and γ-methyl groups as depicted in starting materials 7.18e afforded their respective 3-phenyl carbazole 7.19e in 92% yield. Unfortunately, compound 7.18f produced only trace amounts of 7.19f. These results were very surprising to us, considering the fact that in our previous study,
these substituents were found to generate a \textit{trans}-double bond, an orientation unfavorable for cyclization, in the forming \(\gamma\)-indole silyldienol ether adducts.\textsuperscript{249}

Table 7.2 5- and 6-Membered Ring Substrate Compatibility

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield\textsuperscript{c}(time)</th>
<th>Entry</th>
<th>Product</th>
<th>Yield\textsuperscript{c}(time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Image](7.11 n = 1; 7.15 n = 2)</td>
<td>7.16a n = 1, 99% (5h) 7.17a n = 2, 71% (22h)</td>
<td>5</td>
<td>![Image](7.16 n = 1; 7.17 n = 2)</td>
<td>7.16c n = 1, 84% (5h) 7.17c n = 2, 90% (20h)</td>
</tr>
<tr>
<td>2</td>
<td>![Image](7.11 n = 1; 7.15 n = 2)</td>
<td>7.16b n = 1, 97% (5h) 7.17b n = 2, 62% (22h)</td>
<td>6</td>
<td>![Image](7.11 n = 1; 7.15 n = 2)</td>
<td>7.16f n = 1, 99%\textsuperscript{d,e} (7h) 7.17f n = 2, 29% (20h)</td>
</tr>
<tr>
<td>3</td>
<td>![Image](7.11 n = 1; 7.15 n = 2)</td>
<td>7.16c n = 1, 91% (5h) 7.17c n = 2, 76% (22h)</td>
<td>7</td>
<td>![Image](7.11 n = 1; 7.15 n = 2)</td>
<td>7.16g n = 1, 51%\textsuperscript{d,f} (7h) 7.17g n = 2, degradation</td>
</tr>
<tr>
<td>4</td>
<td>![Image](7.11 n = 1; 7.15 n = 2)</td>
<td>7.16d n = 1, 67% (5h) 7.17d n = 2, 88% (20h)</td>
<td>8</td>
<td>![Image](7.11 n = 1; 7.15 n = 2)</td>
<td>7.16h n = 1, 48% (8d) 7.17h n = 2, 43% (8d)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Starting materials 7.11 were run at room temperature, 0.5 equiv of CSA and 1.0 equiv of indole; \textsuperscript{b}Starting materials 7.15 were run at 40\textdegree C and 1.0 equiv of CSA; \textsuperscript{c}Isolated yields based on flash column chromatography; \textsuperscript{d}Reactions run at 40\textdegree C with 1.0 equiv of CSA; \textsuperscript{e}53\% was isolated when using 5-membered ring ionization conditions; \textsuperscript{f}37\% carbazole and 43\% ketone were isolated when using 5-membered ring ionization conditions.
Table 7.3 Carbazole Formation of Starting Material Substituent Variation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield(^a) (time)</th>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield(^a) (time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="7.18a" alt="Image" /></td>
<td><img src="7.19a" alt="Image" /></td>
<td>51% (5 h)</td>
<td>5</td>
<td><img src="7.18e" alt="Image" /></td>
<td><img src="7.19e" alt="Image" /></td>
<td>92% (19 h)</td>
</tr>
<tr>
<td>2</td>
<td><img src="7.18b" alt="Image" /></td>
<td><img src="7.19b" alt="Image" /></td>
<td>74% (96 h)</td>
<td>6</td>
<td><img src="7.18f" alt="Image" /></td>
<td><img src="7.19f" alt="Image" /></td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td><img src="7.18c" alt="Image" /></td>
<td><img src="7.19d" alt="Image" /></td>
<td>63% (24 h)</td>
<td>7</td>
<td><img src="7.18g" alt="Image" /></td>
<td><img src="7.19g" alt="Image" /></td>
<td>70% (96 h)</td>
</tr>
<tr>
<td></td>
<td><img src="7.18d" alt="Image" /></td>
<td></td>
<td>43% (19 h)</td>
<td>8</td>
<td><img src="7.18h" alt="Image" /></td>
<td><img src="7.19h" alt="Image" /></td>
<td>71% (20 h)[^b]</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield based on flash column chromatography; \(^b\) Reaction was carried out using six-membered ring optimized conditions
Similarly, it was remarkable to observe that carbazole annulation reactions involving \(\alpha\)-hydroxy silylenol ethers 7.18g and 7.18h successfully produced the corresponding products 7.19g and 7.19h in excellent yields, despite the fact that upon addition of indole to their corresponding 2-silyloxoypentadienyl cations, these unsubstituted vinyl groups would have installed the E-double bond geometry, unfitting for intramolecular cyclization. Aromatic placement on the vinyl side chain as shown in entry 4 was also compatible with our reaction conditions providing carbazole 7.21d in 92% yield. Allylic starting material 7.20f will also be subjected to our optimized conditions to showcase the applicability to nonaromatic side chains.

### 7.6 Proposed Mechanism

Based on these experimental results, the mechanism of our carbazole annulation reaction is proposed as follows: commencing with a \(\gamma\)-functionalization of vinyl substituted \(\alpha'\)-hydroxy silylenol ethers 7.4 in the presence of Brønsted acid and indole. As shown in Scheme 7.2, this nucleophilic substitution reaction would produce either \(\gamma\)-indole adducts 7.20 or 7.21 (or as a mixture of both double bond isomers) depending upon the steric effects exhibited by the \(\beta\)-substituent (\(R_b\)). In the presence of a stronger Brønsted acid, such as CSA, and stoichiometric water produced in the initial ionization sequence, silyldienol ethers 7.20 and 7.21 then proceeded to undergo protodesilylation to the corresponding ketones that were further activated to give cationic intermediates 7.22 and 7.23 upon proton transfer. These cationic species enable reversible alkene isomerization, therefore, funneling formation of Z-isomer 7.24 to undergo intramolecular indole addition to generate a spirocyclic iminium ion 7.25, which then undergoes Pictet-Spengler type ring expansion via C-C bond migration to 7.26. Ensuing dehydration via the loss of a hydronium ion equivalent allows for the regeneration of aromaticity and produces the target carbazole 7.27.
As the key protodesilylation step involves the generation of a stereocenter at the $\alpha'$-position, this step would offer an opportunity for introducing chirality via enantioselective protonation of the silylenol ether. This stereocenter was ultimately carried throughout the synthesis and ended up in the product. Naturally, we thought about carrying this reaction with chiral Brønsted acid.\(^{252-253}\)

### 7.7 Attempts at Enantioselection

The optimization of an enantioselective method for this reaction was a rather lengthy process. The sheer size of binol-derived phosphoric acid catalysts significantly decreased the
reaction rate to around 5-8 days depending on the equivalents of the catalyst. In the case of Table 7.4 entry 1, the use of THF at reflux resulted in degradation of product, leading us to use dichloromethane as the solvent for the rest of our studies. With a 1M reaction concentration, relative to starting material 7.11, our yield was significantly low, however, we did see a selectivity in our resultant $er$ of 20 : 80 selectivity as determined by chiral HPLC.

We then tried to use a thioamide catalyst in entry 3, which eroded enantioselectivity even with 0.1 equivalents of our catalyst. In order to speed the reaction rate, we also tried an R-TRIP/CSA mixture, which also afforded a decrease in selectivity to 35:65 in 69% yield. Similarly, an attempt at raising reaction temperature to reflux in entry 6, lowered our yield with moderate selectivity. Entries 7 through 9 depict reaction selectivity studies involving water, where we saw no reaction with addition of 4Å molecular sieves. We did see selectivity, however in entries 8 and 9 with 68% and 72% yields, respectively with approximately 70% $ee$.

Table 7.4 Enantioselective Method Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Temp(°C)</th>
<th>Equiv. (cat.)</th>
<th>% Yield$^a$</th>
<th>$er^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>R-TRIP</td>
<td>70</td>
<td>0.5</td>
<td>degradation</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$Cl$_2$</td>
<td>R-TRIP$^c$</td>
<td>rt</td>
<td>0.5</td>
<td>34</td>
<td>20 : 80</td>
</tr>
<tr>
<td>3</td>
<td>CH$_2$Cl$_2$</td>
<td>1174193-01-1$^d$</td>
<td>rt</td>
<td>0.1</td>
<td>86</td>
<td>56 : 44</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$Cl$_2$</td>
<td>R-TRIP/CSA</td>
<td>30</td>
<td>0.5/0.4</td>
<td>69</td>
<td>35 : 65</td>
</tr>
<tr>
<td>5</td>
<td>CH$_2$Cl$_2$</td>
<td>R-TRIP</td>
<td>rt</td>
<td>0.5</td>
<td>63</td>
<td>25 : 75</td>
</tr>
<tr>
<td>6</td>
<td>CH$_2$Cl$_2$</td>
<td>R-TRIP</td>
<td>rt</td>
<td>0.5</td>
<td>72</td>
<td>16 : 84</td>
</tr>
<tr>
<td>7</td>
<td>CH$_2$Cl$_2$</td>
<td>R-TRIP/4Å MS</td>
<td>rt</td>
<td>0.5</td>
<td>no reaction</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>CH$_2$Cl$_2$</td>
<td>R-TRIP/H$_2$O</td>
<td>rt</td>
<td>0.5/2.0</td>
<td>68</td>
<td>15 : 85</td>
</tr>
<tr>
<td>9</td>
<td>CH$_2$Cl$_2$</td>
<td>R-TRIP/H$_2$O</td>
<td>rt</td>
<td>0.5/10.0</td>
<td>78</td>
<td>17 : 83</td>
</tr>
</tbody>
</table>

$^a$Isolated yields based on flash column chromatography; $^b$Determined with chiral HPLC
$^c$Reaction carried out in 1M concentration; $^d$Refers to catalyst's CAS number
In an attempt to determine which enantiomer (R or S) is in excess, we ran a large scale R-TRIP catalyzed reaction using 5-bromoindole (Scheme 7.3). The heavy atom effect induced from the bromine, we hope, will promote crystal formation so that we may use X-ray diffraction to resolve this issue of absolute configuration. We are in the process of isolating and analyzing the carbazole formation and expect to report our findings in due course.

Scheme 7.3 Enantioselective Carbazole Formation

7.8 Conclusion

In conclusion, this group has developed a robust method to generate a novel class of synthetic carbazole compounds using 2-siloxypentadienyl cations. 5- and 6-membered ring starting materials were analyzed and found to suitably give their respective carbaizes in good yields. An enantioselective variant is also possible, as we have demonstrated that the use of chiral phosphoric acid R-TRIP has successfully produced a slight enantioenrichment of our desired products, however at much longer reaction times. Future work includes establishing a strategy for total enantioselectivity, and screening for biological activity.
CHAPTER 8: EXPERIMENTAL METHODS

8.1 General Experimental Information

Unless otherwise noted, all materials were used as received from commercial suppliers without further purification. All anhydrous reactions were performed using oven-dried or flame-dried glassware, which was then cooled under vacuum and purged with nitrogen gas. Tetrahydrofuran (THF), dichloromethane (CH$_2$Cl$_2$), acetonitrile, toluene, and diethyl ether (Et$_2$O) were filtered through activated 4Å molecular sieves under nitrogen contained in an M-Braun Solvent Purification System. All reactions were monitored by EMD analytical thin layer chromatography (TLC Silica Gel 60 F$_{254}$, Glass Plates) and analyzed with 254 nm UV light and/or anisaldehyde – sulfuric acid or potassium permanganate treatment. Silica gel for column chromatography was purchased from Dynamic Adsorbents, Inc. (Flash Silica Gel 32-63u). Unless otherwise noted, all $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ using a Bruker DPX-250 spectrometer operating at 250 MHz for $^1$H and 62.5 MHz for $^{13}$C. Chemical shifts (δ) are reported in ppm relative to residual CHCl$_3$ as an internal reference ($^1$H: 7.26 ppm, $^{13}$C: 77.00 ppm). Coupling constants (J) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), x (septet), h (heptet), b (broad), and m (multiplet). FT-IR spectra were recorded on Bruker Tensor 27 spectrometer and OPUS 6.5 Data Collection Program, and absorption frequencies were reported in reciprocal centimeters (cm$^{-1}$). High Resolution Mass Spectrometry – Electron Spray Ionization (HRMS-ESI) analyses were performed by the Louisiana State University Mass Spectrometry Facility using an Agilent 6210 Instrument. X-ray structure analyses were performed by the Louisiana State University X-ray Structure Facility using a Bruker APEX-II CCD diffractometer. Gas Chromatography – Mass Spectrometry (GC-MS) studies were conducted on an Agilent Technologies 6890N
Network GC System model number G1530N with 7683B series injector. The column used for this system was an Agilent HP-5MS 5% phenyl methyl siloxane (model number 19091S-433), which was 30 meters in length. The column had an internal diameter of 250 µm and film thickness of 0.25 µm. Solvent delay was set to 3.50 minutes for each trial. Low and high mass readings were set to parameters of 40 to 800 m/z, respectively. Oven, inlet, and detector temperatures were set to 250°C, and helium was used as the inert carrier gas. HPLC analyses were carried out using Dionex Utlimate 3000 system on Chiralcel column (OD-H 0.46 cm x 25 cm) for 35 or 70 minute elution times, 12% iPrOH in hexanes.

8.2 General Primary Chlorination Procedure

Unless otherwise noted, into an oven-dried round-bottomed flask, alcohol starting material (2.00 mmol) was dissolved in anhydrous dichloromethane (15 mL), and the solution was then cooled to 0°C. Triethylamine (0.70 mL, 5.00 mmol) was then added via syringe, followed by triphosgene (297 mg, 1.00 mmol) in one portion. The mixture was stirred at 0°C for 3 minutes and then allowed to warm up to room temperature. After stirring for 3 hours, the reaction mixture was poured into a separatory funnel containing a saturated aqueous solution of NaHCO₃ (30 mL), and the biphasic mixture was then shaken vigorously. Upon separation of layers, the aqueous layer was re-extracted with dichloromethane (2 x 30 mL). The organic layers were combined, dried over MgSO₄, filtered, and concentrated under vacuum. The resulting crude material was purified using flash column chromatography using silica gel as the stationary phase and a mixture of either hexanes/ethyl acetate, pentane/diethyl ether or pentane/dichloromethane as the mobile phase.
8.2.1 Synthetic Procedures for Novel Primary Alkyl Chlorides

Synthesis of (3)-chloropropyl)benzene (2.7a)

Alcohol 2.4a (0.27 mL, 2.00 mmol, CAS #122-97-4) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.7a in 82% yield as a colorless oil (252 mg, 1.63 mmol). Product was eluted with 100% hexanes.

$^1$H NMR (250 MHz, CDCl$_3$); δ (ppm) = 7.38-7.22 (5H, m), 3.56 (2H, t, J = 6.5 Hz), 2.82 (2H, t, J = 7.1 Hz), 2.14 (1H, dt, J = 7.4, 6.7 Hz), 2.11 (1H, ddd, J = 7.3, 6.6, 6.6 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); δ (ppm) = 140.61, 128.46, 128.41, 126.05, 44.14, 33.95, 32.68. Compound 7a is known (CAS #104-52-9).

Synthesis of (±)-8-chloro-2,6-dimethyloct-2-ene (2.7b)

Alcohol 2.4b (0.36 mL, 2.00 mmol, CAS #106-22-9) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.7b in 67% yield as a colorless oil (233 mg, S-91.34 mmol). Product was eluted with 100% pentane.

$^1$H NMR (250 MHz, CDCl$_3$); δ (ppm) = 5.09 (1H, m), 3.64-3.48 (2H, m), 1.99 (1H, p, J = 6.35 Hz), 1.82-1.51 (10H, m), 1.35 (1H, m), 1.19 (1H, m) 0.91 (3H, d, J = 6.4 Hz). $^{13}$C NMR (62.5 MHz, CDCl$_3$); δ (ppm) = 131.32, 124.33, 43.16, 39.60, 36.57, 29.97, 25.58, 25.22, 18.84, 17.53. IR (cm$^{-1}$): f = 2963, 2916, 1451, 1378, 658. GC-MS: M$^+$ = 174.7 calculated for C$_{10}$H$_{19}$Cl, experimental = 174.0 (material was not ionizable under ESI).
Synthesis of (±)-2-(2-chloroethyl)-3-phenyloxirane (2.7c)

Alcohol 2.4c (328 mg, 2.00 mmol, CAS #199534-08-2) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.7c in 87% yield as a colorless oil (321 mg, 1.74 mmol). Product was eluted with 60:40 hexanes : CH₂Cl₂.

**¹H NMR (250 MHz, CDCl₃); δ (ppm) = 7.40-7.25 (5H, m), 3.74 (1H, d, J = 1.7 Hz), 3.71 (2H, t, J = 6.4 Hz), 3.14 (1H, dddd, J = 6.4, 4.9, 2.1 Hz), 2.28-2.05 (2H, m).**

**¹³C NMR (62.5 MHz, CDCl₃); δ (ppm) = 136.93, 128.39, 128.15, 125.45, 60.08, 58.55, 40.98, 35.24. IR (cm⁻¹): f = 3065, 2988, 1461, 885, 698. HRMS-ESI: (M+H)+ = 183.0577 calculated for C₁₀H₁₂ClO, experimental = 183.0582**

Synthesis of tert-butyl(3-chloropropoxy)dimethylsilane (2.7d)

Alcohol 2.4d (550 mg, 2.00 mmol, CAS #73842-99-6) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.7d in 78% yield as a colorless oil (327 mg, 1.57 mmol). Product was eluted with 95:5 hexanes : EtOAc.

**¹H NMR (250 MHz, CDCl₃); δ (ppm) = 3.75 (2H, t, J = 5.7 Hz), 3.65 (2H, t, J = 6.4 Hz), 1.95 (2H, p, J = 6.2 Hz), 0.89 (9H, s), 0.06 (6H, s).**

**¹³C NMR (62.5 MHz, CDCl₃); δ (ppm) = 59.27, 41.66, 35.28, 25.76, 18.16, -5.55. IR (cm⁻¹): f = 2956, 2930, 2858, 1255, 774. GC-MS: (M-tBu)+ = 151.7 calculated for C₅H₁₂ClSi, experimental = 151.0 (material was not ionizable under ESI).
Synthesis of 5-chloro-1,1-diphenylpentan-1-ol (2.7e)

Diol 2.4e (512 mg, 2.00 mmol, CAS #60344-50-5) was utilized along with the requisite amounts of triethylamine and triphosgene, producing 2.7e in 89% yield as colorless crystals (491 mg, 1.79 mmol). Purified product was eluted with 95:5 → 90:10 hexanes : EtOAc.

$^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.44-7.20 (10H, m), 3.50 (2H, t, $J = 6.8$ Hz), 2.34-2.27 (2H, m), 2.15 (1H, s), 1.81 (2H, p, $J = 7.0$ Hz), 1.51-1.38 (2H, m). $^{13}$C NMR (62.5 MHz, CDCl$_3$); $\delta$ (ppm) = 146.73, 128.10, 126.81, 125.88, 78.02, 44.66, 41.07, 32.81, 21.22. IR (cm$^{-1}$): $f = 3562, 3465, 3059, 2953, 1447, 699$. HRMS-ESI: (M-OH)$^+$ = 257.1092 calculated for C$_{17}$H$_{18}$Cl, experimental = 257.1099.

Synthesis of (-)-(R)-1-phenylpropan-2-yl diethylcarbamate (2.6c) and (+)-(S)-(2-chloropropyl)benzene (2.7f)

Alcohol 2.4f (545 mg, 4.00 mmol, CAS #1572-95-8) was utilized along with triethylamine (1.39 mL, 10.0 mmol), triphosgene (539 mg, 2.00 mmol), and 30 mL of CH$_2$Cl$_2$ producing 2.6c in 27% yield as a colorless oil (256 mg, 1.09 mmol) and 2.7f in 45% yield as a colorless oil (276 mg, 1.79 mmol). Purified products were eluted with 100% pentane followed by 90:10 hexanes : EtOAc.

The more polar product (2.6c): $^1$H NMR (250 MHz, CDCl$_3$); $\delta$ (ppm) = 7.32-7.16 (5H, m), 5.04 (1H, x, $J = 6.4$ Hz), 3.23 (4H, q, b, $J = 6.4$ Hz), 2.95 (1H, dd, $J = 13.6, 6.4$ Hz), 2.78 (1H, dd, $J = 13.5, 6.6$ Hz), 1.22 (3H, d, $J = 6.2$ Hz), 1.06 (6H, t, b, $J = 6.8$ Hz). $^{13}$C NMR (62.5
MHz, CDCl\textsubscript{3}); \(\delta\) (ppm) = 155.37, 137.84, 129.39, 128.08, 126.13, 71.73, 42.50, 41.28, 19.65, 13.64. IR (cm\textsuperscript{-1}): \(f = 3029, 2976, 2933, 1694, 1317, 1173\). HRMS-ESI: (M+Na\textsuperscript{+}) = 258.1470 calculated for C\textsubscript{14}H\textsubscript{21}NNaO\textsubscript{2}, experimental = 258.1464.

The less polar product (2.7f): \(^1\text{H} NMR (250 MHz, CDCl\textsubscript{3}); \delta\) (ppm) = 7.39-7.23 (5H, m), 4.26 (1H, x, \(J = 6.7\) Hz), 3.13 (1H, dd, \(J = 14.0, 7.0\) Hz), 2.99 (1H, dd, \(J = 13.8, 6.8\) Hz), 1.54 (3H, d, \(J = 6.6\) Hz). \(^{13}\text{C} NMR (62.5 MHz, CDCl\textsubscript{3}); \delta\) (ppm) = 137.85, 129.23, 128.30, 126.68, 58.41, 46.57, 24.55. \([\alpha]_{25}^D = +23.05\) (c = 8.5 in CHCl\textsubscript{3}). Compound 7f is known (CAS #16583-73-6).

### 8.3 General Secondary Alkyl Chloride Procedure

Unless otherwise noted, the alcohol (2.0 mmol) was placed in an oven-dried round-bottomed flask and dissolved in anhydrous dichloromethane (15 mL). The solution was then cooled to 0 °C. Pyridine (0.32 mL, 4.0 mmol) was then added via syringe, followed by triphosgene (297 mg, 1.0 mmol) in one portion. The solution was stirred for 5 min and then warmed to gentle reflux overnight. The reaction mixture was then poured into a separatory funnel containing 1 M HCl aqueous solution (30 mL), and the biphasic mixture was shaken vigorously. Upon separation of layers, the aqueous layer was re-extracted with dichloromethane (2 \(\times\) 30 mL). Organic extracts were collected, dried over MgSO\textsubscript{4}, filtered, and concentrated under vacuum. The resulting crude material was purified using flash column chromatography with silica gel as the stationary phase and a hexanes/ethyl acetate, pentane/diethyl ether, or pentane/dichloromethane mixture as the mobile phase.
8.3.1 Synthetic Procedures for Secondary Alkyl Chlorides

Synthesis of N-Boc-4-chloropiperidine (2.11a)

Alcohol 2.8a (403 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 2.11a in 88% yield as a pale yellow oil (387 mg, 1.76 mmol). The purified product was eluted with 90/10 → 80/20 pentane/diethyl ether.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 4.20 (1H, m), 3.73–3.68 (2H, m), 3.32–3.26 (2H, m) 2.06–1.99 (2H, m), 1.86–1.76 (2H, m), 1.46 (9H, s). $^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm) 154.5, 79.6, 56.8, 41.3 (b), 34.9, 28.3. IR (cm$^{-1}$): f = 2977, 2870, 2839, 1692, 1478, 1419, 1366, 1264, 1218, 1165, 1110, 1001, 895, 767, 719. HRMS-ESI: (M + Na)$^+$ 242.0918 calculated for C$_{10}$H$_{18}$ClNNaO$_2$, experimental 242.0918

Synthesis of Ethyl (±)-3-Chloro-4-phenylbutyrate (2.11b)

Alcohol 2.8b (417 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 2.11b in 82% yield as a pale yellow oil (372 mg, 1.64 mmol). The purified product was eluted with 100% pentane.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.34–7.22 (5H, m), 4.51 (1H, dt, J = 13.4, 7.3 Hz), 4.16 ppm (2H, q, J = 6.8 Hz), 3.09 (2H, dd, J = 6.7, 4.6 Hz), 2.75–2.71 (2H, m), 1.27 (3H, t, J =
7.1 Hz. $^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm) 170.1, 137.0, 129.5, 128.6, 127.1, 60.9, 57.7, 44.3, 42.6, 14.2. IR (cm$^{-1}$): f = 3065, 3030, 2983, 2905, 1737, 1654, 1304, 1150, 1096, 910, 747, 650. HRMS-ESI: (M + H)$^+$ 227.0833 calculated for C$_{12}$H$_{16}$ClO$_2$, experimental 227.0835.

Synthesis of (±)-4-Chloro-5-phenylpent-1-ene (2.11c)

![Chemical structure of 2.11c]

Alcohol 2.8c (324 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 2.11c in 94% yield as a colorless oil (340 mg, 1.88 mmol). The purified product was eluted with 100% pentane.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.36–7.24 (5H, m), 5.93 (1H, m), 5.20–5.15 (2H, m), 4.17 (1H, m), 3.10 (1H, dd, J = 14.1, 6.2 Hz), 3.04 (1H, dd, J = 14.1, 6.4 Hz), 2.59 (1H, m), 2.48 (1H, m). $^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm) 137.8, 134.0, 129.4, 128.5, 126.8, 118.3, 62.5, 44.2, 41.8. IR (cm$^{-1}$): f = 3080, 3030, 2981, 2952, 1643, 1604, 1543, 1433, 1284, 1031, 993, 920, 700, 618. GC-MS: M$^+$ 180.1 calculated for C$_{11}$H$_{13}$Cl, experimental 180.0. Compound 2.11c is known.

Synthesis of (±)-(E)-4-Chloro-1-phenylhepta-1,6-diene (2.11d)

![Chemical structure of 2.11d]

Alcohol 2.11d (377 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 2.11d in 82% yield as a yellow oil (339 mg, 1.64 mmol). The purified product was eluted with 100% pentane.
$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.38–7.17 (5H, m), 6.48 (1H, d, J = 15.8 Hz), 6.25 (1H, m), 5.94–5.83 (1H, m), 5.18–5.10 (2H, m), 4.03 (1H, m), 2.72–2.61 (2H, m), 2.59–2.50 (2H, m). $^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm) 137.1, 134.0, 133.2, 128.6, 127.4, 126.2, 125.5, 118.2, 61.5, 42.0, 41.2. IR (cm$^{-1}$): $f = 3081, 3061, 3028, 2980, 2946, 1644, 1495, 1449, 1289, 967, 918, 744, 694$. HRMS-ESI: (M + H)$^+$ 207.0935 calculated for C$_{13}$H$_{16}$Cl, experimental 207.0936.

Synthesis of (±)-4-Benzylxy-2-chloro-1-phenylbutane (2.11e)

Alcohol 2.8e (256 mg, 2.00 mmol) was utilized along with pyridine (0.32 mL, 4.00 mmol) and triphosgene (297 mg, 1.00 mmol) to produce 2.11e in 84% yield as a colorless oil (462 mg, 1.69 mmol). The purified product was eluted with 98/2 hexanes/EtOAc.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.34–7.21 (10H, m), 4.54–4.45 (2H, m), 3.88 (1H, m), 3.69–3.60 (2H, m), 2.97 (1H, dd, J = 13.5, 6.0 Hz), 2.80 (1H, dd, J = 13.6, 6.4 Hz), 1.96–1.90 (2H, m). $^{13}$C NMR (100, CDCl$_3$): δ (ppm) 138.3, 138.1, 129.5, 128.4, 128.0, 127.8, 126.4, 77.1, 72.1, 41.7, 40.6, 37.4. IR (cm$^{-1}$): $f = 3063, 3023, 2925, 2866, 1496, 1456, 1350, 1289, 1073, 1029, 910, 737, 699, 651$. HRMS-ESI: (M + Na)$^+$ 297.1017 calculated for C$_{17}$H$_{19}$ClNaO, experimental 297.1019.

8.3.2 Synthetic Procedures for Secondary Alcohols

Synthesis of (±)-(E)-1-Phenylehepta-1,6-dien-4-ol (2.8d)
Trans-Styrylacetic acid (2.1c, 3.30 g, 20.35 mmol) was dissolved in THF (50 mL), and carbonyldiimidazole (4.30 g, 26.45 mmol) was then added in one portion. The reaction mixture was then stirred overnight. The crude reaction mixture was concentrated in vacuo, diluted with Et$_2$O (50 mL), and then washed with saturated brine solution (3 × 50 mL). Collected aqueous layers were extracted with Et$_2$O (3 × 50 mL) and combined with the organic layer. The organic fractions were then dried over MgSO$_4$, concentrated under vacuum, and taken to the next step without further purification. This crude material was then dissolved in THF (50 mL), and MeONHMe·HCl (1.85 g, 18.99 mmol) was added. A catalytic amount of sodium hydride (~5 mg) was then added to the solution, and the reaction mixture was stirred for 3 h. The reaction was quenched with a half-saturated NH$_4$Cl solution (50 mL). Upon separation of layers, the organic layer was washed with a saturated NaHCO$_3$ solution (50 mL), which was then back-extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting crude material was purified with 80/20 hexanes/EtOAc to yield the Weinreb amide S-1 in 57% yield (2.39 g, 11.66 mmol) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.38–7.20 (5H, m), 6.51 (1H, d, J = 15.9 Hz), 6.37 (1H, ddd, J = 15.8, 6.9, 6.8 Hz), 3.72 (3H, s), 3.39 (2H, d, J = 6.4 Hz), 3.21 (3H, s). $^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm) 137.1, 133.1, 128.5, 127.4, 126.3, 122.8, 61.2, 36.5, 32.3 (b), 29.7. FT-IR (cm$^{-1}$): ν = 2936, 1749, 1722, 1448, 1419, 1177, 999, 968, 910, 735. HRMS-ESI: (M + H)$^+$ 206.1176 calculated for C$_{12}$H$_{16}$NO$_2$, experimental 206.1170.
The Weinreb amide S-1 (1.16g, 5.65 mmol) was dissolved in dry THF (50 mL), and the solution was cooled to 0 °C. Allylmagnesium bromide (11.3 mL, 11.3 mmol, 1.0 M in Et₂O) was then added slowly over 20 min. The reaction mixture was stirred for 1 h and then quenched with a half-saturated NH₄Cl (50 mL) solution. Upon separation of layers, the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined and dried over MgSO₄. The crude material was concentrated in vacuo and purified with 90/10 hexanes/EtOAc to afford ketone S-2 in 82% yield (855 mg, 4.59 mmol) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.38–7.22 (5H, m), 6.48 (1H, d, J = 15.9 Hz), 6.31 (1H, ddd, J = 16.0, 7.1, 6.9 Hz), 6.00–5.89 (1H, m), 5.23–5.15 (2H, m), 3.36 (2H, d, J = 7.0 Hz), 3.27 (2H, d, J = 6.9 Hz). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 206.4, 136.8, 133.9, 130.3, 128.6, 127.6, 126.3, 121.7, 119.2, 47.3, 46.4. FT-IR (cm⁻¹): f = 3082, 3061, 3027, 2981, 1717, 1639, 1578, 1449, 1424, 1323, 1071, 993, 967, 912, 741, 695, 650. HRMS-ESI: (M + H)⁺ 187.1117 calculated for C₁₃H₁₅O, experimental 187.1117.

Ketone S-2 (855 mg, 4.60 mmol) as a solution in Et₂O (20 mL) was added via cannula to a cooled (0 ⁰C) suspension of lithium aluminum hydride (209 mg, 5.50 mmol). The reaction mixture was then warmed to room temperature and set to reflux for 30 min. After the reaction mixture was cooled to 0 ⁰C, deionized water (0.21 mL) was slowly added, which was followed by 15% aqueous sodium hydroxide solution (0.21 mL) and then deionized water (0.63 mL). This workup sequence resulted in the formation of white precipitates. The solution was then stirred for 1 h. The filtrate was collected using vacuum filtration and concentrated in vacuo. The crude
material was then purified with 90/10 → 80/20 hexanes/EtOAc to give 2.8d with a yield of 94% (811 mg, 4.31 mmol) as a colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.37–7.20 (5H, m), 6.49 (1H, d, J = 16.1 Hz), 6.25 (1H, ddd, J = 15.9, 7.1, 6.9 Hz), 5.87 (1H, m), 5.19–5.14 (2H, m), 3.78 (1H, m), 2.48–2.33 (3H, m), 2.24 (1H, m), 1.76 (1H, m).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 137.2, 134.6, 133.1, 128.5, 127.3, 126.1, 118.2, 70.2, 41.4, 40.5, 29.7. FT-IR (cm$^{-1}$): f = 3416, 3079, 3027, 2930, 1641, 1599, 1495, 1449, 1073, 997, 967, 912, 742. HRMS-ESI: (M + H)$^+$ 189.1274 calculated for C$_{13}$H$_{17}$O, experimental 189.1275.

**Synthesis of (±)-4-Benzylloxy-1-phenylbutan-2-ol (2.8e)**

\[
\begin{align*}
\text{Ph} & \quad \text{OH} & \quad \text{OH} & \quad \text{NaH} & \quad \text{BnBr} & \quad \text{BnO} & \quad \text{Ph} \\
2.12c & \quad & & \rightarrow & \quad & \rightarrow & \quad 2.8e
\end{align*}
\]

Diol 2.12c (2.78 g, 16.8 mmol, CAS #74578-77-1) in a solution of DMF (20 mL) was slowly added via cannula to a cooled suspension (0 °C) of NaH (0.426 g, 18.42 mmol) in DMF (20 mL). After the mixture was stirred for 30 min, benzyl bromide (1.99 mL, 16.8 mmol) was added. The reaction mixture was then warmed to room temperature and stirred overnight. After the reaction was quenched with a half-saturated NH$_4$Cl solution, the mixture was then extracted with EtOAc (3 × 30 mL), and the collected organic layers were washed with water and dried over MgSO$_4$. The crude material was purified with 90/10 → 80/20 → 70/30 hexanes/EtOAc, and alcohol 2.8e was isolated in 24% yield (1.08 g, 3.95 mmol) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.36–7.19 (10H, m), 4.59 (1H, d, J = 11.4 Hz), 4.48 (1H, d, J = 11.4 Hz), 3.86 (1H, m), 3.81–3.70 (2H, m), 3.04 (1H, dd, J = 13.4, 5.8 Hz), 2.79 (1H, dd, J = 13.6, 7.0 Hz), 2.22 (1H, t, J = 5.0 Hz), 1.67–1.81 (2H, m).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 138.4, 138.1, 129.5, 128.5, 128.4, 128.0, 127.8, 126.3, 79.6, 71.6, 60.7, 40.5,
30.1. IR (cm$^{-1}$): $f = 3410, 3086, 3063, 3029, 2875, 1604, 1496, 1454, 1056, 1029, 910, 738, 699$. HRMS-ESI: $(M + H)^+ 257.1536$ calculated for C$_{17}$H$_{21}$O$_2$, experimental 257.1529.

8.4 Synthesis and Characterization of Novel Chapter 4 Compounds

8.4.1 Synthetic Procedures for $\alpha$-Indole Adducts

Synthesis of 3-((2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1H-indole (4.20)

$$\begin{array}{c}
\text{OTBS} \\
\text{H}_3\text{C} \\
\text{OH}
\end{array} \\
\text{4.19} \\
\xrightarrow{\text{Py•TIOH (0.1 equiv)}} \\
\text{indole (2.0 equiv)} \\
\xrightarrow{4\AA \text{ MS, toluene, rt}} \\
\text{H}_3\text{C} \\
\text{OTBS} \\
\text{NH}
\end{array}$$

Compound 4.19 (100 mg, 0.438 mmol) was dissolved in toluene (10 mL). Then, oven-dried 4Å molecular sieves (100 mg) were added, followed by indole (103 mg, 0.879 mmol), and then pyridinium triflate (10.0 mg, 0.044 mmol). Upon stirring at room temperature for 66 hours, the reaction was then quenched with DI water (10 mL). The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 100 hexanes $\rightarrow$ 98 : 2 hexanes : ethyl acetate to give product 4.20 in 91% yield (130 mg, 0.398 mmol) as a clear, pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$); $\delta$ (ppm) = 7.88 (1H, b), 7.59 (1H, d, $J = 7.8$ Hz), 7.34 (1H, d, $J = 8.1$), 7.18-7.15 (1H, m), 7.10-7.07 (1H, m), 7.00 (1H, d, $J = 2.3$ Hz), 3.99-3.95 (1H, m), 2.39 (1H, m), 2.34-2.30 (1H, m), 2.28-2.22 (1H, m), 1.89-1.82 (1H, m), 1.68 (3H, b), 0.81 (9H, s), -0.06 (3H, s), -0.12 (3H, s). $^{13}$C NMR (125 MHz, CDCl$_3$); $\delta$ (ppm) = 147.87, 136.57, 127.19, 121.60, 121.53, 119.42, 119.40, 118.95, 113.55, 110.92, 42.55, 32.30, 29.82, 25.67, 18.14, 12.48, -4.16, -4.24. IR (cm$^{-1}$): $f = 3412, 3057, 2954, 2929, 2902, 2856, 1687, 1619, 1525, 1421, 1379,
1359, 1326, 1251, 1214, 1122, 1091, 1010, 937, 911, 868, 838, 780, 740, 675. HRMS-ESI: [M+H]^+ = 328.2091 calculated for C_{20}H_{30}NOSi; experimental = 328.2082.

Synthesis of 3-((2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1-methyl-1H-indole (4.20a)

![Synthesis reaction diagram]

Compound 4.19 (200 mg, 0.876 mmol) was dissolved in toluene (20 mL). Then, oven-dried 4Å molecular sieves (200 mg) were added, followed by N-methylindole 4.21a (230 mg, 1.75 mmol), and then pyridinium triflate (20.0 mg, 0.088 mmol). Upon stirring at room temperature for 41 hours, the reaction was then quenched with DI water (10 mL). The aqueous layer was then extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 100 hexanes → 98 : 2 hexanes : ethyl acetate to give product 4.20a in 72% yield (214 mg, 0.627 mmol) as a clear, pale yellow oil.

¹H NMR (500 MHz, CDCl₃); δ (ppm) = 7.57 (1H, d, J = 7.9Hz), 7.27 (1H, d, J = 8.1 Hz), 7.20 (1H, t, J = 7.1 Hz), 7.07 (1H, t, J = 7.5 Hz), 6.85 (1H, s), 3.97-3.94 (1H, m), 3.73 (3H, s), 2.41-2.30 (2H, m), 2.27-2.21 (1H, m), 1.87-1.81 (1H, m), 1.68 (3H, s), 0.82 (9H, s), -0.05 (3H, s), -0.11 (3H, s). ¹³C NMR (125 MHz, CDCl₃); δ (ppm) = 148.04, 137.26, 127.60, 126.41, 121.11, 119.45, 118.33, 117.84, 113.45, 108.97, 42.42, 32.53, 32.26, 30.11, 25.68, 18.16, 12.48, -4.14, -4.20. IR (cm⁻¹): f = 2953, 2928, 2905, 2883, 2855, 1686, 1550, 1471, 1443, 1423, 1408, 1377, 1360, 1327, 1250, 1213, 1155, 1131, 1121, 1083, 1065, 980, 937, 910, 869, 836, 778, 735,
673, 580, 561, 541, 529, 474, 451. HRMS-ESI: [M+H]^+ = 342.2248 calculated for C_{13}H_{26}NaOSi; experimental = 342.2238.

Synthesis of 3-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-2-phenyl-1H-indole (4.20b)

\[
\begin{align*}
\text{OTBS} & \quad \text{Py\textbullet{}TfOH (0.1 equiv)} \\
\text{H}_3\text{C} & \quad \text{indole 4.21b (2.0 equiv)} \\
\text{4Å MS, toluene, rt} & \quad \text{TBSO} \\
\text{H}_3\text{C} & \quad \text{Ph} \\
\text{4.20b} & \quad \text{NH}
\end{align*}
\]

Compound 4.19 (200 mg, 0.876 mmol) was dissolved in toluene (20 mL). Then, oven-dried 4Å molecular sieves (200 mg) were added, followed by 2-phenylindole 4.21b (339 mg, 1.75 mmol), and then pyridinium triflate (20.0 mg, 0.088 mmol). Upon stirring at room temperature for 41 hours, the reaction was then quenched with DI water (10 mL). The aqueous layer was then extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 10 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and then concentrated under vacuum. The crude material was purified with flash column chromatography with 100 hexanes → 98 : 2 hexanes : ethyl acetate to give product 4.20b in 83% yield (292 mg, 0.723 mmol) as a clear, pale yellow oil.

\(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3); \delta (\text{ppm}) = 7.93 \ (1\text{H, b}), 7.70 \ (1\text{H, d, J = 7.9Hz}), 7.59-7.57 \ (2\text{H, m}), 7.47 \ (2\text{H, t, J = 7.5 Hz}), 7.40-7.34 \ (2\text{H, m}), 7.20-7.17 \ (1\text{H, m}), 7.10-7.07 \ (1\text{H, m}), 4.22-4.18 \ (1\text{H, m}), 2.53-2.47 \ (1\text{H, m}), 2.44-2.35 \ (2\text{H, m}), 2.21-2.15 \ (1\text{H, m}), 1.70 \ (3\text{H, s}), 0.66 \ (9\text{H, s}), -0.33 \ (3\text{H, s}), -0.43 \ (3\text{H, s}). \ \ ^{13}\text{C} \text{NMR} (125 \text{ MHz, CDCl}_3); \delta (\text{ppm}) = 148.02, 136.24, 135.18, 133.34, 128.61, 128.11, 127.58, 121.93, 120.81, 119.27, 115.55, 112.48, 110.57, 42.35, 32.87, 29.04, 25.50, 18.04, 12.76, -4.46, -4.65. \ \text{IR (cm}^{-1}); f = 3411, 2953, 2928, 2883, 2854, 1686, 1471, 1456, 1448, 1425, 1361, 1324, 1309, 1249, 1212, 1157, 1114, 1082, 1028, 980, 935, 867,
836, 730, 689, 648, 476. HRMS-ESI: [M+H]$^+$ = 404.2404 calculated for C$_{26}$H$_{34}$NOSi; experimental = 404.2410.

Synthesis of 5-bromo-3-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1H-indole (4.20c)

![Chemical structure](image)

Compound 4.19 (200 mg, 0.876 mmol) was dissolved in toluene (20 mL). Then, oven-dried 4Å molecular sieves (200 mg) were added, followed by 5-bromoindole 4.21c (343 mg, 1.75 mmol), and then pyridinium triflate (20.0 mg, 0.088 mmol). Upon stirring at room temperature for 53 hours, the reaction was then quenched with DI water (10 mL). The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 100 hexanes → 98 : 2 hexanes : ethyl acetate to give product 4.20c in 84% yield (298 mg, 0.732 mmol) as a clear, pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$); $\delta$ (ppm) = 7.93 (1H, b), 7.71 (1H, d, J = 1.9 Hz), 7.26-7.24 (1H, m), 7.20-7.19 (1H, m), 6.99 (1H, d, J = 2.3 Hz), 3.94-3.90 (1H, m), 2.41-2.23 (3H, m), 1.87-1.80 (1H, m), 1.69 (3H, b), 0.82 (9H, s), -0.03 (3H, s), -0.09 (3H, s). $^{13}$C NMR (125 MHz, CDCl$_3$); $\delta$ (ppm) = 147.41, 135.13, 128.95, 124.44, 122.75, 121.99, 119.23, 113.91, 112.35, 112.31, 42.38, 32.24, 29.76, 25.62, 18.11, 12.45, -4.17, -4.23. IR (cm$^{-1}$): f = 3427, 2955, 2929, 2884, 2855, 1686, 1470, 1459, 1417, 1380, 1360, 1330, 1252, 1212, 1179, 1151, 1135, 1094, 1053, 1006, 981, 936, 906, 865, 836, 779, 730, 677, 649, 580, 552. HRMS-ESI: [M+H]$^+$ = 406.1194 calculated for C$_{20}$H$_{29}$BrNOSi; experimental = 406.1194.
Synthesis of 3-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-5-methoxy-1H-indole (4.20d)

Compound 4.19 (200 mg, 0.876 mmol) was dissolved in toluene (20 mL). Then, oven-dried 4Å molecular sieves (200 mg) were added, followed by 5-methoxyindole 4.21d (258 mg, 1.75 mmol), and then pyridinium triflate (20.0 mg, 0.088 mmol). Upon stirring at room temperature for 40 hours, the reaction was then quenched with DI water (10 mL). The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 100 hexanes → 98 : 2 hexanes : ethyl acetate to give product 4.20d in 75% yield (234 mg, 0.654 mmol) as a clear, pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$); $\delta$ (ppm) = 7.78 (1H, b), 7.22 (1H, d, J = 8.8 Hz), 7.06 (1H, d, J = 2.5 Hz), 6.97 (1H, d, J = 1.9 Hz), 6.84 (1H, dd, J = 8.7, 2.5 Hz), 3.96-3.92 (1H, m), 3.87 (3H, s), 2.42-2.33 (2H, m), 2.31-2.24 (1H, m), 1.86 (1H, dddd, J = 8.6, 8.7, 5.3, 3.4 Hz), 1.70 (3H, s), 0.83 (9H, s), -0.04 (3H, s), -0.10 (3H, s). $^{13}$C NMR (125 MHz, CDCl$_3$); $\delta$ (ppm) = 153.56, 147.89, 131.79, 127.56, 122.49, 119.08, 113.47, 111.55, 111.52, 101.55, 55.91, 42.55, 32.37, 29.69, 25.68, 18.15, 12.47, -4.15, -4.22. IR (cm$^{-1}$): f = 3414, 2953, 2929, 2900, 2855, 1686, 1644, 1625, 1472, 1333, 1251, 1210, 1067, 1008, 938, 924, 836, 753. HRMS-ESI: [M+H]$^+$ = 358.2917 calculated for C$_{21}$H$_{32}$NO$_2$Si; experimental = 358.2195.
Synthesis of methyl 3-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1H-indole-5-carboxylate (4.20e)

![Chemical structure](image)

Compound 4.19 (200 mg, 0.876 mmol) was dissolved in toluene (20 mL). Then, oven-dried 4Å molecular sieves (200 mg) were added, followed by methyl 5-indolecarboxylate 4.21e (307 mg, 1.75 mmol), and then pyridinium triflate (20.0 mg, 0.088 mmol). Upon stirring at room temperature for 74 hours, the reaction was then quenched with DI water (10 mL). The aqueous layer was then extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 98 : 2 hexanes : ethyl acetate → 95 : 5 hexanes : ethyl acetate → 90 : 10 hexanes : ethyl acetate → 80 : 20 hexanes : ethyl acetate to give product 4.20e in 67% yield (226 mg, 0.586 mmol) as a clear, pale yellow oil.

¹H NMR (500 MHz, CDCl₃); δ (ppm) = 8.36 (1H, s), 8.08 (1H, b), 7.88 (1H, dd, J = 8.6, 1.6 Hz), 7.34 (1H, d, J = 8.5 Hz), 7.05 (1H, d, J = 2.2 Hz), 4.02-3.99 (1H, m), 3.93 (3H, s), 2.46-2.4 (1H, m), 2.40-2.30 (1H, m), 2.29-2.23 (1H, m), 1.84-1.78 (1H, m), 1.68 (3H, s), 0.81 (9H, s), -0.04 (3H, s), -0.11 (3H, s). ¹³C NMR (125 MHz, CDCl₃); δ (ppm) = 168.34, 147.39, 139.09, 126.88, 123.14, 122.64, 122.38, 121.13, 121.03, 114.07, 110.57, 51.80, 42.27, 32.21, 30.00, 25.62, 18.10, 12.42, -4.19, -4.24. IR (cm⁻¹): f = 3340, 2952, 2929, 2903, 2855, 1687, 1646, 1472, 1338, 1319, 1285, 1242, 1153, 1109, 1082, 1006, 937, 869, 836, 752, 733, 675, 649. HRMS-ESI: [M+H]⁺ = 386.2146 calculated for C₂₁H₂₃NO₂Si; experimental = 386.2149.
Synthesis of 3-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1H-indole-4-carbonitrile (4.20f)

![Chemical structure of the compound](image)

Compound 4.19 (200 mg, 0.876 mmol) was dissolved in toluene (20 mL). Then, oven-dried 4Å molecular sieves (200 mg) were added, followed by 4-cyanoindole 4.21f (249 mg, 1.75 mmol), and then pyridinium triflate (20.0 mg, 0.088 mmol). Upon stirring at room temperature for 147 hours, the reaction was then quenched with DI water (10 mL). The aqueous layer was then extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 98 : 2 hexanes : ethyl acetate → 95 : 5 hexanes : ethyl acetate → 90 : 10 hexanes : ethyl acetate → 80 : 20 hexanes : ethyl acetate to give product 4.20f in 60% yield (186 mg, 0.527 mmol) as a yellow crystalline solid.

¹H NMR (500 MHz, CDCl₃); δ (ppm) = 8.44 (1H, b), 7.49 (1H, d, J = 8.1 Hz), 7.37 (1H, d, J = 7.4 Hz), 7.11-7.10 (1H, m), 7.08-7.06 (1H, m), 4.34-4.31 (1H, m), 2.52-2.45 (1H, m), 2.14 (2H, t, J = 7.5 Hz), 1.60 (3H, s), 0.75 (9H, s), -0.04 (3H, s), -0.19 (3H, s). ¹³C NMR (125 MHz, CDCl₃); δ (ppm) = 146.77, 136.62, 126.84, 126.12, 125.01, 121.05, 119.49, 101.66, 41.61, 31.70, 31.45, 25.64, 18.12, 12.33, -4.22, -4.30. IR (cm⁻¹): f = 3334, 2955, 2929, 2903, 2856, 2216, 1688, 1462, 1347, 1273, 1213, 937, 836, 802, 745, 732, 676. HRMS-ESI: [M+H]^+ = 353.2044 calculated for C₂₁H₃₂NO₂Si; experimental = 353.2031. Please see page 34 in the published article’s Supporting Information for X-Ray structure data.
Synthesis of 3-[(2-((2-tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-5-methoxy-1H-benzo[g]indole (4.20h)

Compound 4.19 (200 mg, 0.876 mmol) was dissolved in toluene (20 mL). Then, oven-dried 4Å molecular sieves (200 mg) were added, followed by 5-methoxy-benzindole 4.21h (346 mg, 1.75 mmol), and then pyridinium triflate (20.0 mg, 0.088 mmol). Upon stirring at room temperature for 47 hours, the reaction was then quenched with DI water (10 mL). The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 75 : 25 hexanes : dichloromethane $\rightarrow$ 50 : 50 hexanes : dichloromethane to give product 4.20h in 57% yield (203 mg, 0.497 mmol) as a pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$); $\delta$ (ppm) = 8.78 (1H, b), 8.30 (1H, d, J = 8.4 Hz), 7.89 (1H, d, J = 8.2 Hz), 7.52 (1H, ddd, J = 8.1, 6.8, 1.2 Hz), 7.38 (1H, ddd, J = 8.4, 7.0, 1.2 Hz), 7.00 (1H, s), 6.34 (1H, s), 4.02 (3H, s), 3.99-3.95 (1H, m), 2.44-2.36 (2H, m), 2.31-2.25 (1H, m), 2.04-1.98 (1H, m) 1.69 (3H, s), 0.92 (9H, s), 0.10 (3H, s), 0.03 (3H, s). $^{13}$C NMR (125 MHz, CDCl$_3$); $\delta$ (ppm) = 150.05, 146.49, 140.00, 125.86, 125.00, 123.77, 123.32, 122.96, 122.69, 122.10, 119.02, 115.72, 100.81, 98.15, 55.85, 44.74, 32.28, 29.32, 25.72, 18.14, 12.59, -4.13, -4.19. IR (cm$^{-1}$): $f$ = 3438, 2953, 2929, 2903, 2858, 1686, 1632, 1598, 1579, 1537, 1519, 1477, 1442, 1405, 1380, 1361, 1327, 1251, 1210, 1174, 1158, 1118, 1098, 1075, 1051, 1034, 1006, 986, 938, 908, 868, 835, 779, 759, 731, 699, 675, 649, 624, 581, 515, 473, 455. HRMS-ESI: [M+H]$^+$= 408.2353 calculated for C$_{25}$H$_{34}$NO$_2$Si; experimental = 408.2353.
Synthesis of 3-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-yl)-1H-indole (4.33a)

![Chemical structure](image)

Compound 4.29a (200 mg, 0.876 mmol) was dissolved in toluene (8.76 mL). Then, oven-dried 4Å molecular sieves (200 mg) were added, followed by indole (205 mg, 1.752 mmol), and then pyridinium triflate (20 mg, 0.088 mmol). Upon stirring at room temperature for 10 hours, the reaction mixture was then directly purified with flash column chromatography with 100 hexanes → 98 : 2 hexanes : ethyl acetate → 80 : 20 hexanes : ethyl acetate to give product 4.33a in 75% yield (215 mg, 0.655 mmol) as a clear, pale yellow oil.

\[ ^1H \text{NMR (500 MHz, CDCl}_3\ ]; \delta (ppm) = 7.88 (1H, b), 7.59 (1H, d, J = 7.9 Hz), 7.34 (1H, d, J = 8.1 Hz), 7.16 (1H, t, J = 7.4 Hz), 7.08 (1H, t, J = 7.1 Hz), 6.99 (1H, d, J = 2.3 Hz), 3.98-3.96 (1H, m), 2.42-2.30 (2H, m), 2.28-2.22 (1H, m), 1.89-1.83 (1H, m), 1.68 (3H, s), 0.81 (9H, s), -0.06 (3H, s), -0.12 (3H, s). \]

\[ ^13C \text{NMR (125 MHz, CDCl}_3\ ); \delta (ppm) = 147.85, 136.56, 127.18, 121.59, 121.51, 119.41, 118.93, 113.53, 110.89, 42.54, 32.29, 29.80, 25.65, 18.12, 12.45, -4.18, -4.25. \]

Synthesis of 3-(3-allyl-2-((tert-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl)-1H-indole (4.33b)

![Chemical structure](image)

Compound 4.29b (167 mg, 0.656 mmol) was dissolved in toluene (6.56 mL). Then, oven-dried 4Å molecular sieves (150 mg) were added, followed by indole (154 mg, 1.313 mmol), and then pyridinium triflate (15 mg, 0.066 mmol). Upon stirring at room temperature for
six days, the reaction mixture was then directly purified with flash column chromatography with
100 hexanes → 99 : 1 hexanes : ethyl → 98 : 2 hexanes : ethyl acetate → 97 : 3 hexanes : ethyl acetate → 96 : 4 hexanes : ethyl acetate to give product 4.33b in 60% yield (138 mg, 0.392 mmol) as a clear oil.

$^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 7.89 (1H, b), 7.60 (1H, d, J = 7.9 Hz), 7.35 (1H, d, J = 8.1 Hz), 7.17 (1H, t, J = 7.6), 7.09 (1H, t, J = 7.4 Hz), 6.98 (1H, d, J = 2.2 Hz), 5.85 (1H, dddd, J = 16.8, 13.5, 10.1, 3.3 Hz), 5.09 (1H, dddd, J = 17.2, 3.7, 2.0 Hz), 5.02 (1H, dddd, J = 10.0, 3.2, 1.6 Hz), 3.99 (1H, t, J = 5.6 Hz), 2.92 (2H, d, J = 6.6 Hz), 2.41-2.29 (2H, m), 2.27-2.22 (1H, m), 1.89-1.83 (1H, m), 0.81 (9H, s), -0.03 (3H, s), -0.15 (3H, s). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) = 148.33, 136.58, 136.51, 127.14, 121.64, 121.53, 121.53, 119.37, 119.10, 118.99, 115.54, 114.92, 110.93, 42.57, 31.48, 29.83, 29.58, 25.63, 18.12, -4.21, -4.24. IR (cm$^{-1}$): f = 3418, 3057, 2954, 2929, 2893, 2856, 1679, 1638, 1471, 1457, 1418, 1360, 1333, 1291, 1092, 1034, 992, 890, 864, 837, 780. HRMS-ESI: [M+H]$^+$ = 354.2248 calculated for C$_{12}$H$_{23}$OSi; experimental = 354.2244.

Synthesis of 3-(2-((tert-butyldimethylsilyl)oxy)-3-(3-((tert-butyldimethylsilyl)oxy)propyl)cyclopent-2-en-1-yl)-1H-indole (4.33c)

Compound 4.29c (78 mg, 0.196 mmol) was dissolved in toluene (1.96 mL). Then, oven-dried 4Å molecular sieves (55 mg) were added, followed by indole (46 mg, 0.392 mmol), and then pyridinium triflate (4.5 mg, 0.02 mmol). Upon stirring at room temperature for 96 hours,
the reaction mixture was then directly purified with flash column chromatography with 98 : 2 hexanes : ethyl acetate → 95 : 5 hexanes : ethyl acetate → 90 : 10 hexanes : ethyl acetate to give product 4.33c in 93% yield (91 mg, 0.183 mmol) as a clear oil.

$^1$H NMR (500 MHz, CDCl$_3$); δ (ppm) = 7.89 (1H, b), 7.59 (1H, d, J = 8.2 Hz), 7.34 (1H, d, J = 8.2 Hz), 7.17 (1H, t, J = 7.1 Hz), 7.08 (1H, t, J = 7.6 Hz), 6.97 (1H, d, J = 2.3 Hz), 5.76-5.58 (2H, m), 4.17-4.14 (2H, m), 3.99-3.97 (1H, m), 2.89 (2H, d, J = 5.9 Hz), 2.39-2.28 (2H, m), 2.26-2.21 (1H, m), 1.88-1.82 (1H, m), 0.92 (9H, s), 0.80 (9H, s), 0.09 (6H, s), -0.04 (3H, s), -0.16 (3H, s). $^{13}$C NMR (125 MHz, CDCl$_3$); δ (ppm) = 148.15, 136.57, 129.89, 128.81, 127.14, 121.62, 121.54, 119.37, 119.09, 118.97, 115.87, 110.91, 64.00, 42.55, 29.85, 29.83, 29.60, 26.01, 25.63, 18.45, 18.11, -4.20, -4.24, -5.06. IR (cm$^{-1}$): ν = 3420, 2953, 2928, 2886, 2855, 1681, 1471, 1459, 1420, 1389, 1377, 1360, 1335, 1287, 1251, 1091, 1037, 1007, 969, 939, 834, 777, 738, 674, 582, 485. HRMS-ESI: [M+H]$^+$ = 498.3218 calculated for C$_{29}$H$_{47}$O$_2$NSi$_2$; experimental = 498.3223.

Synthesis of 3-(2-((tert-butyldimethylsilyl)oxy)-3-phenylcyclopent-2-en-1-yl)-1H-indole (4.33e)

Compound 4.29e (230 mg, 0.792 mmol) was dissolved in toluene (7.92 mL). Then, oven-dried 4Å molecular sieves (220 mg) were added, followed by indole (186 mg, 1.584 mmol), and then pyridinium triflate (18 mg, 0.079 mmol). Upon stirring at room temperature for 30 hours, the reaction mixture was then directly purified with flash column chromatography with 100 hexanes → 99 : 1 hexanes : ethyl → 98 : 2 hexanes : ethyl → 95 : 5 hexanes : ethyl → 90 :
10 hexanes : ethyl acetate to give product 4.33e in 86% yield (264 mg, 0.678 mmol) as a clear, pale yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$); $\delta$ (ppm) = 7.97 (1H, b), 7.75 (2H, d, $J$ = 7.8 Hz), 7.68 (1H, d, $J$ = 8.0 Hz), 7.38-7.35 (3H, m), 7.23-7.19 (2H, m), 7.13 (1H, t, $J$ = 7.5 Hz), 7.02 (1H, d, $J$ = 2.4 Hz), 4.23-4.20 (1H, m), 2.85-2.79 (1H, m), 2.73-2.66 (1H, m), 2.52-2.45 (1H, m), 1.97 (1H, ddd, $J$ = 12.9, 12.9, 4.5), 0.84 (9H, s), -0.01 (3H, s), -0.11 (3H, s). $^{13}$C NMR (125 MHz, CDCl$_3$); $\delta$ (ppm) = 151.69, 136.86, 136.63, 127.86, 127.04, 126.95, 125.48, 121.76, 121.74, 119.25, 119.20, 118.52, 115.62, 111.07, 44.17, 29.83, 29.80, 25.75, 18.25, -3.77, -3.87. IR (cm$^{-1}$): $f$ = 3421, 3055, 2953, 2929, 2894, 2856, 1688, 1633, 1599, 1495, 1471, 1457, 1417, 1390, 1360, 1306, 1281, 1252, 1219, 1097, 1067, 1032, 1009, 960, 939, 927, 837, 781, 762, 740, 695, 677, 582, 484. HRMS-ESI: [M+H]$^+$ = 390.2248 calculated for C$_{25}$H$_{32}$ONSi; experimental = 390.2231.

Synthesis of 3-(2-((tert-butyldimethylsilyl)oxy)-3-(4-fluorophenyl)cyclopent-2-en-1-yl)-1H-indole (4.33f)

![Chemical Structure](image)

Compound 4.29f (207 mg, 0.670 mmol) was dissolved in toluene (6.70 mL). Then, oven-dried 4Å molecular sieves (145 mg) were added, followed by indole (157 mg, 1.34 mmol), and then pyridinium triflate (15 mg, 0.07 mmol). Upon stirring at room temperature for 19 hours, the reaction mixture was then directly purified with flash column chromatography with 100 hexanes → 98 : 2 hexanes : ethyl acetate → 95 : 5 hexanes : ethyl acetate → 90 : 10 hexanes : ethyl acetate to give product 4.33f in 91% yield (250 mg, 0.613 mmol) as a clear, pale pink oil.
\(^1\)H NMR (500 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 7.94 (1H, b), 7.68-7.65 (2H, m), 7.63 (1H, d, J = 7.9 Hz), 7.36 (1H, d, J = 8.2 Hz), 7.21-7.18 (1H, m), 7.12-7.09 (1H, m), 7.05-7.00 (4H, m), 4.20-4.17 (1H, m), 2.79-2.73 (1H, m), 2.66-2.60 (1H, m), 2.50-2.42 (1H, m), 1.98-1.92 (1H, m), 0.80 (9H, s), -0.06 (3H, s), -0.14 (3H, s). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 161.74, 159.80, 151.22, 151.20, 136.61, 132.92, 128.39, 128.33, 126.98, 121.82, 121.64, 119.22, 119.20, 118.52, 114.73, 114.65, 114.49, 111.03, 44.03, 29.94, 29.71, 18.19, -3.83, -3.92. IR (cm\(^{-1}\)): \(f\) =3416, 2954, 2930, 2896, 2857, 1687, 1638, 1601, 1509, 1471, 1458, 1409, 1390, 1361, 1339, 1300, 1278, 1254, 1228, 1158, 1085, 1012, 962, 938, 837, 783, 742, 678, 597, 559, 531, 502. HRMS-ESI: [M+H]\(^+\) = 408.2153 calculated for C\(_{25}\)H\(_{31}\)OFNSi; experimental = 408.2163.

Synthesis of 3-(2-((tert-butyldimethylsilyl)oxy)-3-(p-tolyl)cyclopent-2-en-1-yl)-1H-indole (4.33gg)

Compound 4.29g (205 mg, 0.675 mmol) was dissolved in toluene (6.75 mL). Then, oven-dried 4Å molecular sieves (141 mg) were added, followed by indole (158 mg, 1.35 mmol), and then pyridinium triflate (15 mg, 0.067 mmol). Upon stirring at room temperature for 60 hours, the reaction mixture was then directly purified with flash column chromatography with → 97 : 3 hexanes : ethyl acetate → 90 : 10 hexanes : ethyl acetate to give product 4.33g in 92% yield (249 mg, 0.618 mmol) as a clear, pale yellow oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 7.92 (1H, b), 7.65-7.62 (3H, m), 7.36 (1H, d, J = 8.1 Hz), 7.19 (1H, t, J = 7.3 Hz), 7.16 (2H, d, J = 8.0 Hz), 7.10 (1H, d, J = 7.5 Hz), 7.01 (1H, d, J = 2.3 Hz), 4.19-4.17 (1H, m), 2.80-2.74 (1H, m), 2.68-2.62 (1H, m), 2.49-2.42 (1H, m), 2.36
(3H, s), 1.94 (1H, ddddd, J = 8.6, 8.5, 4.3, 4.3, 4.2 Hz), 0.82 (9H, s), -0.11 (3H, s), -0.17 (3H, s).

$^{13}$C NMR (125 MHz, CDCl$_3$); $\delta$ (ppm) = 150.84, 136.61, 134.97, 133.93, 128.52, 127.05, 126.80, 121.75, 121.68, 119.25, 119.17, 118.70, 115.45, 110.98, 44.09, 29.82, 29.70, 25.75, 21.20, 18.22, -3.77, -3.88. IR (cm$^{-1}$): $\nu$ = 3419, 2953, 2928, 2895, 2855, 1634, 1512, 1470, 1456, 1418, 1390, 1359, 1339, 1307, 1277, 1252, 1211, 1181, 1151, 1122, 1092, 1062, 1034, 1010, 959, 939, 927, 836, 816, 779, 738, 704, 675, 603, 581, 558, 525, 490, 451. HRMS-ESI: [M+H]$^+$= 404.2404 calculated for C$_{26}$H$_{34}$ONSi; experimental = 404.2400.

Synthesis of 3-((tert-butyldimethylsilyl)oxy)-3-(3-methylthiophen-2-yl)cyclopent-2-en-1-yl)-1H-indole (4.33h)

Compound 4.29h (190 mg, 0.612 mmol) was dissolved in toluene (6.12 mL). Then, oven-dried 4Å molecular sieves (127 mg) were added, followed by indole (143 mg, 1.22 mmol), and then pyridinium triflate (14 mg, 0.061 mmol). Upon stirring at room temperature for 46 hours, the reaction mixture was then directly purified with flash column chromatography with 98 : 2 hexanes : ethyl acetate → 97 : 3 hexanes : ethyl acetate → 93 : 7 hexanes : ethyl acetate to give product 4.33h in 86% yield (217 mg, 0.528 mmol) as a clear, yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$); $\delta$ (ppm) = 7.94, (1H, b), 7.67 (1H, dq, J = 7.9, 0.9 Hz), 7.37 (1H, dt, J = 8.1, 0.9 Hz), 7.20 (1H, ddd, J = 8.2, 7.0, 1.2 Hz), 7.14 (1H, d, J = 5.1 Hz), 7.11 (1H, ddd, J = 8.0, 7.0, 1.0 Hz), 7.06 (1H, d, J = 2.4 Hz), 6.81 (1H, d, J = 5.1 Hz), 4.14-4.10 (1H, m), 2.79 (1H, dddd, J = 14.5, 9.0, 5.0, 1.5 Hz), 2.70 (1H, dddd, J = 14.5, 8.7, 5.7, 2.3 Hz), 2.50 (1H, dddd, J = 10.8, 9.0, 9.0, 5.7 Hz), 2.29 (3H, s), 2.01 (1H, dddd, J = 12.6, 5.0, 5.0, 5.0), 0.72 (9H,
\[ \delta (ppm) = 151.63, 136.62, 133.65, 130.03, 126.97, 122.58, 121.79, 121.61, 119.33, 119.12, 111.80, 111.03, 43.27, 32.49, 30.10, 25.55, 18.12, 15.51, -4.34, -4.39. \]

IR (cm\(^{-1}\)): \( \nu = 3416, 2953, 2928, 2896, 2855, 1649, 1625, 1470, 1456, 1418, 1359, 1323, 1283, 1252, 1207, 1093, 1010, 939, 925, 902, 838, 782, 740, 707, 678, 620, 581, 492. \]

HRMS - ESI: [M+H]\(^+\) = 410.1968 calculated for C\(_{24}\)H\(_{32}\)ONSSi; experimental = 410.1964.

### 8.4.2 Synthetic Procedures for \( \alpha \)-Hydroxy Silylenol Ether Formation

**Synthesis of 2-((tert-butyldimethylsilyl)oxy)cyclopent-2-en-1-one (4.28a)**

\[
\begin{align*}
\text{O} & \quad \text{HO} & \quad \text{OTBS} \\
\text{4.27} & \quad \text{TBSCl} & \quad \text{imidazole} \\
\end{align*}
\]

Purified ketone 4.27 (1.62 g, 16.5 mmol) was dissolved in DCM. TBSCl (2.86 g, 19.0 mmol) and imidazole (2.25 g, 33.0 mmol) were added to the solution and allowed to stir overnight. Upon completion, the reaction was rinsed with 2M HCl and the aqueous layer extracted three times with DCM. Combined organic layers were dried over Na\(_2\)SO\(_4\), and then concentrated under vacuum. Desired product was purified with flash column chromatography 100 Hexanes \( \rightarrow \) 98 : 2 Hexanes : EtOAC \( \rightarrow \) 95 : 5 \( \rightarrow \) 90 : 10, giving 4.28 in 46% yield (1.62 g, 7.63 mmol) as a clear, colorless oil.

\[ \delta (ppm) = 6.61 (1H, t, J = 2.8 \text{ Hz}), 2.49-2.45 (2H, m), 2.39-2.36 (2H, m), 0.94 (9H, s), 0.19 (6H, s). \]

IR (cm\(^{-1}\)): \( \nu = 2954, 2930, 2887, 2857, 1755, 1715, 1629, 1472, 1464, 1408, 1362, 1332, 1300, 1275, 1253, 1212, 1162, 1106, 1035, 1015, 855, 840, \]
Synthesis of 2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ol (4.19)

A flask containing 3-methylcyclopentane-1,2-dione S-3 (10.0 g, 89.2 mmol) was dissolved in CH$_2$Cl$_2$ (100 mL). TBSCl (15.5 g, 103 mmol) was then added, followed by imidazole (9.1 g, 134 mmol). Upon stirring overnight, the reaction was quenched with 2M HCl (50 mL) and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum to yield crude ketone S-4 (25.2 g).

$^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm) = 2.43-2.40 (2H, m), 2.34-2.31 (2H, m), 1.96 (3H, s), 0.96 (9H, s), 0.19 (6H, s). $^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ (ppm) = 202.76, 151.34, 149.53, 32.13, 26.94, 25.71, 18.30, 14.77, -4.09. IR (cm$^{-1}$): $f$ = 2954, 2929, 2857, 1710, 1646, 1472, 1463, 1409, 1390, 1360, 1339, 1247, 1112, 920, 857, 838, 782, 681, 670, 494, 467. HRMS-ESI: [M+Na]$^+$= 227.1462 calculated for C$_{13}$H$_{26}$NaOSi; experimental = 227.1459.

Crude ketone S-4 (25.2 g) was dissolved in CH$_2$Cl$_2$ (150 mL) and cooled to 0°C. DIBAL (134 mL, 1.0 M solution in toluene) was added slowly. Once the reaction was complete, an aqueous HCl solution (100 mL) was added slowly. The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 90 : 10 hexanes : ethyl acetate $\rightarrow$ 80 : 20 hexanes : ethyl acetate $\rightarrow$ 70 : 30 hexanes : ethyl
acetate to yield compound 4.19 in 77% yield (15.6 g, 68.3 mmol) over two steps as a clear, colorless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\); \(\delta\) (ppm) = 4.49 (1H, b), 2.34-2.27 (1H, m), 2.24-2.18 (1H, m), 2.12-2.06 (1H, m), 1.69-1.63 (1H, m), 1.60 (3H, b), 0.96 (9H, s), 0.16 (6H, b). \(^{13}\)C NMR (125 MHz, CDCl\(_3\); \(\delta\) (ppm) = 147.90, 117.15, 76.03, 30.51, 30.39, 25.73, 18.18, 12.35, -4.03, -4.12. IR (cm\(^{-1}\)): \(f\) = 3346, 2957, 2929, 2895, 2856, 1688, 1472, 1440, 1361, 1331, 1251, 1218, 1043, 1000, 867, 837, 780, 676. HRMS-ESI: [M-H\(_2\)O]\(^+\) = 211.1513 calculated for C\(_{12}\)H\(_{23}\)OSi; experimental = 211.1502.

Synthesis of 2-((tert-butyldimethylsilyl)oxy)-1-methylcyclopent-2-en-1-ol (4.29a)

Ketone 4.28 (350 mg, 1.65 mmol) was dissolved in CH\(_2\)Cl\(_2\) (10 mL) and cooled to 0\(^\circ\)C. Methylmagnesium bromide (824 \(\mu\)L, 3.0 M solution in Et\(_2\)O) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring overnight, the reaction was quenched with a half-saturated aqueous NH\(_4\)Cl solution (20 mL). The aqueous layer was then extracted with CH\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and then concentrated under vacuum. The crude material was purified with flash column chromatography with 98 : 2 hexanes : ethyl acetate to give product 4.29a in 72% yield (270 mg, 1.18 mmol) as a clear colorless oil.

\(^1\)H NMR (500 MHz, CDCl\(_3\); \(\delta\) (ppm) = 4.62 (1H, t, \(J = 2.5\) Hz), 2.26 (1H, dddd, \(J = 12.5, 6.3, 6.3, 2.6\)), 2.12 (1H, dddd, \(J = 15.5, 6.7, 6.7, 2.3\)), 1.96 (1H, d, \(J = 5.4\) Hz), 1.95 (1H, d, \(J = 7.2\) Hz), 1.31 (3H, s), 0.95 (9H, s), 0.19 (3H, s), 0.17 (3H, s). \(^{13}\)C NMR (125 MHz, CDCl\(_3\);

Synthesis of 1-allyl-2-((tert-butyldimethylsilyl)oxy)cyclopent-2-en-1-ol (4.29b)

Ketone 4.28 (250 mg, 1.18 mmol) was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. Allylmagnesium bromide (2.4 mL, 1.0 M solution in Et₂O) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring overnight, the reaction was quenched with a half-saturated aqueous NH₄Cl solution (20 mL). The aqueous layer was then extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 100 : 0 hexanes : ethyl acetate → 99 : 1 hexanes : ethyl acetate → 90 : 10 hexanes : ethyl acetate to give product 4.29b in 80% yield (241 mg, 0.948 mmol) as a clear colorless oil.

¹H NMR (400 MHz, CDCl₃); δ (ppm) = 5.85-5.74 (1H, m), 5.12-5.05 (2H, m), 4.65 (1H, t, J = 2.2 Hz), 2.41 (1H, dd, J = 13.6, 7.6), 2.32-2.19 (2H, m), 2.10-1.96 (3H, m), 1.87-1.80 (1H, m), 0.93 (9H, s), 0.18 (3H, s), 0.17 (3H, s). ¹³C NMR (100 MHz, CDCl₃); δ (ppm) = 155.59, 134.06, 117.90, 102.04, 81.53, 43.39, 34.29, 25.66, 24.43, 18.08, -4.87, -4.95. IR (cm⁻¹): f = 3459, 2955, 2931, 2899, 2858, 1649, 1472, 1437, 1390, 1252, 1131, 1065, 994, 884, 858, 839, 781, 678. HRMS-ESI: [M-H₂O]+ = 237.1669 calculated for C₁₄H₂₅OSi; experimental = 237.1669.
Synthesis of 2-((tert-butyldimethylsilyl)oxy)-1-(3-((tert-butyldimethylsilyl)oxy)propyl)cyclopent-2-en-1-ol (4.29c)

Alcohol 4.31 (210 mg, 0.826 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL) and methyl acrylate (372 µL, 4.13 mmol) was added, followed by Grubb’s 2$^{\text{nd}}$ generation catalyst (7 mg, 0.008 mmol). The mixture was then warmed to reflux and allowed to stir for two days. On the third day, a second portion of Grubb’s 2$^{\text{nd}}$ generation catalyst (14 mg, 0.016 mmol) was added. Upon completion, the reaction was then cooled to room temperature and solvent was evaporated under vacuum. Crude material was then purified with flash column chromatography with 95 : 5 hexanes : ethyl acetate → 90 : 10 hexanes : ethyl acetate → 80 : 20 hexanes : ethyl acetate to yield α,β-unsaturated ester 4.32 in 65% yield (169 mg, 0.540 mmol) as a clear colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$); δ (ppm) = 6.96 (1H, q, J = 7.7 Hz), 5.89 (1H, d, J = 15.7 Hz), 4.69 (1H, t, J = 2.3 Hz), 3.72 (3H, s), 2.55 (1H, dd, J = 14.3, 7.7 Hz), 2.43 (1H, dd, J = 13.9, 7.8 Hz), 2.29-2.23 (1H, m), 2.13-2.06 (1H, m), 2.04-1.85 (2H, m), 0.95 (9H, s), 0.19 (6H, d, J = 6.3 Hz). $^{13}$C NMR (125 MHz, CDCl$_3$); δ (ppm) = 166.71, 155.08, 144.85, 123.68, 102.41, 81.63, 51.43, 41.73, 34.70, 25.66, 24.41, 18.10, -4.89, -4.92. IR (cm$^{-1}$): f = 3485, 2952, 2931, 2901, 2858, 1726, 1712, 1649, 1472, 1463, 1437, 1390, 1362, 1331, 1263, 1194, 1174, 1063, 1042, 1007, 982, 960, 858, 841, 783, 679. HRMS-ESI: [M+H]$^+$ = 313.1830 calculated for C$_{16}$H$_{29}$O$_4$Si; experimental = 313.1835.
Ester 4.32 (160 mg, 0.510 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL), and then cooled to -78°C. DIBAL (1.79 mL, 1.0 M solution in toluene) was then added, and the reaction was warmed to 0°C. The mixture was allowed to stir for 2.5 hours and quenched with saturated Rochelle’s salt solution (20mL) and saturated sodium chloride solution was added (5 mL). Upon separation of layers, the aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were concentrated under vacuum, and the resulting crude material was then carried on to the next step.

The crude material obtained from the DIBAL reduction was dissolved in CH$_2$Cl$_2$ (20 mL), and TBSCl (84.5 mg, 0.561 mmol) and imidazole (52.1 mg, 0.765 mmol) were added. Upon stirring overnight, another portion of TBSCl (45.2 mg, 0.300 mmol) and imidazole (17.4 mg, 0.26 mmol) were added. The mixture was allowed to stir overnight again and then quenched with 2M HCl (20 mL). The aqueous was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 95 : 5 hexanes : ethyl acetate $\rightarrow$ 90 : 10 hexanes : ethyl acetate to give product 4.29c in 45% yield (92.3 mg, 0.231 mmol) over two steps as a clear colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$); $\delta$ (ppm) = 5.64-5.62 (2H, m), 4.66 (1H, t, J = 2.3 Hz), 4.13 (2H, d, J = 3.2 Hz), 2.40-2.36 (1H, m), 2.32-2.25 (1H, m), 2.25-2.20 (1H, m), 2.09-2.00 (2H, m), 1.88-1.80 (1H, m), 0.95 (9H, s), 0.90 (9H, s), 0.20 (3H, s), 0.18 (3H, s), 0.06 (6H, s). $^{13}$C NMR (125 MHz, CDCl$_3$); $\delta$ (ppm) = 155.50, 132.86, 126.04, 102.17, 81.79, 63.83, 41.71, 34.19, 25.98, 25.84, 25.69, 24.46, 18.42, 18.10, -4.85, -4.89, -5.16. IR (cm$^{-1}$): f = 3464, 2954, 2929, 2897, 2857, 1649, 1472, 1463, 1439, 1389, 1253, 1131, 1099, 1061, 1006, 971, 837, 779, 677, 578,
HRMS-ESI: [M-H$_2$O-TBS]$^+$ = 267.1775 calculated for C$_{15}$H$_{27}$O$_2$Si; experimental =267.1783.

Synthesis of 2-((tert-butyldimethylsilyl)oxy)cyclopent-2-en-1-ol (4.29d)

Ketone 4.28 (50 mg, .235 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to 0°C. DIBAL (259 µL, 1.0 M solution in toluene) was then added dropwise. After stirring for three hours, the reaction was quenched with 2M HCl (10 mL). The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 98 : 2 hexanes : ethyl acetate → 95 : 5 hexanes : ethyl acetate → 90 : 10 hexanes : ethyl acetate to give product 4.29d in 63% yield (32 mg, 0.147 mmol) as a clear colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$); δ (ppm) = 4.58 (1H, b), 4.33 (1H, t, J = 6.2 Hz), 2.17-2.03 (2H, m), 2.01-1.94 (1H, m), 1.69 (1H, s), 1.56-1.47 (1H, m), 0.75 (9H, s), 0.00 (6H, b). $^{13}$C NMR (100 MHz, CDCl$_3$); δ (ppm) =155.17, 104.10, 75.58, 30.71, 25.69, 25.41, 18.16, -4.73. IR (cm$^{-1}$): f = 3404, 2954, 2930, 2899, 2857, 1647, 1472, 1463, 1440, 1407, 1390, 1361, 1336, 1252, 1195, 1049, 1006, 968, 926, 878, 838, 814, 781, 676, 643, 581, 533. HRMS-ESI: [M+H]$^+$ = 215.1462 calculated for C$_{12}$H$_{23}$OSi; experimental =215.1461.

Synthesis of 2-((tert-butyldimethylsilyl)oxy)-1-phenylcyclopent-2-en-1-ol (4.29e)
Ketone 4.28 (250 mg, 1.18 mmol) was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. Phenylmagnesium bromide (785 µL, 3.0 M solution in Et₂O) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring overnight, the reaction was quenched with a half-saturated aqueous NH₄Cl solution (20 mL). The aqueous layer was then extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 100 : 0 hexanes : ethyl acetate → 99 : 1 hexanes : ethyl acetate → 95 : 5 hexanes : ethyl acetate to give product 4.29e in 68% yield (232 mg, 0.798 mmol) as a clear colorless oil.

¹H NMR (500 MHz, CDCl₃); δ (ppm) = 7.43-7.41 (2H, m), 7.31 (2H, t, J = 7.3 Hz), 7.24-7.20 (1H, m), 4.90-4.89 (1H, m), 2.42-2.35 (2H, m), 2.32-2.23 (3H, m), 0.78 (9H, s), 0.16 (3H, s), 0.03 (3H, s). ¹³C NMR (125 MHz, CDCl₃); δ (ppm) = 155.77, 145.78, 127.99, 126.72, 125.07, 103.31, 84.15, 39.61, 25.46, 24.90, 17.96, -4.79, -5.27. IR (cm⁻¹): f = 3588, 3457, 3061, 3027, 2953, 2929, 2897, 2857, 1649, 1463, 1447, 1390, 1361, 1338, 1251, 1053, 1034, 1003, 836, 779, 762, 698, 674, 575, 555, 473. HRMS-ESI: [M+Na]⁺ = 313.1594 calculated for C₁₇H₂₆NaO₂Si; experimental =313.1608.

Synthesis of 2-((tert-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)cyclopent-2-en-1-ol (4.29f)

Ketone 4.28 (300 mg, 1.413 mmol) was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. 4-Fluorophenylmagnesium bromide (2.83 mL, 1.0 M solution in THF) was then added dropwise. After stirring for one hour, the reaction was quenched with a half-saturated aqueous NH₄Cl
solution (20 mL). The aqueous layer was then extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 100 : 0 hexanes : ethyl acetate → 98 : 2 hexanes : ethyl acetate → 95 : 5 hexanes : ethyl acetate to give product 4.29f in 73% yield (317 mg, 1.03 mmol) as a clear colorless oil.

¹H NMR (500 MHz, CDCl₃); δ (ppm) = 7.39-7.37 (2H, m), 7.01-6.99 (2H, m), 4.88 (1H, t, J = 2.2 Hz), 2.42-2.35 (1H, m), 2.33 (1H, s), 2.30-2.18 (3H, m), 0.79 (9H, s), 0.16 (3H, s), 0.05 (3H, s). ¹³C NMR (125 MHz, CDCl₃); δ (ppm) = 162.76, 160.82, 155.58, 141.57, 141.55, 126.83, 126.75, 114.77, 114.60, 103.35, 83.83, 39.67, 25.45, 24.81, 17.94, -4.82, -5.25. IR (cm⁻¹): f = 3467, 2954, 2930, 2898, 2857, 1712, 1649, 1602, 1507, 1471, 1463, 1440, 1390, 1362, 1336, 1252, 1223, 1157, 1056, 1004, 938, 912, 834, 780, 733, 678, 617, 565, 494. HRMS-ESI: [M-H₂O]+= 291.1576 calculated for C₁₇H₂₄OFSi; experimental = 291.1575.

Synthesis of 2-((tert-butyldimethylsilyl)oxy)-1-(p-tolyl)cyclopent-2-en-1-ol (4.29g)

Ketone 4.28 (350 mg, 1.65 mmol) was dissolved in CH₂Cl₂ (10 mL) and cooled to 0°C. p-Tolylmagnesium bromide (6.6 mL, 0.5 M solution in Et₂O) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring overnight, the reaction was quenched with a half-saturated aqueous NH₄Cl solution (20 mL). The aqueous layer was then extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column
chromatography with 97 : 3 hexanes : ethyl acetate → 90 : 10 hexanes : ethyl acetate to give product 4.29g in 57% yield (287 mg, 0.944 mmol) as a clear colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$); $\delta$ (ppm) = 7.30 (2H, d, J = 8.1 Hz), 7.12 (2H, d, J = 7.9 Hz), 4.88-4.87 (1H, m), 2.38-2.33 (5H, m), 2.29-2.19 (2H, m), 0.80 (9H, s), 0.17 (3H, s), 0.06 (3H, s). $^{13}$C NMR (125 MHz, CDCl$_3$); $\delta$ (ppm) = 155.81, 142.78, 136.24, 128.69, 125.03, 103.21, 83.99, 39.69, 25.52, 24.78, 21.02, 17.99, -4.79, -5.18. IR (cm$^{-1}$): $f$ = 3589, 3451, 3024, 2951, 2929, 2898, 2857, 1649, 1511, 1471, 1462, 1440, 1407, 1390, 1336, 1251, 1183, 1154, 1055, 1020, 1004, 939, 913, 36, 817, 780, 724, 677, 619, 567, 480. HRMS-ESI: [M+H]$^+$ = 303.1775 calculated for C$_{18}$H$_{27}$O$_2$Si; experimental =303.1777.

Synthesis of 2-((tert-butyldimethylsilyl)oxy)-1-(3-methylthiophen-2-yl)cyclopent-2-en-1-ol (4.29h)

Ketone 4.28 (200 mg, 0.942 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to 0°C. 3-Methyl-2-thienylmagnesium bromide (3.78 mL, 0.5 M solution in THF) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring overnight, the reaction was quenched with a half-saturated aqueous NH$_4$Cl solution (20 mL). The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 97 : 3 hexanes : ethyl acetate → 90 : 10 hexanes : ethyl acetate to give product 4.29h in 59% yield (172 mg, 0.555 mmol) as a clear yellow oil.
$^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm) = 7.02 (1H, d, $J = 5.1$ Hz), 6.79 (1H, d, $J = 5.2$ Hz), 4.85 (1H, d), 2.64-2.36 (2H, m), 2.34-2.27 (2H, m), 2.24 (3H, s), 0.84 (9H, s), 0.19 (3H, s), 0.14 (3H, s). $^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ (ppm) = 154.53, 142.62, 132.34, 131.46, 103.46, 82.88, 38.14, 25.48, 24.41, 17.96, 14.30, -4.90, -5.12. IR (cm$^{-1}$): $f = 3580, 3469, 2953, 2929, 2899, 2857, 1650, 1543, 1471, 1463, 1439, 1390, 1362, 1352, 1186, 1153, 1092, 1059, 1004, 932, 891, 834, 782, 707, 677, 630, 593, 549, 476, 456$. HRMS-ESI: [M-H$_2$O]$^+$ = 293.1390 calculated for C$_{16}$H$_{25}$SOSi; experimental = 293.1388.

### 8.4.3 Synthetic Procedures for Applications of Indole Adducts

Synthesis of (±)-(2R,5R)-2-(1H-indol-3-yl)-5-(p-tolyl)cyclopentan-1-one (4.34)

In a round bottom flask, silylenol ether 4.33g (20 mg, 0.049 mmol) was dissolved in dry THF (1 mL, 0.05M). After cooling to 0°C, TBAF (53 $\mu$L, 0.053 mmol, 1M in THF) was then added. The reaction mixture was stirred at 0°C for 15 minutes until the completion of reaction, as monitored by TLC. The reaction mixture was then partitioned between CH$_2$Cl$_2$ and H$_2$O (20 mL, 1:1). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were then washed thoroughly with water, followed by brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to obtain crude product. NMR analyses of the crude material indicated 3:1 mixture of diastereomers. The crude product was further purified by flash column chromatography with 90 : 10 hexanes : ethyl acetate to afford separable mixture diastereomers (10 mg combined, 71%). X-ray crystal data revealed that the major diastereomer 4.34 possessed anti relative stereochemistry (see page 46 in this Supporting Information).
Anti diastereomer 4.34: $^1$H NMR (500 MHz, CDCl$_3$); $\delta$ (ppm) = 8.14 (bs, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.21 (s, 5H), 7.16 – 7.09 (m, 1H), 7.01 (d, J = 2.3 Hz, 1H), 3.77 (dd, J = 11.5, 8.4 Hz, 1H), 3.55 (dd, J = 11.5, 8.4 Hz, 1H), 2.73 – 2.66 (m, 1H), 2.66 – 2.58 (m, 1H), 2.37 (s, 3H), 2.28 – 2.13 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$); $\delta$ (ppm) = 216.91, 136.74, 136.64, 135.89, 129.54, 128.24, 126.92, 122.27, 122.13, 119.63, 119.50, 113.20, 111.58, 55.33, 48.05, 30.22, 29.54, 21.27. IR (cm$^{-1}$): f = 3404, 2963, 2871, 1736, 1514, 1456, 1422, 1339, 1138, 1101, 996, 908, 826, 740. HRMS-ESI: [M + Na]$^+$ = 312.1359 calculated for C$_{20}$H$_{19}$NNaO; experimental = 312.1355.

**Synthesis of 1-(3-(2-((tert-butyldimethylsilyl)oxy)-3-(p-tolyl)cyclopent-2-en-1-yl)-1H-indol-1-yl)ethan-1-one (4.35)**

In a round bottom flask, a solution of n-BuLi (1.5 mL, 3.72 mmol, 2.5 M in hexanes) was added dropwise into a solution of diisopropylamine (0.52 mL, 3.72 mmol) in dry THF (6 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 min. A solution of 4.33g (500 mg, 1.24 mmol) in dry THF (6 mL) was the added dropwise. The reaction mixture was further stirred at 0°C for 60 min. Then, acetic anhydride (0.35 mL, 3.72 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 60 min until the completion of reaction, as monitored by TLC. The reaction quenched with saturated aqueous solution of ammonium chloride (10 mL). The reaction mixture was partitioned between EtOAc and H$_2$O (50 mL, 1:1). The aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers was then washed thoroughly with water, followed by brine, dried over Na$_2$SO$_4$, and concentrated in vacuo to obtain crude
product. The crude product was further purified by flash column chromatography with 90 : 10 hexanes : ethyl acetate to afford compound 4.35 as yellow oil (320 mg, 58%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 8.46 (d, \(J = 7.7\) Hz, 1H), 7.61 (d, \(J = 8.0\) Hz, 2H), 7.57 (d, \(J = 7.6\) Hz, 1H), 7.40 – 7.33 (m, 1H), 7.28 (td, \(J = 7.8, 1.0\) Hz, 1H), 7.21 (s, 1H), 7.17 (d, \(J = 8.0\) Hz, 2H), 4.13 (dd, \(J = 9.1, 4.5\) Hz, 1H), 2.87 – 2.77 (m, 1H), 2.69 – 2.63 (m, 1H), 2.58 (s, 3H), 2.53 – 2.46 (m, 1H), 2.37 (s, 3H), 1.94 – 1.88 (m, 1H), 0.85 (s, 9H), -0.02 (s, 3H), -0.06 (s, 3H). \(^1\)C NMR (125 MHz, CDCl\(_3\)); \(\delta\) (ppm) = 168.75, 149.23, 136.51, 135.69, 133.64, 130.34, 128.82, 127.10, 125.36, 123.67, 122.31, 119.37, 116.91, 44.06, 30.08, 28.91, 25.93, 24.28, 21.43, 18.40, -3.52, -3.63. IR (cm\(^{-1}\)):\(f = 2957, 2926, 2855, 1707, 1450, 1382, 1349, 1331, 1258, 1090, 1016, 796, 781, 746\). HRMS-ESI: [M+H]\(^+\) = 446.251 calculated for C\(_{28}\)H\(_{36}\)NO\(_2\)Si; experimental = 446.2506.

Synthesis of (±)-(1R,2S,3R)-2-((tert-butyldimethylsilyl)oxy)-3-(1H-indol-3-yl)-1-(p-tolyl)cyclopentan-1-ol (4.36)

In a round bottom flask, BH\(_3\)•THF (0.45 mL, 0.449 mmol, 1M in THF) was added dropwise into a solution of 4.35 (50 mg, 0.112 mmol) in dry THF (2.5 mL) at -30 °C. The reaction mixture was slowly warmed to room temperature and stirred for 3 hours. Then, the reaction mixture was cooled to -10°C. NaOH (1 mL, 1M aqueous solution) was added dropwise, immediately followed by H\(_2\)O\(_2\) (0.5 mL, 30% aqueous solution). The reaction mixture was vigorously stirred at room temperature for 18 hours and subsequently quenched with a saturated aqueous solution of sodium sulfite (5 mL). The biphasic layer was partitioned between EtOAc
and H₂O (50 mL, 1:1). The aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers was washed thoroughly with water, followed by brine, dried over Na₂SO₄, and concentrated in vacuo to obtain crude product. NMR analyses of the crude material indicated a single diastereomer. The crude product was further purified by flash column chromatography with 90 : 10 hexanes : ethyl acetate to afford 4.36 as colorless oil (30 mg, 64 % ). The relative stereochemistry of the product was deduced using X-ray crystallography (see page 59 in this Supporting Information).

^1^H NMR (500 MHz, CDCl₃); δ (ppm) = 7.96 (bs, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 1H), 7.19 – 7.11 (m, 4H), 7.07 (d, J = 2.0 Hz, 1H), 4.22 (td, J = 9.9, 3.4 Hz, 1H), 3.99 (d, J = 3.4 Hz, 1H), 2.87 (ddd, J = 13.8, 11.0, 5.4 Hz, 1H), 2.42 – 2.24 (m, 5H), 1.90 – 1.80 (m, 2H), 0.56 (s, 9H), -1.03 (s, 3H), -1.30 (s, 3H). ^1^C NMR (125 MHz, CDCl₃); δ (ppm) = 140.91, 136.96, 136.42, 128.62, 128.59, 127.49, 123.02, 121.94, 119.36, 119.31, 115.80, 111.04, 86.58, 81.83, 40.80, 36.33, 26.98, 26.34, 21.20, 18.07, -5.91, -5.93. IR (cm⁻¹): f = 3417, 2951, 2930, 2893, 2855, 1461, 1255, 1109, 974, 836, 807, 777, 742. HRMS: ESI [M + H⁺] = 422.2510 calculated for C₂₆H₃₆NO₂Si; experimental = 422.2518.

Synthesis of 5-(1-acetyl-1H-indol-3-yl)-2-(p-tolyl)cyclopent-2-en-1-one (4.37)

In a round bottom flask, a solution of N-bromosuccinimide (12 mg, 0.067 mmol) in dry THF (0.5 mL) was added dropwise into a solution of 4.35 (20 mg, 0.045 mmol) in dry THF (0.5 mL) at 0°C. The reaction mixture was stirred at 0°C for 6 hours and then room temperature for 12 hours. The reaction was then quenched with a solution of sodium thiosulfate (300 mg)
dissolved in saturated aqueous solution of sodium bicarbonate (5 mL). The reaction mixture was then partitioned between EtOAc and H₂O (50 mL, 1:1). The aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers was then washed thoroughly with water, followed by brine, dried over Na₂SO₄, and concentrated in vacuo to obtain crude product. The crude product was further purified by flash column chromatography with 95 : 5 hexanes : ethyl acetate to afford cyclopentenone 4.37 as yellow oil (10 mg, 67%).

1H NMR (500 MHz, CDCl₃); δ (ppm) = 8.57 (dd, J = 7.8, 1.4 Hz, 1H), 8.40 (s, 1H), 8.24 (dd, J = 3, 3 Hz, 1H), 7.85 (d, J = 7.4 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.17 (d, J = 8 Hz, 2H), 7.11 (d, J = 8 Hz, 2H), 3.73 (dd, J = 7.1, 2.8 Hz, 1H), 3.44 – 3.31 (m, 1H), 2.97 (dt, J = 20.0, 2.8 Hz, 1H), 2.64 (s, 3H), 2.34 (s, 3H). 13C NMR (125 MHz, CDCl₃); δ (ppm) = 208.07, 169.28, 155.49, 137.04, 136.38, 135.96, 135.63, 129.85, 128.80, 127.69, 125.76, 125.74, 124.30, 119.83, 117.32, 112.71, 51.20, 37.00, 24.20, 21.28. IR (cm⁻¹): f = 2922, 1706, 1449, 1376, 1348, 1327, 1262, 1221, 1116, 1075, 908, 800, 729. HRMS: ESI [M + H]⁺ = 330.1489 calculated for C₂₂H₂₀NO₂; experimental = 330.1488.

8.5 Synthesis and Characterization of Novel Chapter 5 Compounds

8.5.1 Synthetic Procedures for Indole Containing Quaternary Center Formation

Synthesis of (+)-3-(2-methoxy-1-methyl-3-phenylcyclopent-2-enyl)-1H-indole (5.14a)

![Chemical Structure](image)

Compound 5.12 (50 mg, 0.245 mmol) was dissolved in toluene (1.2 mL). Indole (57 mg, 0.490 mmol) and then pyridinium triflate (6 mg, 0.024 mmol) were added. Upon stirring at room temperature for 2 hours, the reaction mixture was concentrated under vacuum and then directly
purified with flash column chromatography with 90 : 10 hexanes : Et₂O to give product 5.14a (60 mg, 81% yield) as green solid.

1H NMR (500 MHz, CDCl₃): δ (ppm) = 7.96 (bs, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8 Hz, 2H), 7.37 (dd, J = 6, 6 Hz, 3H), 7.24 – 7.17 (m, 2H), 7.12 – 7.02 (m, 2H), 3.44 (s, 3H), 2.88 (dt, J = 15, 8.0 Hz, 1H), 2.78 (ddd, J = 15, 9.0, 3.4 Hz, 1H), 2.52 (dt, J = 12.8, 9.0 Hz, 1H), 2.04 (ddd, J = 12.4, 9.0, 3.4 Hz, 1H), 1.74 (s, 3H). 13C NMR (125 MHz, CDCl₃): δ (ppm) = 160.15, 137.26, 137.22, 128.25, 127.61, 126.43, 126.21, 123.46, 122.01, 120.87, 120.72, 119.45, 115.40, 111.39, 59.10, 48.30, 37.63, 29.99, 25.07. IR (cm⁻¹): 3412, 2960, 2933, 2844, 1629, 1598, 1456, 1416, 1335, 1260, 1128, 1078, 739, 697. HRMS (M + Na)⁺ = 326.1515 calculated for C₂₁H₂₁NNaO; experimental = 326.1519.

Synthesis of (±)-3-(2-methoxy-1-methyl-3-phenylcyclopent-2-ynyl)-1-methyl-1H-indole (5.14b)

Compound 5.12 (50 mg, 0.245 mmol) was dissolved in toluene (1.2 mL). N-methylindole (64 mg, 0.490 mmol) and then pyridinium triflate (6 mg, 0.024 mmol) were added. Upon stirring at room temperature for 2 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 85 : 15 hexanes : Et₂O to give product 5.14b (58 mg, 74% yield) as white solid.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.77 (d, $J = 8.0$ Hz, 1H), 7.64 (d, $J = 7.5$ Hz, 2H), 7.38 (dd, $J = 7.6, 7.6$ Hz, 2H), 7.31 (d, $J = 8.2$ Hz, 1H), 7.23 (dd, $J = 7.4, 6.5$ Hz, 2H), 7.07 (dd, $J = 7.5, 7.5$ Hz, 1H), 6.96 (s, 1H), 3.78 (s, 3H), 3.46 (s, 3H), 2.88 (dt, $J = 15.4, 7.8$ Hz, 1H), 2.83 – 2.71 (m, 1H), 2.51 (dt, $J = 16.0, 8.2$ Hz, 1H), 2.05 (ddd, $J = 12.5, 8.7, 3.5$ Hz, 1H), 1.74 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) = 160.30, 137.92, 137.27, 128.24, 127.63, 126.78, 126.19, 125.63, 121.83, 121.56, 120.93, 118.86, 115.30, 109.44, 59.28, 48.32, 37.87, 32.88, 30.02, 25.13. IR (cm$^{-1}$): 2959, 2930, 2845, 1630, 1462, 1373, 1342, 1327, 1260, 1221, 1079, 1044, 737. HRMS (M + H)$^+$ = 318.1852 calculated for C$_{22}$H$_{24}$NO; experimental = 318.1845.

Synthesis of (±)-5-bromo-3-(2-methoxy-1-methyl-3-phenylcyclopent-2-enyl)-1H-indole (5.14c)

Compound 5.12 (50 mg, 0.245 mmol) was dissolved in toluene (1.2 mL). 5-Bromoindole (96 mg, 0.490 mmol) and then pyridinium triflate (6 mg, 0.024 mmol) were added. Upon stirring at room temperature for 2 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 85 : 15 hexanes : Et$_2$O to give product 5.14c (80 mg, 85% yield) as white solid.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ (ppm) = 7.99 (bs, 1H), 7.91 (d, $J = 1.6$ Hz, 1H), 7.60 (d, $J = 7.1$ Hz, 2H), 7.39 (dd, $J = 7.7, 7.7$ Hz, 2H), 7.31 – 7.18 (m, 3H), 7.09 (d, $J = 2.4$ Hz, 1H), 3.45 (s, 3H), 2.87 (ddd, $J = 15.0, 9.0, 7.0$ Hz, 1H), 2.75 (ddd, $J = 15.0, 9.0, 3.7$ Hz, 1H), 2.44 (ddd, $J = 13.0, 9.0, 7.0$ Hz, 1H), 2.05 (ddd, $J = 13.0, 9.0, 3.7$ Hz, 1H), 1.72 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ (ppm) = 159.59, 137.18, 135.83, 128.28, 128.11, 127.77, 126.38, 124.89, 123.36, 123.15, 122.07, 115.62, 112.81, 112.74, 59.51, 48.31, 37.48, 30.34, 24.99. IR (cm$^{-1}$): 3421, 2959,
2930, 2850, 1637, 1459, 1325, 1239, 1105, 796, 762, 698. HRMS (M + Na)^+ = 404.0620 calculated for C_{21}H_{20}BrNNaO; experimental = 404.0622.

Synthesis of (±)-methyl 3-(2-methoxy-1-methyl-3-phenylcyclopent-2-enyl)-1H-indole-5-carboxylate (5.14d)

Compound 5.12 (50 mg, 0.245 mmol) was dissolved in toluene (1.2 mL). Methyl indole-5-carboxylate (86 mg, 0.490 mmol) and then pyridinium triflate (6 mg, 0.024 mmol) were added. Upon stirring at room temperature for 6 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 65 : 35 hexanes : Et_2O to give product 5.14d (60 mg, 68% yield) as white solid.

^1H NMR (500 MHz, CDCl_3): δ (ppm) = 8.61 (s, 1H), 8.18 (bs, 1H), 7.90 (d, J = 10.0 Hz, 1H), 7.61 (d, J = 7.2 Hz, 2H), 7.43 – 7.32 (m, 3H), 7.24 (dd, J = 7.4, 7.4 Hz, 1H), 7.15 (d, J = 2.3, 2.3 Hz, 1H), 3.89 (s, 3H), 3.44 (s, 3H), 2.87 (ddd, J = 15.0, 8.5, 6.6 Hz, 1H), 2.83 – 2.74 (m, 1H), 2.44 (ddd, J = 13, 8.5, 6.6 Hz, 1H), 2.10 (ddd, J = 13, 8.5, 4.2 Hz, 1H), 1.74 (s, 3H). ^13C NMR (125 MHz, CDCl_3): δ (ppm) = 168.45, 159.42, 139.82, 137.40, 128.20, 127.96, 126.39, 125.97, 124.96, 123.90, 123.49, 122.05, 121.53, 115.70, 111.08, 59.69, 51.98, 48.47, 37.77, 30.85, 25.15. IR (cm\(^{-1}\)): 3337, 2958, 2927, 2849, 1691, 1616, 1435, 1315, 1296, 1257, 1096, 987, 907, 801, 754. HRMS (M + H)^+ = 362.1751 calculated for C_{22}H_{24}NO_3; experimental = 362.1754.
Synthesis of (±)-3-(2-methoxy-1-methyl-3-phenylcyclohex-2-enyl)-1H-indole (5.15a)

Compound 5.13 (50 mg, 0.229 mmol) was dissolved in toluene (1.1 mL). Indole (54 mg, 0.459 mmol) and then pyridinium triflate (5 mg, 0.023 mmol) were added. Upon stirring at room temperature for 24 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 85:15 hexanes:Et₂O to give product 5.15a (58 mg, 80% yield) as white solid.

$^1$H NMR (500 MHz, CDCl₃): δ (ppm) = 7.94 (bs, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 7.1 Hz, 2H), 7.35 (dd, J = 7.6, 7.6 Hz, 3H), 7.24 (dd, J = 7.4, 7.4 Hz, 1H), 7.19 (dd, J = 7.9, 7.9 Hz, 1H), 7.12 (dd, J = 7.9, 7.9 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 3.09 (s, 3H), 2.57 (dd, J = 16.8, 7.7, 5.2 Hz, 1H), 2.48 – 2.38 (m, 1H), 1.88 – 1.76 (m, 3H), 1.73 (s, 3H). $^{13}$C NMR (125 MHz, CDCl₃): δ (ppm) = 158.06, 141.61, 137.25, 128.61, 128.35, 126.44, 125.99, 123.78, 122.11, 121.76, 121.00, 119.65, 119.20, 111.61, 61.19, 40.89, 39.22, 31.85, 25.05, 20.47. IR (cm⁻¹): 3412, 2928, 2858, 1490, 1457, 1335, 1192, 1132, 1011, 762, 739, 699. HRMS (M + Na)$^+$ = 340.1672 calculated for C₂₂H₂₃NNaO; experimental = 340.1668.

Synthesis of (±)-3-(2-methoxy-1-methyl-3-phenylcyclohex-2-enyl)-1-methyl-1H-indole (5.15b)

Compound 5.13 (50 mg, 0.229 mmol) was dissolved in toluene (1.1 mL). N-Methylindole (60 mg, 0.459 mmol) and then pyridinium triflate (5 mg, 0.023 mmol) were added.
Upon stirring at room temperature for 96 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 60 : 40 hexanes : Et₂O to give product 5.15b (40 mg, 53% yield) as colorless oil.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.87 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.41 – 7.29 (m, 3H), 7.26 – 7.18 (m, 2H), 7.10 (dd, J = 7.5, 7.5 Hz, 1H), 6.98 (s, 1H), 3.79 (s, 3H), 3.11 (s, 3H), 2.70 – 2.61 (m, 1H), 2.55 (dt, J = 16.9, 6.5 Hz, 1H), 2.47 – 2.37 (m, 1H), 1.86 – 1.77 (m, 3H), 1.72 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 158.23, 141.61, 137.87, 128.61, 128.33, 126.95, 126.41, 126.32, 122.17, 121.32, 121.07, 119.55, 118.63, 109.64, 61.26, 40.89, 39.49, 32.90, 31.84, 25.12, 20.51. IR (cm⁻¹): 2928, 1464, 1324, 1259, 1011, 907, 731, 697. HRMS (M + Na)⁺ = 354.1828 calculated for C₂₃H₂₅NNaO; experimental = 354.1822.

Synthesis of (±)-5-bromo-3-(2-methoxy-1-methyl-3-phenylcyclohex-2-enyl)-1H-indole (5.15c)

Compound 5.13 (50 mg, 0.229 mmol) was dissolved in toluene (1.1 mL). 5-Bromoindole (90 mg, 0.459 mmol) and then pyridinium triflate (5 mg, 0.023 mmol) were added. Upon stirring at room temperature for 24 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 95 : 5 hexanes : Et₂O to give product 5.15c (77 mg, 85% yield) as white solid.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 8.01 (s, 1H), 7.99 (bs, 1H), 7.46 (d, J = 7.4 Hz, 2H), 7.37 (dd, J = 7.4, 7.4 Hz, 2H), 7.27 – 7.17 (m, 3H), 7.08 (s, 1H), 3.09 (s, 3H), 2.69 – 2.48 (m, 2H), 2.40 – 2.25 (m, 1H), 1.84 – 1.7 (m, 3H), 1.70 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 157.39, 141.47, 135.80, 128.58, 128.46, 127.72, 126.58, 124.61, 123.61, 123.58,
123.32, 120.06, 112.96, 112.54, 61.26, 40.82, 39.28, 31.97, 25.03, 20.36. IR (cm⁻¹): 3423, 3323, 2927, 2856, 1460, 1261, 1136, 1106, 1015, 796, 762, 699. HRMS (M + H)⁺ = 418.0777 calculated for C₂₃H₂₂BrNaN; experimental = 418.077.

Synthesis of (±)-methyl 3-(2-methoxy-1-methyl-3-phenylethoxycyclohex-2-enyl)-1H-indole-5-carboxylate (5.15d)

\[
\begin{align*}
\text{HO} & \quad \text{Me} \\
\text{OMe} & \quad \text{Me} \\
5.13 & \quad + \quad \text{Me}_2\text{CO}_2\text{Me} \\
\text{Py}•\text{TiOH} & \quad \text{toluene, rt} \\
\text{5.15d} & \quad \text{MeO} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

Compound 5.13 (50 mg, 0.229 mmol) was dissolved in toluene (1.1 mL). Methyl indole-5-carboxylate (80 mg, 0.459 mmol) and then pyridinium triflate (5 mg, 0.023 mmol) were added. Upon stirring at room temperature for 30 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 60:40 hexanes:Et₂O to give product 5.15d (30 mg, 35% yield) as white solid.

\(^1\)H NMR (500 MHz, CDCl₃): δ (ppm) = 8.70 (s, 1H), 8.14 (bs, 1H), 7.90 (dd, J = 8.6, 1.5 Hz, 1H), 7.48 (d, J = 7.1 Hz, 2H), 7.39 – 7.31 (m, 3H), 7.23 (t, J = 7.4, 7.4 Hz, 1H), 7.17 (d, J = 2.3 Hz, 1H), 3.90 (s, 3H), 3.05 (s, 3H), 2.66 – 2.51 (m, 2H), 2.36 (ddd, J = 13.2, 9.9, 3.4 Hz, 1H), 1.86 – 1.75 (m, 3H), 1.73 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl₃): δ (ppm) = 168.44, 157.17, 141.67, 139.78, 128.63, 128.36, 126.50, 125.71, 125.50, 124.14, 123.35, 123.24, 121.36, 120.26, 111.20, 61.24, 51.97, 40.89, 39.80, 32.16, 25.26, 20.40. IR (cm⁻¹): 3341, 2921, 2852, 1690, 1647, 1435, 1247, 1115, 1092, 906, 733. HRMS (M + H)⁺ = 376.1907 calculated for C₂₄H₂₆NO₃; experimental = 398.1914.
Synthesis of (±)-3-(2-methoxy-3-(4-methoxyphenyl)-1-methylcyclopent-2-enyl)-1H-indole (5.18a)

Compound 23a (50 mg, 0.214 mmol) was dissolved in toluene (1.0 mL). Indole (50 mg, 0.427 mmol) and then pyridinium triflate (5 mg, 0.021 mmol) were added. Upon stirring at room temperature for 1 hour, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 90 : 10 hexanes : Et₂O to give product 26a (64 mg, 90% yield) as light green solid.

¹H NMR (500 MHz, CDCl₃): δ (ppm) = 7.95 (s, 1H), 7.80 (dd, J = 8.0, 1.2 Hz, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.39 – 7.33 (m, 1H), 7.21 (ddd, J = 8.3, 7.1, 1.2 Hz, 1H), 7.13 – 7.04 (m, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.88 (s, 3H), 3.46 (s, 3H), 2.94 – 2.74 (m, 2H), 2.54 (ddd, J = 12.8, 9.1, 7.0 Hz, 1H), 2.07 (ddd, J = 12.6, 8.7, 3.8 Hz, 1H), 1.77 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 158.75, 158.03, 137.23, 129.75, 128.68, 126.41, 123.47, 121.90, 120.83, 120.77, 119.35, 115.33, 113.71, 111.38, 58.99, 55.46, 48.13, 37.48, 29.95, 25.19. IR (cm⁻¹): 3411, 3056, 2958, 2837, 1606, 1509, 1455, 1243, 1177, 1098, 1030, 831, 796, 733. HRMS (M+Na)+ = 356.1621 calculated for C₂₂H₂₃NNaO₂; experimental = 356.1622.

Synthesis of (±)-3-(3-(4-chlorophenyl)-2-methoxy-1-methylcyclopent-2-enyl)-1H-indole (5.18b)
Compound 5.16b (50 mg, 0.209 mmol) was dissolved in toluene (1.1 mL). Indole (49 mg, 0.418 mmol) and then pyridinium triflate (5 mg, 0.021 mmol) were added. Upon stirring at room temperature for 1 hour, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 90 : 10 hexanes : Et₂O to give product 5.18b (64 mg, 90% yield) as light green solid.

\(^1^H\) NMR (400 MHz, CDCl₃): \(δ\) (ppm) = 7.95 (s, 1H), 7.75 (d, \(J = 8.0\) Hz, 1H), 7.59 (d, \(J = 8.2\) Hz, 2H), 7.36 (t, \(J = 8.9\) Hz, 3H), 7.21 (t, \(J = 7.6\) Hz, 1H), 7.16 – 6.99 (m, 2H), 3.45 (s, 3H), 2.86 (dt, \(J = 15.4, 7.9\) Hz, 1H), 2.80 – 2.69 (m, 1H), 2.62 – 2.46 (m, 1H), 2.05 (ddd, \(J = 12.5, 8.5, 3.5\) Hz, 1H), 1.76 (s, 3H).

\(^{13}\)C NMR (100 MHz, CDCl₃): \(δ\) (ppm) = 160.68, 137.22, 135.55, 131.58, 128.72, 128.35, 126.31, 123.17, 122.06, 120.70, 120.68, 119.50, 114.34, 111.43, 58.78, 48.17, 37.80, 29.63, 25.06. IR (cm\(^{-1}\)): 3411, 3057, 2961, 2937, 2845, 1629, 1544, 1489, 1260, 1091, 906, 829, 765, 728, 530. HRMS (M + Na)\(^{+}\) = 360.1126 calculated for C\(_{21}\)H\(_{20}\)ClNNaO; experimental =360.1129.

Synthesis of (±)-3-(3-(4-fluorophenyl)-2-methoxy-1-methylcyclopent-2-enyl)-1H-indole (5.18c)

![Chemical structure](image)

Compound 5.16c (50 mg, 0.223 mmol) was dissolved in toluene (1.1 mL). Indole (53 mg, 0.446 mmol) and then pyridinium triflate (5 mg, 0.022 mmol) were added. Upon stirring at room temperature for 1 hour, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 90 : 10 hexanes : Et₂O to give product 5.18c (67 mg, 93% yield) as white solid.
**Synthesis of (±)-3-(2-methoxy-1-octyl-3-phenylcyclopent-2-enyl)-1H-indole (5.18d)**

Compound 5.17d (23 mg, 0.076 mmol) was dissolved in toluene (0.4 mL). Indole (18 mg, 0.152 mmol) and then pyridinium triflate (2 mg, 0.009 mmol) were added. Upon stirring at room temperature for 18 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 85 : 15 hexanes : Et₂O to give product 5.18d (25 mg, 80% yield) as white solid.

**1H NMR (500 MHz, CDCl₃):** δ (ppm) = 7.95 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.22 (dd, J = 7.4, 7.4 Hz, 1H), 7.17 (dd, J = 7.2, 7.2 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 7.5, 7.5 Hz, 1H), 3.38 (s, 3H), 2.81 (qdd, J = 15.0, 9.3, 5.3 Hz, 2H), 2.45 (dd, J = 13.4, 9.6, 6.2 Hz, 1H), 2.18 (dd, J = 13.5, 9.1, 4.5 Hz, 1H), 2.10 (dd, J = 9.6, 6.6, 3.0 Hz, 2H), 1.54 – 1.29 (m, 12H), 0.89 (t, J = 7.0 Hz, 3H).
120.96, 120.61, 119.38, 116.32, 111.34, 59.23, 52.30, 38.48, 33.99, 32.13, 31.37, 30.70, 29.92, 29.64, 24.60, 22.90, 14.34. IR (cm⁻¹): 3417, 3054, 2955, 2921, 2851, 1492, 1258, 1090, 1013, 865, 795, 740, 698. HRMS (M + Na)⁺ = 424.2611 calculated for C₂₈H₃₅NNaO; experimental = 424.2613.

Synthesis of (±)-3-(1-isopropyl-2-methoxy-3-phenylcyclopent-2-enyl)-1H-indole (5.18e)

Compound 5.17e (20 mg, 0.086 mmol) was dissolved in toluene (0.4 mL). Indole (20 mg, 0.173 mmol) and then pyridinium triflate (2 mg, 0.009 mmol) were added. Upon stirring at room temperature for 26 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 85 : 15 hexanes : Et₂O to give product 5.18e as an inseparable mixture of regioisomers (13 mg, 46% yield) as white solid.

¹H NMR (500 MHz, CDCl₃, * denotes the minor regioisomer): δ (ppm) = 7.96 (bs, 1H, 1H*), 7.91 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H, 1H*), 7.41 (d, J = 8.1 Hz, 1H, 1H*), 7.35 (dd, J = 10.5, 8.1 Hz, 2H, 2H*), 7.33 – 7.28 (m, 2H, 2H*), 7.24 – 7.14 (m, 3H, 2H*), 7.11 – 7.10 (m, 1H, 1H*), 6.98 (dd, J = 7.6 Hz, 1H), 3.32 (s, 3H*), 3.23 (s, 3H), 3.03 (p, J = 6.9 Hz, 1H), 2.97 – 2.88 (m, 1H), 2.80 (p, J = 6.8 Hz, 1H*), 2.74 – 2.65 (m, 1H, 1H*), 2.61 (ddd, J = 13.0, 8.2, 4.9 Hz, 1H), 2.43 – 2.22 (m, 2H, 2H*), 1.13 (dd, J = 9.6, 7.3 Hz, 3H, 3H*), 1.07 (d, J = 6.6
Hz, 3H*), 0.98 (d, J = 6.5 Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$, * denotes the minor regioisomer): $\delta$ (ppm) = 159.10*, 155.04, 147.34, 137.73*, 137.17, 137.13*, 128.07, 128.06*, 128.03*, 127.98, 127.90, 126.96, 126.79*, 126.21*, 126.00, 122.77, 122.13*, 121.90*, 121.86, 121.77, 121.75*, 121.70, 121.53*, 119.17*, 119.11, 115.42*, 111.27*, 111.21, 61.12, 59.89*, 56.98, 56.01*, 38.19, 32.93, 32.06*, 29.92, 28.03*, 25.99*, 24.89, 21.46*, 21.40, 18.67*, 18.49. HRMS (M + H)$^+$ = 354.1828 calculated for C$_{23}$H$_{25}$NNaO; experimental = 354.1834.

Synthesis of ($\pm$)-3-(2-methoxy-3-phenylcyclopent-2-enyl)-1H-indole (5.18f)

Compound 5.17f (27 mg, 0.143 mmol) was dissolved in toluene (0.7 mL). Indole (34 mg, 0.286 mmol) and then pyridinium triflate (3 mg, 0.014 mmol) were added. Upon stirring at room temperature for 3 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 85:15 hexanes:Et$_2$O to give product 5.18f (41 mg, 99% yield) as white solid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.97 (s, 1H), 7.76 (d, J = 7.1 Hz, 2H), 7.69 (d, J = 7.9 Hz, 1H), 7.38 (t, J = 7.8 Hz, 3H), 7.27 – 7.11 (m, 3H), 7.06 (d, J = 2.4 Hz, 1H), 4.53 (d, J = 9.2 Hz, 1H), 3.65 (s, 3H), 2.91 – 2.65 (m, 2H), 2.49 (dq, J = 12.5, 8.7 Hz, 1H), 2.10 – 1.90 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ (ppm) = 156.18, 136.86, 136.64, 128.26, 126.91, 126.76, 125.71, 122.28, 121.59, 119.64, 119.13, 118.24, 113.69, 111.40, 56.67, 39.88, 30.10, 29.74. IR (cm$^{-1}$): 3416, 3053, 2957, 2923, 2852, 1637, 1456, 1230, 1008, 796, 764, 695. HRMS (M + H)$^+$ = 290.1539 calculated for C$_{20}$H$_{20}$NO; experimental = 290.1542.
8.5.2 Synthetic Procedures for α-Hydroxy Methyl Enol Ethers

Synthesis of (±)-2-methoxy-3-methylcyclopent-2-enol (5.7b)

\[
\begin{array}{c}
\text{Me} - \text{CH(OH)} - \text{Me} \\
\text{5.10} \\
\text{Me} - \text{CH(OH)} - \text{Me} \\
\text{5.10b} \\
\text{Me} - \text{CH} = \text{O} \\
\text{5.7b}
\end{array}
\]

2-hydroxy-3-methylcyclopent-2-enone 5.10 (4.00 g, 35.71 mmol) was dissolved in anhydrous acetone (180 mL). K₂CO₃ (9.90 g, 71.43 mmol) and then methyl iodide (4.2 mL, 71.41 mmol) were added. The reaction mixture was stirred at room temperature for 48 hours until the completion of reaction, as monitored by TLC. After concentrating the reaction mixture in vacuo, the crude residue was partitioned in EtOAc/H₂O (200 mL, 1:1). The aqueous layer extracted with EtOAc (3 x 100 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated in vacuo to yield crude 2-methoxy-3-methylcyclopent-2-en-1-one 5.10b (4.50 g).

Crude 2-methoxy-3-methylcyclopent-2-en-1-one (4.50 g) was dissolved in CH₂Cl₂ (180 mL) and cooled to 0°C. DIBAL (53 mL, 1 M solution in toluene) was then added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 hour until the completion of reaction, as monitored by TLC. After recoothing the reaction mixture to 0°C, EtOAc (50 mL) was added slowly, followed by water (100 mL). The mixture was vigorously stirred for 30 minutes. The resulting solid precipitate was then filtered through pad of celite. Upon separation of layers, the aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were then washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified with flash column chromatography with 80 : 20 hexanes : EtOAc to give product 5.7b (3.50 g, 76% yield over 2 steps) as colorless oil.
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ (ppm) = 4.82 – 4.73 (m, 1H), 3.71 (s, 3H), 2.38 – 2.32 (m, 1H), 2.26 – 2.19 (m, 1H), 2.12 – 2.06 (m, 1H), 1.71 – 1.68 (m, 2H), 1.65 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ (ppm) = 152.28, 116.85, 73.58, 57.41, 31.33, 30.99, 12.31. IR (cm$^{-1}$): 3353, 2928, 2850, 1690, 1453, 1332, 1192, 964, 696. HRMS (M + H)$^+$ = 127.0754 calculated for C$_7$H$_{11}$O$_2$; experimental = 127.0749.

Synthesis of (±)-2-methoxy-3-methyl-1-phenylcyclopent-2-enol (5.12)

Crude 2-methoxy-3-methylcyclopent-2-enone 5.10 (500 mg, 3.97 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to 0°C. Phenylmagnesium chloride (5.9 mL, 2 M solution in THF) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was quenched with H$_2$O (15 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 2% TEA) with 85 : 15 hexanes : EtOAc to give product 5.12 (524 mg, 65% yield) as colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.47 – 7.41 (m, 2H), 7.34 (dd, J = 8.5, 6.9 Hz, 2H), 7.28 – 7.20 (m, 1H), 3.63 (s, 3H), 2.39 – 2.25 (m, 2H), 2.23 – 2.17 (m, 2H), 1.84 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) = 153.39, 146.36, 128.43, 126.97, 125.09, 116.99, 85.20, 59.67, 40.64, 31.14, 13.30. IR (cm$^{-1}$): 3449, 2937, 2847, 1685, 1447, 1325, 1214, 1029, 761, 674. HRMS (M + Na)$^+$ = 227.1043 calculated for C$_{13}$H$_{16}$NaO$_2$; experimental = 227.1035.
Synthesis of (±)-2-(tert-butyldimethylsilyloxy)-3-methyl-1-phenylcyclopent-2-enol (5.7a)

Crude 2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-one 5.10a (500 mg, 2.21 mmol) was dissolved in CH₂Cl₂ (5.5 mL) and cooled to 0°C. Phenylmagnesium chloride (2.2 mL, 2 M solution in THF) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was quenched with H₂O (15 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 2% TEA) with 85 : 15 hexanes : EtOAc to give product 5.7a (250 mg, 37% yield) as colorless oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.46 – 7.36 (m, 2H), 7.36 – 7.29 (m, 2H), 7.25 – 7.18 (m, 1H), 2.39 – 2.27 (m, 2H), 2.25 – 2.20 (m, 2H), 2.14 (s, 1H), 1.73 (s, 3H), 0.81 (s, 9H), 0.04 (s, 3H), -0.16 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 149.23, 146.39, 128.21, 126.87, 125.48, 116.00, 84.96, 40.17, 30.45, 26.09, 25.93, 18.50, 13.21, -3.66, -3.86. IR (cm⁻¹): 2929, 2855, 1686, 1327, 1251, 1214, 1068, 1004, 855, 836, 779, 699. HRMS (M + Na)⁺ = 327.1751 calculated for C₁₈H₂₈NaO₂Si; experimental = 327.1765.

Synthesis of 2-methoxy-3-methyl-1-phenylcyclohex-2-enol (5.20)
2-hydroxy-3-methylcyclohex-2-en-1-one S-5 (2.50 g, 19.84 mmol) was dissolved in anhydrous acetone (100 mL). K$_2$CO$_3$ (8.21 g, 59.52 mmol) and then methyl iodide (2.4 mL, 39.65 mmol) were added. The reaction mixture was stirred at room temperature for 96 hours until the completion of reaction, as monitored by TLC. After concentrating the reaction mixture in vacuo, the crude residue was partitioned in EtOAc/H$_2$O (60 mL, 1:1). The aqueous layer extracted with EtOAc (3 x 50 mL). The combined organic layers were then washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude material was purified with flash column chromatography with 85 : 15 hexanes : EtOAc to give product S-6 (2.00 g, 72% yield) as colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) = 3.56 (s, 3H), 2.37 (t, J = 8.0 Hz, 2H), 2.33 (t, J = 6.0 Hz, 2H), 1.93 – 1.82 (m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm) = 194.72, 149.27, 146.06, 59.83, 38.71, 31.43, 22.16, 17.54. IR (cm$^{-1}$): 2929, 1672, 1632, 1430, 1376, 1304, 1186, 1144, 1132, 1032, 999, 926, 847, 731. HRMS (M + H)$^+$ = 141.091 calculated for C$_8$H$_{13}$O$_2$; experimental = 141.0908.

Ketone S-6 (1.00 g, 7.14 mmol) was dissolved in CH$_2$Cl$_2$ (18 mL) and cooled to 0°C. Phenylmagnesium chloride (5.5 mL, 2 M solution in THF) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was quenched with H$_2$O (50 mL). The aqueous layer was then extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 90 : 10 hexanes : EtOAc to give product 5.20 (1.10 g, 70% yield) as colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.55 – 7.49 (m, 2H), 7.38 – 7.31 (m, 2H), 7.29 – 7.21 (m, 1H), 3.52 (s, 3H), 2.74 (bs, 1H), 2.26 – 2.08 (m, 2H), 2.07 – 1.86 (m, 2H), 1.81 (s, 3H),
1.71 – 1.61 (m, 1H), 1.58 – 1.46 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm) = 150.43, 146.92, 128.03, 127.05, 126.32, 121.23, 76.25, 61.48, 41.01, 31.28, 18.97, 16.87. IR (cm$^{-1}$): 3456, 2934, 2832, 1446, 1273, 1198, 1152, 1090, 1071, 759, 699. HRMS (M + Na)$^+$ = 241.1199 calculated for C$_{14}$H$_{18}$NaO$_2$; experimental = 241.1191.

Synthesis of (±)-1-(4-methoxyphenyl)-2-methoxy-3-methylcyclopent-2-enol (5.16a)

Crude 2-methoxy-3-methylcyclopent-2-enone 5.10b (250 mg, 1.98 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) and cooled to 0ºC. 4-Methoxyphenylmagnesium bromide (6.0 mL, 0.5 M solution in THF) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was quenched with H$_2$O (15 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 85 : 15 hexanes : EtOAc to give product 5.16a (375 mg, 80% yield) as colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ (ppm) = 7.36 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 3.80 (s, 3H), 3.63 (s, 3H), 2.55 (s, 1H), 2.39 – 2.28 (m, 1H), 2.30 – 2.15 (m, 3H), 1.83 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ (ppm) = 158.47, 153.47, 138.49, 126.22, 116.70, 113.63, 84.70, 59.51, 55.30, 40.59, 30.90, 13.17. IR (cm$^{-1}$): 3465, 2935, 2845, 1684, 1609, 1508, 1243, 1171, 1031, 829, 544. HRMS (M + Na)$^+$ = 257.1148 calculated for C$_{14}$H$_{18}$NaO$_3$; experimental = 257.1142.
Synthesis of (±)-1-(4-chlorophenyl)-2-methoxy-3-methylcyclopent-2-enol (5.16b)

Crude 2-methoxy-3-methylcyclopent-2-enone 5.10b (500 mg, 3.97 mmol) was dissolved in CH₂Cl₂ (20 mL) and cooled to 0°C. 4-Chlorophenylmagnesium bromide (6.0 mL, 1 M solution in THF) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was quenched with H₂O (15 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 85 : 15 hexanes : EtOAc to give product 5.16b (689 mg, 83% yield) as pale yellow oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.37 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 3.63 (s, 3H), 2.49 – 2.11 (m, 5H), 1.84 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 153.04, 144.93, 132.70, 128.51, 126.69, 117.20, 84.86, 59.69, 40.59, 31.11, 13.30. IR (cm⁻¹): 3443, 2968, 2936, 2848, 1902, 1684, 1488, 1324, 1089, 1012, 827, 537. HRMS (M + Na)⁺ = 261.0653 calculated for C₁₃H₁₅ClNaO₂; experimental= 261.0655.

Synthesis of (±)-2-methoxy-3-methyl-1-(3-methylthiophen-2-yl)cyclopent-2-enol (5.16c)

Crude 2-methoxy-3-methylcyclopent-2-enone 5.10b (200 mg, 1.56 mmol) was dissolved in CH₂Cl₂ (8.0 mL) and cooled to 0°C. 3-Methyl-2-thienylmagnesium bromide (6.4 mL, 0.5 M solution in THF) was then added dropwise, and the mixture was allowed to warm to room
temperature. After stirring for 1 hour, the reaction was quenched with H$_2$O (15 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 2% TEA) with 85 : 15 hexanes : EtOAc to give product 5.16c (250 mg, 70% yield) as yellow oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ (ppm) = 7.05 (d, J = 5.1 Hz, 1H), 6.80 (d, J = 5.1 Hz, 1H), 3.71 (s, 3H), 2.56 (bs, 1H), 2.44 – 2.33 (m, 2H), 2.30 – 2.24 (m, 2H), 2.23 (s, 3H), 1.82 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ (ppm) = 152.55, 143.42, 132.14, 131.83, 121.70, 117.49, 83.97, 59.47, 39.25, 31.07, 14.29, 13.12. IR (cm$^{-1}$): 3441, 2969, 2848, 1684, 1440, 1324, 1262, 1214, 1175, 1066, 991, 925, 855, 707. HRMS (M + Na)$^+$ = 247.0763 calculated for C$_{12}$H$_{16}$NaO$_2$S; experimental = 247.0761.

Synthesis of (±)-2-methoxy-1-octyl-3-phenylcyclopent-2-en-1-ol (5.17d)

Ketone S-7 (20 mg, 0.106 mmol) was dissolved in CH$_2$Cl$_2$ (0.5 mL) and cooled to 0°C. Octylmagnesium bromide (106 µL, 2 M solution in Et$_2$O) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was quenched with H$_2$O (15 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 90 : 10 hexanes : EtOAc to give product 5.17d (25 mg, 78% yield) as colorless oil.

$^1$H NMR (500 MHz, CDCl$_3$): δ (ppm) = 7.55 – 7.48 (m, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 3.70 (s, 3H), 2.72 (ddd, J = 15.0, 9.1, 3.8 Hz, 1H), 2.49 (ddd, J = 15.0,
8.7, 5.4 Hz, 1H), 2.18 (ddd, J = 13.6, 8.7, 3.8 Hz, 1H), 1.94 (ddd, J = 13.9, 9.1, 5.3 Hz, 1H), 1.78
(ddd, J = 13.2, 11.2, 4.7 Hz, 1H), 1.70 (ddd, J = 12.8, 11.3, 3.9 Hz, 1H), 1.31 (ddd, J = 18.0, 8.8,
4.3 Hz, 12H), 0.89 (t, J = 6.9 Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ (ppm) = 156.04, 136.41,
128.23, 127.84, 126.89, 84.76, 59.96, 39.16, 34.42, 32.09, 30.33, 29.78, 29.50, 29.14,
24.35, 22.87, 14.31. IR (cm⁻¹): 3382, 3055, 3023, 2924, 2852, 1639, 1493, 1459, 1444, 1260,
1068, 1016, 798, 760. HRMS (M*)$^{+}$ = 302.2245 calculated for C$_{20}$H$_{30}$O$_2$; experimental =
302.2240.

Synthesis of (±)-1-isopropyl-2-methoxy-3-phenylcyclopent-2-enol (5.17e)

Ketone S-7 (37 mg, 0.198 mmol) was dissolved in CH$_2$Cl$_2$ (1.0 mL) and cooled to 0°C.
Isopropylmagnesium bromide (492 μL, 2 M solution in THF) was then added dropwise, and the
mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was
quenched with H$_2$O (15 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL).
The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The
crude material was purified with flash column chromatography with 90 : 10 hexanes : EtOAc to
give product 5.17e (28 mg, 61% yield) as colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) = δ 7.49 (d, J = 7.7 Hz, 2H), 7.34 (t, J = 7.7 Hz,
2H), 7.23 (t, J = 7.4 Hz, 1H), 3.68 (s, 3H), 2.76 (ddd, J = 15.2, 9.3, 4.1 Hz, 1H), 2.44 (ddd, J =
15.0, 9.0, 4.8 Hz, 1H), 2.18 (ddd, J = 13.5, 9.0, 4.0 Hz, 1H), 2.11 (p, J = 6.8 Hz, 1H), 1.90 (s,
1H), 1.76 (ddd, J = 14.0, 9.3, 4.8 Hz, 1H), 1.05 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H). $^{13}$C
NMR (100 MHz, CDCl$_3$): δ (ppm) = 155.66, 136.56, 128.21, 127.94, 126.90, 118.49, 87.89,
60.17, 34.82, 29.74, 29.51, 18.33, 16.55. IR (cm⁻¹): 3449, 3055, 3023, 2958, 2936, 2872, 2853, 1642, 1598, 1493, 1466, 1444, 1215, 1036, 1014, 798, 760, 694. HRMS (M + Na)⁺ = 255.1356 calculated for C₁₅H₂₀NaO₂; experimental = 255.1350.

Synthesis of (±)-2-methoxy-3-phenylcyclopent-2-enol (5.17f)

Ketone S-7 (35 mg, 0.186 mmol) was dissolved in CH₂Cl₂ (1.0 mL) and cooled to 0°C. DIBAL (279 μL, 1 M solution in toluene) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was quenched with H₂O (15 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column chromatography with 90 : 10 hexanes : EtOAc to give product 5.17f (27 mg, 76% yield) as colorless oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.67 (dd, J = 8.2, 1.4 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 5.01 (d, J = 7.6 Hz, 1H), 3.88 (s, 3H), 3.01 – 2.73 (m, 1H), 2.61 (ddd, J = 15.0, 8.9, 3.6 Hz, 1H), 2.50 – 2.21 (m, 1H), 1.9 – 1.81 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 154.62, 135.69, 128.25, 127.19, 126.57, 116.10, 74.08, 56.80, 30.67, 28.50. IR (cm⁻¹): 3327, 3052, 2922, 2850, 1737, 1640, 1597, 1353, 1234, 1154, 1123, 1038, 1005, 797, 758, 692. HRMS (M + Na)⁺ = 213.0886 calculated for C₁₂H₁₄NaO₂; experimental = 213.0894.

8.5.3 Synthetic Procedures for Variation in Nucleophilic Addition

Synthesis of (±)-5-methoxy-3-(2-methoxy-1-methyl-3-phenylcyclopent-2-en-1-yl)-1H-benzo[g]indole (5.21a)
Compound 5.19 (50 mg, 0.245 mmol) was dissolved in toluene (1.2 mL). 5-methoxy-1H-benzo[g]indole (97 mg, 0.490 mmol) and then pyridinium triflate (6 mg, 0.025 mmol) were added. Upon stirring at room temperature for 1.5 hours, the reaction mixture was then directly purified with flash column chromatography with 100% hexanes → 90 : 10 hexanes : Et₂O → 80 : 20 hexanes : Et₂O to give product 5.21a (89 mg, 94% yield) as colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 8.81 (bs, 1H), 8.31 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.62-7.60 (m, 2H), 7.53 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.42-7.36 (m, 3H), 7.27-7.23 (m, 1H), 7.03 (s, 1H), 6.45 (d, J = 2.3 Hz, 1H), 4.03 (s, 3H), 3.54 (s, 3H), 2.83-2.80 (m, 2H), 2.95 (ddd, J = 12.8, 7.1, 7.1 Hz, 1H), 2.20-2.15 (m, 1H), 1.75 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 158.04, 150.25, 143.38, 136.15, 129.04, 128.16, 127.49, 126.56, 125.95, 123.52, 123.36, 123.14, 122.95, 122.03, 119.09, 116.86, 99.49, 98.08, 59.23, 55.87, 48.73, 37.53, 29.73, 24.96. IR (neat): cm⁻¹; 3449, 2960, 2936, 2844, 1631, 1598, 1517, 1493, 1479, 1445, 1381, 1342, 1326, 1308, 1291, 1273, 1258, 1217, 1172, 1160, 1126, 1099, 1079, 1035, 1003, 986, 909, 834, 761, 731, 698, 463. HRMS (M + H)⁺ = 384.1958 calculated for C₂₆H₂₆NO₂; experimental = 384.1952.

Synthesis of (±)-2-(2-methoxy-1-methyl-3-phenylcyclopent-2-en-1-yl)-1H-pyrrole (5.21b)
Compound 5.19 (50 mg, 0.245 mmol) was dissolved in toluene (1.2 mL). Pyrrole (34 μL, 0.490 mmol) and then pyridinium triflate (6 mg, 0.025 mmol) were added. Upon stirring at room temperature for 1.5 hours, the reaction mixture was then directly purified with flash column chromatography with 100% hexanes → 90 : 10 hexanes : Et₂O to give product 5.21b (28 mg, 45% yield) as yellow oil.

¹H NMR (500 MHz, CDCl₃): δ  = 8.32 (bs, 1H), 7.56 (d, J = 9.7 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 6.73-6.72 (m, 1H), 6.18-6.16 (m, 1H), 6.06-6.04 (m, 1H), 3.48 (s, 3H), 2.78-2.68 (m, 2H), 2.32-2.26 (m, 1H), 2.07 (ddd, J = 12.7, 8.5, 5.7 Hz, 1H), 1.61 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ = 158.63, 138.23, 136.30, 128.08, 127.39, 126.37, 116.59, 116.29, 108.04, 103.37, 59.00, 48.14, 37.30, 29.61, 24.78. IR (neat): cm⁻¹; 3442, 2963, 2935, 2846, 1634, 1599, 1493, 1444, 1417, 1341, 1325, 1308, 1272, 1239, 1211, 1173, 1102, 1077, 1032, 988, 787, 763, 719, 697, 536. HRMS (M + H)⁺ = 254.1539 calculated for C₁₇H₂₀NO; experimental = 254.1529.

Synthesis of (±)-2-(2-methoxy-1-methyl-3-phenylcyclopent-2-en-1-yl)-3,5-dimethyl-1H-pyrrole (5.21c)

Compound 5.19 (50 mg, 0.245 mmol) was dissolved in toluene (1.2 mL). 2,4-Dimethylpyrrole (50 μL, 0.490 mmol) and then pyridinium triflate (6 mg, 0.025 mmol) were added. Upon stirring at room temperature for 30 minutes, the reaction mixture was then directly
purified with flash column chromatography with 100% hexanes → 95 : 5 hexanes : Et₂O → 90 : 10 hexanes : Et₂O → 80 : 20 hexanes : Et₂O to give product 5.21c (57 mg, 83% yield) as yellow oil.

¹H NMR (500 MHz, CDCl₃): δ = 8.01 (bs, 1H), 7.56-7.54 (m, 2H), 7.37-7.33 (m, 2H), 7.24-7.20 (m, 1H), 5.67 (d, J = 2.9 Hz, 1H), 3.56 (s, 3H), 2.79 (ddd, J = 14.8, 8.8, 6.8 Hz, 1H), 2.61 (ddd, J = 14.8, 9.0, 3.8 Hz, 1H), 2.36 (ddd, J = 12.8, 9.2, 6.8 Hz, 1H), 2.22 (s, 3H), 2.14-2.09 (m, 1H), 2.11 (s, 3H), 1.60 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 158.66, 136.55, 131.20, 128.56, 127.38, 126.27, 123.78, 116.40, 113.28, 109.51, 59.48, 48.73, 37.08, 29.77, 24.93, 12.95, 12.40. IR (cm⁻¹): 3442, 2963, 2935, 2846, 1634, 1599, 1493, 1444, 1417, 1341, 1325, 1308, 1272, 1239, 1211, 1173, 1102, 1077, 1032, 988, 787, 763, 719, 697, 536. HRMS (M + H)⁺ = 282.1852 calculated for C₁₉H₂₄NO; experimental = 282.1850.

Synthesis of (±)-1-(2-methoxy-1-methyl-3-phenylcyclopent-2-en-1-yl)azulene (5.21e)

Compound 5.19 (20 mg, 0.098 mmol) was dissolved in toluene (0.6 mL). Azulene (14 mg, 0.108 mmol) and then pyridinium triflate (2 mg, 0.010 mmol) were added. Upon stirring at room temperature for 30 minutes, the reaction mixture was then directly purified with flash column chromatography with 100% hexanes → 99.75 : 0.25 hexanes : Et₂O to give product 5.21e (19 mg, 62% yield) as a blue oil.

¹H NMR (500 MHz, CDCl₃): δ = 8.70 (d, J = 9.9 Hz, 1H), 8.30 (d, J = 9.7 Hz, 1H), 7.96 (d, J = 3.9 Hz, 1H), 7.69-7.63 (m, 2H), 7.55 (t, J = 9.8 Hz, 1H), 7.41-7.37 (m, 2H), 7.34 (d, J = 4.0 Hz, 1H), 7.25-7.21 (m, 1H), 7.08 (ddd, J = 9.7, 9.7, 7.3 Hz, 2H), 3.31 (s, 3H), 2.95 (dt, J =
14.7, 8.3 Hz, 1H), 2.79 (ddd, J = 14.7, 9.3, 2.6 Hz, 1H), 2.57 (dt, J = 12.9, 8.9 Hz, 1H), 2.16 
(ddd, J = 12.9, 8.5, 2.6 Hz, 1H), 1.92 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 160.67, 141.54, 
137.45, 137.06, 136.78, 135.76, 135.66, 135.55, 135.04, 128.08, 127.21, 125.86, 122.37, 121.83, 
116.28, 114.00, 54.30, 49.75, 40.37, 29.49, 26.36. IR (neat): cm\(^{-1}\): 3085, 3064, 3048, 3024, 2962, 
2930, 2871, 2845, 1735, 1628, 1598, 1573, 1493, 1454, 1444, 1397, 1371, 1353, 1342, 1273, 1250, 1219, 
1170, 1130, 1103, 1078, 1063, 1051, 1032, 1004, 760, 743, 695. HRMS (M + 
Na\(^{+}\)) = 337.1563 calculated for C\(_{23}\)H\(_{22}\)NO; experimental = 337.1575.

Synthesis of (±)-5-(2-methoxy-1-methyl-3-phenylcyclopent-2-en-1-yl)furan-2(5H)-one (5.21f)

![Diagram](image)

Compound 5.19 (50 mg, 0.245 mmol) was dissolved in toluene (1.2 mL). 2-(Trimethylsiloxy)furan (82 µL, 0.490 mmol) and then pyridinium triflate (6 mg, 0.025 mmol) were added. Upon stirring at room temperature for 72 hours, the reaction mixture was then directly purified with flash column chromatography with 100% hexanes → 90 : 10 hexanes : Et\(_2\)O → 80 : 20 hexanes : Et\(_2\)O to give product 5.21f as a single diastereomer (41 mg, 62% yield) as a pale yellow crystal.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta (ppm) = 7.48 (dd, J = 5.8, 1.4 Hz, 1H), 7.40-7.31 (m, 4H), 
7.25-7.21 (m, 1H), 6.17 (dd, J = 5.7, 2.1 Hz, 1H), 5.09 (t, J = 1.7 Hz, 1H), 3.53 (s, 3H), 2.66-2.58 
(m, 1H), 2.45 (ddd, J = 15.0, 8.9, 6.0 Hz, 1H), 1.77 (ddd, J = 13.3, 8.9, 4.2 Hz, 1H), 1.65-1.58 
(m, 1H), 1.43 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 173.32, 155.40, 155.11, 136.11, 128.08, 
127.92, 126.84, 122.21, 117.70, 88.39, 60.11, 52.85, 31.13, 28.55, 22.91. IR (neat): cm\(^{-1}\): 3056, 
3023, 2966, 2937, 2851, 1787, 1753, 1644, 1599, 1494, 1445, 1374, 1312, 1273, 1256, 1216,
Synthesis of (±)-(2,3-dimethoxy-3-methylcyclopent-1-en-1-yl)benzene (5.21g)

Compound 5.19 (100 mg, 0.490 mmol) was dissolved in toluene (2.4 mL). 4Å molecular sieves (118 mg), methanol (40 μL, 0.980 mmol), and then pyridinium triflate (12 mg, 0.050 mmol) were added. Upon stirring at room temperature for 23 hours, the reaction mixture was then directly purified with flash column chromatography (buffered with 2% TEA) with 100% hexanes → 85 : 15 hexanes : Et₂O to give product 5.21g (74 mg, 69% yield) as colorless oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.61-7.58 (m, 2H), 7.38-7.34 (m, 2H), 7.27-7.23 (m, 1H), 3.77 (s, 3H), 3.30 (s, 3H), 2.68 (ddd, J = 15.1, 8.9, 5.1 Hz, 1H), 2.59 (ddd, J = 15.1, 8.9, 4.4 Hz, 1H), 2.20 (ddd, J = 13.6, 9.0, 4.4 Hz, 1H), 1.91 (ddd, J = 14.0, 8.9, 5.1 Hz, 1H), 1.52 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 153.71, 135.96, 128.08, 127.43, 126.71, 119.66, 86.77, 58.46, 50.55, 31.34, 28.92, 24.90. IR (cm⁻¹): 2968, 2934, 2850, 1638, 1599, 1493, 1444, 1370, 1345, 1328, 1308, 1279, 1250, 1218, 1189, 1154, 1125, 1089, 1064, 1031, 988, 911, 876, 856, 760, 719, 693, 653, 596, 534. HRMS (M + Na)⁺ = 241.1199 calculated for C₁₄H₁₈NaO₂; experimental = 241.1211.

Synthesis of (±)-3-((2-methoxy-1-methyl-3-phenylcyclopent-2-en-1-yl)oxy)propyl)benzene (5.21h)
Compound 5.19 (50 mg, 0.245 mmol) was dissolved in toluene (1.2 mL). 3-Phenyl-1-propanol (67 μL, 0.490 mmol) and then pyridinium triflate (6 mg, 0.025 mmol) were added. Upon stirring at room temperature for 1 hour, the reaction mixture was then directly purified with flash column chromatography (buffered with 2% TEA) with 100% hexanes → 98 : 2 hexanes : Et₂O → 95 : 5 hexanes : Et₂O → 90 : 10 hexanes : Et₂O to give product 5.21h (31 mg, 39% yield) as colorless oil.

\[ ^1H \text{ NMR (500 MHz, CDCl}_3\] : δ = 7.57 (d, J = 7.9 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.29-7.16 (m, 6H), 3.75 (s, 3H), 3.43 (t, J = 6.6 Hz, 2H), 2.71 (t, J = 7.8 Hz, 2H), 2.62 (ddd, J = 15.0, 8.8, 5.4 Hz, 1H), 2.54 (ddd, J = 15.1, 8.9, 4.4 Hz, 1H), 2.18-2.12 (m, 1H), 1.95-1.87 (m, 3H), 1.51 (s, 3H).

\[ ^{13}\text{C NMR (125 MHz, CDCl}_3\] : δ = 154.48, 142.20, 136.02, 128.44, 128.26, 128.05, 127.37, 126.59, 125.69, 119.09, 86.25, 62.02, 58.45, 32.57, 32.30, 31.96, 28.79, 25.13. IR (neat): cm⁻¹; 3084, 3058, 3025, 2931, 2853, 1707, 1638, 1600, 1494, 1453, 1445, 1369, 1344, 1329, 1308, 1279, 1252, 1217, 1187, 1121, 1087, 1065, 1030, 988, 911, 862, 797, 761, 746, 695, 581, 543, 493. HRMS (M + Na)⁺ = 345.1825 calculated for C_{22}H_{26}N_{32}O_{12} ; experimental = 345.1835

Synthesis of (±)-(2-methoxy-1-methyl-3-phenylcyclopent-2-en-1-yl)(phenyl)sulfane (5.21j)

Compound 5.19 (50 mg, 0.245 mmol) was dissolved in toluene (1.2 mL). Thiophenol (50 μL, 0.490 mmol) and then pyridinium triflate (6 mg, 0.025 mmol) were added. Upon stirring
at room temperature for 1.5 hours, the reaction mixture was then directly purified with flash column chromatography with 100% hexanes → 90 : 10 hexanes : Et₂O → 80 : 20 hexanes : Et₂O to give product 5.21j (57 mg, 78% yield) as colorless oil.

¹H NMR (400 MHz, CDCl₃): δ = 7.62-7.59 (2H, m), 7.38-7.19 (8H, m), 3.73 (3H, s), 2.36-2.26 (2H, m), 2.08-2.01 (1H, m), 1.86-1.78 (1H, m), 1.59 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ = 155.42, 136.91, 136.17, 132.93, 128.64, 128.32, 127.97, 127.53, 126.59, 119.37, 62.55, 60.08, 36.52, 30.11, 25.98. IR (neat): cm⁻¹: 3054, 3020, 3962, 2924, 2851, 1633, 1598, 1582, 1275, 1249, 1210, 1173, 1157, 1104, 989, 915, 830, 803, 761, 749, 692, 655, 618, 560, 536, 499, 478. HRMS (M + Na)⁺ = 319.1127 calculated for C₁₉H₂₀NaOS; experimental = 319.1140.

Synthesis of (±)-2-(2-methoxy-3-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)-1H-pyrrole (5.22b)

Compound 5.20 (50 mg, 0.229 mmol) was dissolved in toluene (1.2 mL). Pyrrole (32 μL, 0.458 mmol) and then pyridinium triflate (25 mg, 0.115 mmol) were added. Upon stirring at room temperature for 18 hours, the reaction mixture was then directly purified with flash column chromatography with 100% hexanes → 90 : 10 hexanes : Et₂O → 80 : 20 hexanes : Et₂O to give product 5.22b (55 mg, 89% yield) as colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 8.68 (bs, 1H), 7.39-7.36 (m, 2H), 7.34-7.31 (m, 2H), 7.24-7.20 (m, 1H), 6.72 (ddd, J = 2.6, 2.6, 1.5 Hz, 1H), 6.17 (dd, J = 6.0, 2.7 Hz, 1H), 6.03-6.02 (m, 1H), 3.17 (s, 3H), 2.56-2.49 (m, 2H), 2.34-2.28 (m, 1H), 2.23-2.18 (m, 1H), 1.89-1.71 (m,
3H), 1.53 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 156.11, 140.96, 138.85, 128.26, 128.15, 126.42, 120.79, 116.18, 107.68, 102.95, 60.85, 40.34, 38.25, 31.56, 27.20, 19.92. IR (cm$^{-1}$): 3443, 2932, 2865, 2834, 1644, 1598, 1554, 1492, 1442, 1416, 1368, 1289, 1271, 1245, 1229, 1193, 1142, 1122, 1078, 1034, 992, 950, 884, 832, 786, 762, 716, 698, 634, 609, 548, 502, 464. HRMS (M + H)$^+$ = 268.1696 calculated for C$_{18}$H$_{22}$NO; experimental = 268.1702.

Synthesis of (±)-2-(2-methoxy-3-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)azulene (5.22e)

![Chemical structure](image)

Compound 5.20 (20 mg, 0.092 mmol) was dissolved in toluene (0.46 mL). Azulene (13 mg, 0.101 mmol) and then pyridinium triflate (10 mg, 0.046 mmol) were added. Upon stirring at room temperature for 39 hours, the reaction mixture was then directly purified with flash column chromatography with 100% hexanes $\rightarrow$ 99.5 : 0.5 hexanes : Et$_2$O to give product 5.22e (12 mg, 39% yield) as blue oil.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.87$ (d, J = 9.9 Hz, 1H), 8.29 (d, J = 9.4 Hz, 1H), 7.99 (d, J = 3.9 Hz, 1H), 7.56 (t, J = 9.8 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.36-7.33 (m, 3H), 7.25-7.21 (m, 1H), 7.10 (dt, J = 13.0, 9.9 Hz, 2H), 3.04 (s, 3H), 2.74-2.69 (m, 1H), 2.66-2.59 (m, 1H), 2.45-2.39 (m, 1H), 1.96-1.87 (m, 2H), 1.89 (s, 3H), 1.84-1.78 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 158.94, 141.49, 141.37, 137.29, 136.92, 136.74, 136.53, 135.14, 134.31, 128.38, 128.23, 126.31, 122.23, 121.24, 118.27, 116.41, 61.10, 42.63, 40.88, 31.69, 26.56, 20.54. IR (neat): cm$^{-1}$: 2967, 2933, 2863, 2834, 1643, 1571, 1455, 1442, 1396, 1136, 1025, 1009, 999, 762, 742, 698. HRMS (M + H)$^+$ = 329.1900 calculated for C$_{24}$H$_{25}$O; experimental = 329.1911.
Synthesis of (±)-6-methoxy-5-methyl-5-(3-phenylpropoxy)-2,3,4,5-tetrahydro-1′,1′-biphenyl (5.22h)

![Chemical structure of 5.20 and 5.22h](image)

Compound 5.20 (50 mg, 0.229 mmol) was dissolved in toluene (1.2 mL). 3-Phenyl-1-propanol (62 μL, 0.458 mmol) and then pyridinium triflate (5 mg, 0.023 mmol) were added. Upon stirring at room temperature for 4 hours, the reaction mixture was then directly purified with flash column chromatography (buffered with 2% TEA) with 100% hexanes → 98 : 2 hexanes : Et₂O → 95 : 5 hexanes : Et₂O → 90 : 10 hexanes : Et₂O to give product 5.22h (72 mg, 94% yield) as colorless oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.36-7.17 (m, 10H), 3.53-3.47 (m, 2H), 3.28 (s, 3H), 2.76-2.72 (m, 2H), 2.38 (t, J = 5.9 Hz, 1H), 2.06 (ddd, J = 13.4, 7.8, 3.0 Hz, 1H), 1.96-1.85 (m, 3H), 1.69-1.62 (m, 1H), 1.61-1.55 (m, 1H), 1.42 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ = 154.00, 142.39, 140.54, 128.51, 128.32, 128.25, 120.08, 126.54, 125.63, 123.46, 75.94, 61.62, 60.76, 35.07, 32.61, 32.23, 31.43, 23.75, 19.70. IR (neat): cm⁻¹: 3082, 3058, 3025, 2932, 2862, 2833, 1645, 1600, 1493, 1475, 1453, 1443, 1385, 1365, 1339, 1299, 1275, 1237, 1191, 1156, 1131, 1104, 1071, 1043, 1011, 990, 961, 930, 909, 881, 858, 805, 759, 747, 696, 666, 656, 653, 633, 620, 599, 577, 541, 494. HRMS (M + Na)⁺ = 359.1982 calculated for C₂₃H₂₈NaO₂; experimental = 359.1987.

Synthesis of (±)-(2-methoxy-3-methyl-3,4,5,6-tetrahydro-[1,1′-biphenyl]-3-yl)(phenyl)sulfane (5.22j)
Compound 5.20 (50 mg, 0.229 mmol) was dissolved in toluene (1.2 mL). Thiophenol (47 μL, 0.458 mmol) and then pyridinium triflate (5 mg, 0.023 mmol) were added. Upon stirring at room temperature for 20 hours, the reaction mixture was then directly purified with flash column chromatography (buffered with 2% TEA) with 100% hexanes → 98 : 2 hexanes : Et₂O → 95 : 5 hexanes : Et₂O → 90 : 10 hexanes : Et₂O → 80 : 20 hexanes : Et₂O to give product 5.22j (66 mg, 93% yield) as colorless oil.

1H NMR (500 MHz, CDCl₃): δ = 7.63-7.61 (m, 2H), 7.39-7.32 (m, 7H), 7.26-7.22 (m, 1H), 3.30 (s, 3H), 2.43-2.29 (m, 2H), 2.09-2.02 (m, 1H), 2.01-1.95 (m, 1H), 1.72-1.66 (m, 2H), 1.46 (s, 3H). 13C NMR (125 MHz, CDCl₃): δ = 154.21, 140.51, 137.36, 132.67, 129.07, 128.61, 128.45, 128.32, 128.16, 127.53, 127.16, 126.63, 122.88, 61.40, 54.39, 37.45, 31.33, 26.34, 19.49. IR (neat): cm⁻¹; 3054, 3019, 2930, 2861, 2833, 1637, 1598, 1491, 1475, 1438, 1368, 1335, 1287, 1265, 1236, 1194, 1168, 1144, 1126, 1084, 1068, 1039, 1016, 1001, 990, 956, 922, 866, 849, 802, 748, 692, 645, 633, 609, 585, 566, 554, 524, 480. HRMS (M + Na)⁺ = 333.1284 calculated for C₂₀H₂₂NaOS; experimental = 333.1273.

8.5.4 Synthetic Procedures for Applications of Indole Containing Quaternary Centers

Synthesis of (±)-2-(1H-indol-3-yl)-2-methyl-5-phenylcyclopentanone (5.25)
Compound 5.24 (50 mg, 0.165 mmol) was dissolved in THF (1.7 mL). After cooling the solution to -20°C, TsOH•H₂O (63 mg, 0.320 mmol) was added, and the reaction mixture was stirred at this temperature for 72 hours until the completion of reaction, as monitored by TLC. The reaction mixture was neutralized with aqueous sodium bicarbonate (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were then washed with water, followed by brine, and concentrated in vacuo. The crude residue was further purified by flash column chromatography with 90:10 hexanes : EtOAc to afford product 5.25 as a 5.5:1 mixture of diastereoisomers (35 mg, 73% yield) as a white solid.

Major diastereomer: ¹H NMR (500 MHz, CDCl₃): δ (ppm) = 8.00 (bs, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.27 – 7.18 (m, 5H), 7.14 (d, J = 7.1 Hz, 1H), 7.12 – 7.08 (m, 2H), 6.77 (d, J = 2.5 Hz, 1H), 3.49 (dd, J = 10.9, 8.4 Hz, 1H), 2.99 – 2.92 (m, 1H), 2.43 – 2.35 (m, 1H), 2.14 – 2.03 (m, 2H), 1.64 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 218.12, 139.08, 137.57, 128.67, 128.38, 126.93, 125.50, 122.43, 122.40, 120.94, 119.71, 115.94, 111.70, 55.09, 50.17, 35.88, 28.12, 24.86. IR (cm⁻¹): 3334, 2959, 2922, 2853, 1722, 1457, 1259, 1089, 1022, 798, 742. HRMS (M + H)⁺ = 290.1545 calculated for C₂₀H₂₀NO; experimental = 290.1539.

Synthesis of (±)-3-(2-methoxy-1-methyl-3-phenylcyclopentyl)-1H-indole (5.26)
Compound 5.24 (50 mg, 0.165 mmol) was dissolved in THF (1.7 mL), and Pd/C (100 mg) was then added. The reaction mixture was stirred at room temperature under a hydrogen balloon for 24 hours until the completion of reaction, as monitored by TLC. The suspension was then filtered through a pad of celite and washed with EtOAc. After concentrating the filtrate in vacuo, the crude residue was further purified by flash column chromatography with 85:15 hexanes : EtOAc to afford product 5.26 as a 2.3:1 mixture of diastereoisomers (33 mg, 64% yield) as a white solid.

Major diastereomer: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ (ppm) = 7.96 (bs, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 7.3 Hz, 2H), 7.37 – 7.30 (m, 3H), 7.23 (dd, J = 7.3, 7.3 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.15 – 7.06 (m, 1H), 6.99 (d, J = 2.4 Hz, 1H), 3.91 (d, J = 4.2 Hz, 1H), 3.73 (td, J = 9.5, 4.2 Hz, 1H), 2.71 – 2.58 (m, 1H), 2.50 (s, 3H), 2.38 – 2.23 (m, 2H), 1.98 (ddd, J = 12.6, 8.0, 4.9 Hz, 1H), 1.56 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ (ppm) = 141.72, 137.23, 129.39, 128.08, 126.78, 126.23, 122.83, 121.63, 121.20, 121.11, 118.92, 111.42, 92.89, 59.84, 48.81, 48.67, 36.10, 28.13, 27.88. IR (cm$^{-1}$): 3290, 2960, 2925, 1455, 1261, 1092, 1014, 802, 738, 698. HRMS (M + H)$^+$ = 328.1672 calculated for C$_{21}$H$_{23}$NNaO; experimental = 328.1670.

Synthesis of ($\pm$)-1-(3-(2-methoxy-1-methyl-3-phenylcyclopent-2-enyl)-1H-indol-1-yl)ethanone (5.27)
A solution of diisopropylamine (0.7 mL, 4.95 mmol) in THF (8 mL) was cooled to 0°C. n-BuLi (1.98 mL, 2.5M in hexane) was then added dropwise. After stirring for 30 minutes, a solution of compound 5.24 (500 mg, 1.65 mmol) in THF (8 mL) was added dropwise. Upon further stirring for 60 minutes, acetic anhydride (0.47 mL, 4.95 mmol) was added. The reaction was continued for another 60 minutes until the completion of reaction, as monitored by TLC. The reaction was then quenched with saturated aqueous solution of NH₄Cl (10 mL), and the mixture was partitioned between EtOAc/H₂O (50 mL, 1:1). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were then washed thoroughly with water, followed by brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was further purified by flash column chromatography with 85:15 hexanes : EtOAc to afford compound 5.27 (500 mg, 88%) as white solid.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 8.50 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.7 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H), 7.38 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 10.2 Hz, 1H), 7.27 (dd, J = 7.5, 7.5 Hz, 2H), 3.49 (s, 3H), 3.02 – 2.90 (m, 1H), 2.80 (dd, J = 14.9, 9.4, 3.2 Hz, 1H), 2.67 (s, 3H), 2.51 (ddd, J = 13.0, 9.3, 7.5 Hz, 1H), 2.11 – 1.99 (m, 1H), 1.76 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 168.63, 158.94, 136.83, 136.79, 129.62, 129.26, 128.30, 127.72, 126.57, 125.16, 123.56, 121.47, 120.85, 116.93, 116.04, 59.55, 48.37, 36.38, 30.29, 24.63, 24.32. IR (cm⁻¹): 2962, 2936, 1698, 1633, 1492, 1449, 1379, 1343, 1228, 994, 933, 909, 731, 697. HRMS (M + H)⁺ = 346.1802 calculated for C₂₃H₂₄NO₂; experimental = 346.1800.
Synthesis of (±)-1-(3-(1-methoxy-2-methyl-5-phenyl-6-oxabicyclo[3.1.0]hexan-2-yl)-1H-indol-1-yl)ethanone (5.28)

Compound 5.27 (40 mg, 0.116 mmol) was dissolved in dichloromethane (1.3 mL), and the solution was then cooled to -30°C. Meta-chloroperoxybenzoic acid (31 mg, 0.139 mmol, 77% purity) was then added dropwise as a solution in dichloromethane (1 mL). The reaction mixture was slowly warmed to room temperature and then stirred for 2 hours until the completion of reaction, as monitored by TLC. The reaction mixture was neutralized with aqueous sodium bicarbonate (5 mL) and extracted with dichloromethane (3 x 5 mL). The combined organic layers were then washed with water, followed by brine, and then concentrated in vacuo. The crude residue was further purified by flash column chromatography with 90:10 hexanes : EtOAc to afford product 5.28 as a 5:1 mixture diastereomers (35 mg, 83% yield) as a white solid.

Major diastereomer: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ (ppm) = 8.53 (d, $J = 8.1$ Hz, 1H), 7.71 (d, $J = 7.9$ Hz, 1H), 7.48 (d, $J = 6.9$ Hz, 3H), 7.42 (t, $J = 7.5$ Hz, 2H), 7.40 – 7.34 (m, 2H), 7.32 – 7.28 (m, 1H), 3.48 (s, 3H), 2.57 (s, 3H), 2.23 – 2.10 (m, 2H), 2.08 – 1.98 (m, 1H), 1.82 (s, 3H), 1.81 – 1.71 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ (ppm) = 168.73, 136.67, 136.08, 129.28, 128.58, 127.99, 126.54, 125.15, 123.44, 122.79, 120.90, 117.19, 97.57, 73.79, 54.91, 45.51, 33.74, 29.71, 24.33, 21.71. IR (cm$^{-1}$): 2965, 2928, 1705, 1449, 1391, 1229, 1199, 1073, 1023, 1009, 907, 730, 697. HRMS (M + H)$^+$ = 362.1751 calculated for C$_{23}$H$_{24}$NO$_3$; experimental = 362.1756.
Synthesis of (±)-methyl 2-(1-acetyl-1H-indol-3-yl)-2-methyl-5-oxo-5-phenylpentanoate (5.29)

Compound 5.27 (50 mg, 0.145 mmol) was dissolved in a mixture of H₂O/CCl₄/CH₃CN (1.3:1:1, 0.05 M). NaIO₄ (124 mg, 0.579 mmol) was then added, followed by RuCl₃ (1.5 mg, 0.0073 mmol). The reaction mixture was stirred at room temperature for 1.5 hours until the completion of reaction, as monitored by TLC. The reaction mixture was quenched with saturated aqueous Na₂S₂O₃ (5mL), stirred for 15 min, and then extracted with dichloromethane (3 x 5 mL). The combined organic layers were then washed with water, followed by brine, and then concentrated in vacuo. The crude residue was further purified by flash column chromatography with 80:20 hexanes : EtOAc to afford product 5.29 (40 mg, 73% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 8.47 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 7.3 Hz, 2H), 7.54 (d, J = 7.1 Hz, 2H), 7.42 (dd, J = 7.7, 7.7 Hz, 2H), 7.39 – 7.33 (m, 2H), 7.26 (dd, J = 7.4, 7.4 Hz, 1H), 3.68 (s, 3H), 3.05 – 2.89 (m, 2H), 2.66 (s, 3H), 2.61 (dt, J = 9.2, 6.2 Hz, 2H), 1.72 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ (ppm) = 199.55, 175.89, 168.61, 136.79, 136.51, 133.32, 128.76, 128.73, 128.20, 125.52, 125.34, 123.85, 122.19, 120.09, 116.9, 52.66, 45.42, 34.21, 32.11, 24.34, 23.15. IR (cm⁻¹): 2949, 2926, 1728, 1706, 1685, 1452, 1380, 1332, 1295, 1230, 1105, 746. HRMS (M + Na)⁺ = 400.1519 calculated for C₂₃H₂₃NNaO₄; experimental = 400.1519.
8.6 Synthesis and Characterization of Novel Chapter 6 Compounds

8.6.1 Synthetic Procedures for \(\gamma\)-Indole Adducts

Synthesis of \((Z)-3-(2-(2-((\text{tert-butyl}dimo\text{ethyl}silyl})\text{oxy})-3\text{-methylcyclopent}-2\text{-en}-1\text{-ylidene})\text{propyl})-1\text{H-indole}\) (6.11)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). Indole (24 mg, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.02 mmol). The reaction was allowed to stir for 2.5 hours, and the mixture was purified directly using 100% hexanes \(\rightarrow\) 95 : 5 hexanes : Et\(_2\)O \(\rightarrow\) 90 : 10 hexanes : Et\(_2\)O to give compound 6.11 in 99% yield as a colorless oil (68 mg, 0.184 mmol).

\(^1\text{H NMR} (400 \text{ MHz}) \delta = 7.84 (bs, 1H), 7.65 (d, J = 7.9 \text{ Hz}, 1H), 7.32 (d, J = 8.1 \text{ Hz}, 1H), 7.16 (t, J = 7.7 \text{ Hz}, 1H), 7.08 (t, J = 7.7 \text{ Hz}, 1H), 6.94 (s, 1H), 3.94 (s, 2H), 2.46-2.43 (m, 2H), 2.25-2.22 (m, 2H), 1.74 (s, 3H), 1.62 (s, 3H), 0.98 (s, 9H), 0.17 (s, 6H). \(^{13}\text{C NMR} (100 \text{ MHz}) \delta = 148.64, 136.28, 134.87, 128.14 124.32, 121.99, 121.50, 121.41, 119.63, 118.92, 116.16, 110.71, 30.69, 28.53, 27.41, 26.03, 20.17, 18.31, 14.43, -3.69. \text{IR f} (\text{cm}^{-1}) = 3415, 2953, 2928, 2904, 2856, 1638, 1472, 1456, 1419, 1382, 1334, 1303, 1253, 1215, 1172, 1091, 1008, 930, 869, 839, 780, 741, 685, 479. \text{HRMS} (M + H)^+ = 368.2404 \text{ calculated for C}_{23}\text{H}_{34}\text{NSi}; 368.2399 \text{ experimental.}
Synthesis of (Z)-2-(1-(1H-indol-3-yl)propan-2-ylidene)-5-methylcyclopentan-1-one (6.13)

Alcohol 6.10 (20 mg, 0.0745 mmol) was dissolved in toluene (0.370 mL). Indole (10 mg, 0.082 mmol) was then added, followed by triflic acid (1 µL, 0.01 mmol). The reaction was allowed to stir for 10 minutes, and the mixture was purified directly using 100% hexanes → 95 : 5 hexanes : Et₂O → 80 : 20 hexanes : Et₂O to give compound 6.11 in 45% yield (12 mg, 0.033 mmol) and 6.12 in 48% yield (9 mg, 0.036 mmol), both as colorless oils.

Compound 6.12: ¹H NMR (500 MHz) δ = 7.96 (bs, 1H), 7.60-7.58 (m, 1H), 7.34-7.32 (m, 1H), 7.18-7.15 (m, 1H), 7.10-7.07 (m, 1H), 7.05-7.04 (m, 1H), 4.32 (d, J = 14.3 Hz, 1H), 4.23 (d, J = 14.3 Hz, 1H), 2.61 (dd, J = 16.1, 7.9 Hz, 1H), 2.50-2.43 (m, 1H), 2.39-2.33 (m, 1H), 2.21-2.14 (m, 1H), 1.80 (s, 3H), 1.26 (s, 3H). ¹³C NMR (125 MHz) δ = 209.08, 150.07, 136.11, 130.85, 127.82, 122.55, 121.83, 119.32, 114.03, 110.93, 45.65, 29.70, 28.28, 28.12, 25.72, 21.85, 14.86. IR f (cm⁻¹) = 3408, 3361, 2958, 2925, 2852, 1696, 1621, 1456, 1436, 1371, 1339, 1250, 1229, 1196, 1159, 1094, 1010, 991, 964, 858, 771, 741, 425. HRMS (M + H)+ = 254.1539 calculated for C₁₇H₂₀NO; 254.1546 experimental.
Synthesis of (Z)-3-(2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)propyl)-2-phenyl-1H-indole (6.14a)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.930 mL). 2-Phenylindole (40 mg, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.02 mmol). The reaction was allowed to stir for 30 minutes, and the mixture was purified directly with 100% hexanes → 98 : 2 hexanes : Et₂O → 95 : 5 hexanes : Et₂O to give compound 6.14a in 91% yield as a colorless oil (75 mg, 0.169 mmol).

¹H NMR (400 MHz) δ = 7.94 (bs, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.65-7.63 (m, 2H), 7.49-7.45 (m, 2H), 7.42-7.37 (m, 2H), 7.28-7.24 (m, 1H), 7.22-7.18 (m, 1H), 4.24 (s, 2H), 2.45-2.42 (m, 2H), 2.31-2.28 (m, 2H), 1.86 (s, 3H), 1.49 (s, 3H), 1.06 (s, 9H), 0.27 (s, 6H). ¹³C NMR (100 MHz) δ = 148.74, 135.75, 135.05, 134.97, 133.42, 128.34, 127.12, 124.15, 121.77, 120.08, 119.31, 112.67, 110.46, 30.70, 27.74, 27.34, 25.97, 19.52, 18.22, 14.34, -3.77. IR ν (cm⁻¹) = 3404, 3054, 2955, 2929, 2856, 1703, 1638, 1619, 1531, 1487, 1471, 1457, 1382, 1334, 1304, 1264, 1215, 1154, 1092, 1027, 1008, 967, 925, 869, 839, 780, 765, 735, 700, 575, 531, 494. HRMS (M + H)⁺ = 444.2717 calculated for C₂₉H₃₈NOSi; 444.2713 experimental.
Synthesis of (Z)-5-bromo-3-(2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)propyl)-1H-indole (6.14b)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). 5-Bromoindole (40 mg, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.02 mmol). The reaction was allowed to stir for 30 minutes, and the mixture was purified directly with 100% hexanes → 98 : 2 hexanes : Et₂O → 95 : 5 hexanes : Et₂O to give compound 6.14b in 91% yield as a colorless oil (75 mg, 0.169 mmol).

¹H NMR (400 MHz) δ = 7.88 (bs, 1H), 7.79 (s, 1H), 7.23-7.16 (m, 2H), 6.94 (s, 1H), 3.85 (s, 2H), 2.42-2.40 (m, 2H), 2.24-2.22 (m, 2H), 1.74 (s, 3H), 1.58 (s, 3H), 0.97 (s, 9H), 0.15 (s, 6H). ¹³C NMR (100 MHz) δ = 148.41, 135.21, 134.96, 139.83, 124.90, 124.26, 123.13, 122.54, 120.83, 116.00, 112.33, 112.12, 30.67, 28.40, 27.43, 25.98, 20.14, 18.28, 14.31, -3.79. IR f (cm⁻¹) = 3421, 2954, 2928, 2904, 2856, 1705, 1638, 1460, 1382, 1361, 1332, 1253, 1215, 1164, 1092, 1042, 1006, 970, 930, 908, 868, 839, 780, 734, 685, 617, 583, 536, 474. HRMS (M + H)⁺ = 446.1509 calculated for C₂₃H₃₃NOBrSi; 446.1496 experimental.

Synthesis of (Z)-3-(2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)propyl)-5-methoxy-1H-indole (6.14c)
Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). 5-Methoxylindole (30 mg, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.02 mmol). The reaction was allowed to stir for 2.5 hours, and the crude mixture was then purified with 100% hexanes → 90 : 10 hexanes : Et₂O to give compound 6.14c in 97% yield as pale yellow crystals (72 mg, 0.180 mmol).

¹H NMR (400 MHz) δ = 7.73 (bs, 1H), 7.20-7.17 (m, 2H), 6.94 (s, 1H), 6.80 (d, J = 7.9 Hz, 1H), 3.87 (s, 2H), 3.79 (s, 3H), 2.42-2.41 (m, 2H), 2.23-2.20 (m, 2H), 1.71 (s, 3H), 1.60 (s, 3H), 0.99 (s, 9H), 0.18 (s, 6H). ¹³C NMR (100 MHz) δ = 153.55, 148.76, 134.58, 131.36, 128.39, 124.44, 122.57, 121.50, 115.87, 112.18, 111.36, 101.03, 55.24, 30.67, 28.90, 27.44, 26.03, 20.06, 18.27, 14.17, -3.87. IR f(cm⁻¹) = 3413, 2951, 2928, 2902, 2858, 1638, 1584, 1485, 1472, 1453, 1440, 1382, 1320, 1302, 1253, 1211, 1180, 1158, 1089, 1053, 1028, 1006, 928, 908, 868, 837, 795, 779, 732, 713, 685, 650, 602, 537, 476. HRMS (M + Na)⁺ = 420.2329 calculated for C₂₄H₃₅NNaO₂Si; 420.2316 experimental.

Synthesis of Methyl (Z)-3-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)propyl)-1H-indole-5-carboxylate (6.14d)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). Methyl indole-5-carboxylate (36 mg, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.02 mmol). The reaction was allowed to stir for one hour, and mixture was then purified with 50 : 50 hexanes : CH₂Cl₂ → 25 : 75 hexanes : CH₂Cl₂ to give compound 6.14d in 74% yield as a white solid (58 mg, 0.136 mmol).
\[ ^1H \text{ NMR (500 MHz)} \delta = 8.43 \text{ (ddd, } J = 9.4, 1.7, 0.9 \text{ Hz, } 1H), 8.09 \text{ (bs, } 1H), 7.91 \text{ (dd, } J = 8.6, 1.7 \text{ Hz, } 1H), 7.87 \text{ (dd, } J = 8.5, 1.7 \text{ Hz, } 1H), 7.40 \text{ (dt, } J = 8.6, 0.8 \text{ Hz, } 1H), 7.31 \text{ (d, } 8.6 \text{ Hz, } 1H), 7.28-7.26 \text{ (m, } 1H), 6.99-6.98 \text{ (m, } 1H), 6.66-6.65 \text{ (m, } 1H), 3.94 \text{ (s, } 3H), 3.91 \text{ (s, } 3H), 2.44-2.41 \text{ (m, } 2H), 2.24-2.22 \text{ (m, } 2H), 1.74 \text{ (s, } 3H), 1.61 \text{ (s, } 3H), 0.96 \text{ (s, } 9H), 0.16 \text{ (s, } 6H). \]

\[ ^{13}C \text{ NMR (125 MHz)} \delta = 168.44, 148.45, 138.85, 135.26, 125.44, 124.75, 123.77, 123.39, 123.15, 123.05, 122.88, 121.16, 120.83, 117.81, 110.68, 110.41, 104.04, 51.67, 30.66, 28.37, 27.42, 25.95, 20.20, 18.29, 14.37, -3.76. \]

IR f (cm\(^{-1}\)) = 3342, 2950, 2928, 2903, 2855, 1690, 1639, 1617, 1472, 1435, 1382, 1360, 1305, 1292, 1245, 1216, 1195, 1129, 1092, 978, 930, 907, 869, 839, 779, 757, 732, 685, 649. HRMS (M + H\(^+\)) = 426.2459 calculated for C\(_{25}\)H\(_{36}\)NO\(_3\)Si; 368.2399 experimental.

Synthesis of (Z)-3-(2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)propyl)-1H-indole-4-carbaldehyde (6.14e)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). Indole-5-carbaldehyde (30 mg, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.02 mmol). The reaction was allowed to stir for 4 hours, and the mixture was then purified with 98 : 2 hexanes : Et\(_2\)O → 95 : 5 hexanes : Et\(_2\)O → 90 : 10 hexanes : Et\(_2\)O to give compound 6.14e in 89% yield as white crystals (65 mg, 0.166 mmol).

\[ ^1H \text{ NMR (500 MHz)} \delta = 10.63 \text{ (s, } 1H), 8.21 \text{ (bs, } 1H), 7.78 \text{ (dd, } J = 10.0, 1.1 \text{ Hz, } 1H), 7.57 \text{ (dd, } J = 8.0, 1.0 \text{ Hz, } 1H), 7.25 \text{ (dd, } J = 7.7 \text{ Hz, } 1H), 7.09-7.08 \text{ (m, } 1H), 4.15 \text{ (s, } 2H), 2.49-2.46 \text{ (m, } 2H), 2.26-2.24 \text{ (m, } 2H), 1.70 \text{ (s, } 3H), 1.63 \text{ (s, } 3H), 0.89 \text{ (s, } 9H), 0.10 \text{ (s, } 6H). \]

\[ ^{13}C \text{ NMR} \delta = 168.44, 148.45, 138.85, 135.26, 125.44, 124.75, 123.77, 123.39, 123.15, 123.05, 122.88, 121.16, 120.83, 117.81, 110.68, 110.41, 104.04, 51.67, 30.66, 28.37, 27.42, 25.95, 20.20, 18.29, 14.37, -3.76. \]

Synthesis of (Z)-3-(2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)propyl)-1H-indole-4-carbonitrile (6.14f)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). 4-Cyanoindole (29 mg, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.02 mmol). The reaction was allowed to stir for 15 minutes, and the mixture was then purified with 98 : 2 hexanes : Et₂O → 95 : 5 hexanes : Et₂O → 90 : 10 hexanes : Et₂O to give compound 6.14f in 95% yield as a pale yellow oil (70 mg, 0.179 mmol).

¹H NMR (400 MHz) δ = 8.27 (1H, b), 7.49 (1H, d, J = 8.3 Hz), 7.49 (1H, d, J = 7.4 Hz), 7.44 (1H, d, J = 7.4 Hz), 7.14 (1H, t, J = 7.9 Hz), 6.97 (1H, s), 4.19 (2H, s), 2.52-2.49 (2H, m), 2.27-2.24 (2H, m), 1.73 (3H, s), 1.67 (3H, s), 0.93 (9H, s), 0.15 (6H, s). ¹³C NMR (100 MHz) δ = 148.50, 136.42, 135.86, 127.38, 126.10, 125.40, 124.56, 120.93, 120.66, 119.70, 116.48, 115.72, 101.97, 30.68, 28.01, 27.32, 25.90, 20.84, 18.26, 14.46, -3.62. IR f(cm⁻¹) = 3341, 2952, 2928, 2905, 2855, 2216, 1638, 1472, 1462, 1430, 1383, 1347, 1334, 1303, 1251, 1214, 1178, 1095,
1041, 1007, 932, 909, 870, 838, 781, 734, 687, 650, 605, 578, 528. HRMS (M + H)* = 393.2357 calculated for C_{24}H_{33}N_{2}OSi; 393.2357 experimental.

Synthesis of 3-(2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)-2-phenylethyl)-1H-indole (6.16a)

Alcohol 6.15a (100 mg, 0.303 mmol) was dissolved in toluene (1.5 mL). Indole (71 mg, 0.606 mmol) and then pyridinium triflate (7 mg, 0.030 mmol) were added. Upon stirring at -15 °C for 48 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 98 : 2 hexanes : Et_{2}O to give product 6.16a in a 3:1 separable mixture of E : Z isomers (98 mg, 75% yield) as colorless liquid.

{^{1}H NMR (500 MHz, CDCl_{3}, *denotes minor-isomer): \( \delta \) (ppm) = 7.82 (bs, 1H*), 7.74 (bs, 1H), 7.57 (ddd, \( J = 10.0, 8.0, 1.1 \) Hz, 1H, 1H*), 7.28 (dt, \( J = 8.2, 1.0 \) Hz, 1H, 1H*), 7.19 – 7.13 (m, 2H, 2H*), 7.13 – 7.08 (m, 1H, 1H*), 7.04 (dt, \( J = 8.0, 1.7 \) Hz, 1H, 1H*), 6.81 – 6.78 (m, 1H*), 6.66 – 6.62 (m, 1H), 4.24 (s, 2H), 3.86 (s, 1H*), 2.73 – 2.68 (m, 1H*), 2.40 – 2.35 (m, 2H), 2.31 – 2.26 (m, 1H*), 2.17 (ddd, \( J = 8.5, 4.5, 1.7 \) Hz, 2H), 1.76 (s, 3H), 1.74 (s, 1H*), 0.95 (s, 9H), 0.72 (s, 3H*), 0.17 (s, 6H), -0.30 (s, 2H*). \(^{13}C NMR (125 MHz, CDCl_{3}, *denotes minor-isomer): \( \delta \) (ppm) = 148.79 , 148.30* , 144.64, 142.24*, 138.97*, 138.21, 136.28*, 136.15, 130.06, 128.55, 128.04*, 127.96, 127.61, 127.55*, 127.40, 127.01, 126.84, 125.60, 125.55*, 125.03*, 122.52, 121.76*, 121.63*, 121.40, 119.49, 119.01*, 118.82*, 118.80, 115.69, 114.94*, 110.89*, 110.61, 32.69*, 31.01, 30.92*, 29.57, 28.48*, 28.00, 26.01*, 25.97, 25.76*, 25.73, 18.29, 18.21*, 14.57*, 14.36, -3.84, -4.39*. IR (cm^{-1}): 2954, 2928, 2855, 1708, 1635, 1471, 1337,
1251, 1212, 1088, 836, 779, 739. HRMS (M + H)$^+$ = 430.2561 calculated for C$_{28}$H$_{36}$NOSi; experimental = 430.2553.

Synthesis of (E)-3-(2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)ethyl)-1H-indole (6.16b)

Alcohol 6.15b (50 mg, 0.197 mmol) was dissolved in toluene (1.0 mL). Indole (25 mg, 0.216 mmol) and then pyridinium triflate (5 mg, 0.0197 mmol) were added. Upon stirring at room temperature for 1 hour, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 98 : 2 hexanes : Et$_2$O to give product 6.16b (45 mg, 64 % yield) as colorless liquid.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ (ppm) = 7.89 (bs, 1H), 7.60 (d, $J$ = 7.8 Hz, 1H), 7.34 (d, $J$ = 8.1 Hz, 1H), 7.18 (dd, $J$ = 7.2, 7.2 Hz, 1H), 7.10 (dd, $J$ = 7.2, 7.2 Hz, 1H), 6.96 (s, 1H), 5.52 (t, $J$ = 7.3 Hz, 1H), 3.50 (d, $J$ = 7.4 Hz, 2H), 2.55 (ddd, $J$ = 8.5, 4.3, 1.9 Hz, 2H), 2.31 (dd, $J$ = 8.6, 3.8 Hz, 2H), 1.71 (s, 3H), 0.97 (s, 9H), 0.11 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ (ppm) = 147.72, 142.69, 136.42, 127.52, 123.20, 121.86, 121.04, 119.07, 119.04, 116.03, 112.68, 110.90, 31.32, 29.70, 25.90, 24.67, 23.89, 18.26, 13.59, -3.72. IR (cm$^{-1}$): 2958, 2925, 2853, 1650, 1457, 1339, 1259, 1089, 1018, 864, 838, 798, 739. HRMS (M + H)$^+$ = 354.2248 calculated for C$_{22}$H$_{32}$NOSi; experimental = 354.2253.
Synthesis of (E)-3-(1-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)propan-2-yl)-1H-indole (6.16c)

Alcohol 6.15c (100 mg, 0.373 mmol) was dissolved in toluene (1.6 mL). Indole (48 mg, 0.410 mmol) and then pyridinium triflate (9 mg, 0.032 mmol) were added. Upon stirring at room temperature for 14 hours, the reaction mixture was concentrated under vacuum and then directly purified with flash column chromatography with 98 : 2 hexanes : Et₂O to give product 6.16c (88 mg, 64 % yield) as colorless liquid.

^1H NMR (500 MHz, CDCl₃): δ (ppm) = 7.88 (bs, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.17 (dd, J = 8.0, 8.0 Hz, 1H), 7.09 (dd, J = 8.0, 8.0 Hz, 1H), 6.98 (d, J = 1.8 Hz, 1H), 5.47 (d, J = 9.5 Hz, 1H), 3.90 – 3.81 (m, 1H), 2.60 – 2.48 (m, 2H), 2.30 (t, J = 5.7 Hz, 2H), 1.70 (s, 3H), 1.45 (d, J = 6.9 Hz, 3H), 0.99 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H). ^13C NMR (125 MHz, CDCl₃): δ (ppm) = 147.64, 140.58, 136.53, 126.84, 123.15, 121.93, 121.71, 119.87, 119.80, 119.70, 118.90, 110.94, 31.35, 30.91, 25.90, 23.71, 21.96, 18.26, 13.57, -3.75. IR (cm⁻¹): 3415, 2956, 2926, 2855, 1650, 1456, 1336, 1255, 1211, 1095, 1011, 861, 838, 779, 736. HRMS (M + H)^+ = 368.2404 calculated for C₂₃H₃₄NOSi; experimental = 368.2401.
Synthesis of (Z)-3-(2-(2-((tert-butyldimethylsilyl)oxy)-3-phenylcyclopent-2-en-1-ylidene)propyl)-1H-indole (6.16d)

Alcohol 6.15d (30 mg, 0.091 mmol) was dissolved in toluene (0.46 mL). Indole (12 mg, 0.100 mmol) was then added, followed by pyridinium triflate (2 mg, 0.0091 mmol). The reaction was allowed to stir for 22 hours, and the mixture was purified directly using 100% hexanes → 98:2 hexanes : Et₂O → 95:5 hexanes : Et₂O → 90:10 hexanes : Et₂O → 85:15 hexanes : Et₂O to give compound 6.16d in 87% yield (34 mg, 0.079 mmol).

¹H NMR (500 MHz) δ = 7.90 (bs, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.3, 1.2 Hz, 2H), 7.35-7.31 (m, 3H), 7.20-7.14 (m, 2H), 7.03 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.00 (d, J = 2.1 Hz, 1H), 4.03 (s, 2H), 2.71-2.68 (m, 2H), 2.56-2.53 (m, 2H), 1.67 (s, 3H), 0.94 (s, 9H), -0.15 (s, 6H). ¹³C NMR (125 MHz) δ = 150.72, 137.61, 136.32, 135.54, 128.07, 127.82, 126.12, 126.20, 125.80, 122.06, 121.62, 119.68, 119.09, 115.88, 110.78, 29.70, 28.98, 28.15, 26.59, 26.13, 20.47, 18.16, -4.32. IR f (cm⁻¹) = 3417, 3055, 2955, 2928, 2855, 16.92, 15.96, 1492, 1471, 1456, 1374, 1350, 1308, 1281, 1253, 1222, 1120, 1088, 1067, 1039, 1008, 931, 838, 781, 759, 741, 695, 591, 532, 475, 422. HRMS (M + Na)⁺ = 452.2380 calculated for C₂₈H₃₅NNaOSi; 452.2379 experimental.
Synthesis of (Z)-3-(2-(2-((tert-butyldimethylsilyl)oxy)-3-(5-methylthiophen-3-yl)cyclopent-2-en-1-ylidene)propyl)-1H-indole (6.16e)

Alcohol 6.15e (23 mg, 0.064 mmol) was dissolved in toluene (0.32 mL). Indole (8 mg, 0.070 mmol) was then added, followed by pyridinium triflate (2 mg, 0.01 mmol). The reaction was allowed to stir for 14.5 hours, and the mixture was purified directly using 100% hexanes → 95 : 5 hexanes : CH\textsubscript{2}Cl\textsubscript{2} → 90 : 10 hexanes : CH\textsubscript{2}Cl\textsubscript{2} → 70 : 30 hexanes : CH\textsubscript{2}Cl\textsubscript{2} → 50 : 50 hexanes : CH\textsubscript{2}Cl\textsubscript{2} to give compound 6.16e in 52% yield (15 mg, 0.033 mmol).

\textsuperscript{1}H NMR (500 MHz) \(\delta = 7.88\) (bs, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.32 (dt, 8.1, 1.0 Hz, 1H), 7.14 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 7.05 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 3.6 Hz, 1H), 6.66 (dd, J = 3.6, 1.0 Hz, 1H), 3.97 (s, 2H), 2.63-2.60 (m, 2H), 2.53-2.50 (m, 2H), 2.49 (s, 3H), 1.65 (s, 3H), 1.03 (s, 9H), 0.06 (s, 6H). \textsuperscript{13}C NMR (125 MHz) \(\delta = 149.17, 138.24, 137.79, 136.27, 134.99, 125.38, 124.73, 124.22, 122.07, 121.69, 121.61, 119.68, 119.16, 115.75, 110.74, 29.29, 28.74, 27.03, 26.38, 20.42, 18.18, 15.41, -4.06. IR f (cm\(^{-1}\)) = 3415, 2958, 2928, 2855, 1591, 1456, 1344, 1258, 1221, 1091, 1011, 838, 784, 742, 687. HRMS (M + H)\(^{+}\) = 450.2281 calculated for C\textsubscript{27}H\textsubscript{36}NOSSi; 450.2261 experimental.

Synthesis of (E)-3-(2-((tert-butyldimethylsilyl)oxy)-3-(prop-1-en-1-yl)cyclopent-2-en-1-yl)-1H-indole (6.16f)

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Alcohol 6.15f (50 mg, 0.197 mmol) was dissolved in toluene (1.0 mL). Indole (25 mg, 0.216 mmol) and then pyridinium triflate (5 mg, 0.019 mmol) were added. Upon stirring at room temperature for 24 hours, the reaction mixture was concentrated under vacuum and then directly purified using preparative thin layer chromatography with 90 : 10 hexanes : Et₂O (developed 4 times) to give an inseparable 3:1 mixture of E/Z-isomers 6.16f (40 mg, 57 % yield) as colorless liquid.

1H NMR (500 MHz, CDCl₃, *denotes minor-isomer): δ (ppm) = 7.89 (bs, 1H), 7.62 (d, J = 8.0 Hz, 0.4H*), 7.59 (d, J = 8.0 Hz, 1H), 7.36 – 7.33 (m, 1H, 0.4H*), 7.20 – 7.17 (m, 1H, 0.4H*), 7.14 – 7.07 (m, 1H, 0.4H*), 6.99 (d, J = 2.2 Hz, 0.4H*), 6.98 – 6.95 (m, 1H), 6.50 (d, J = 15.7 Hz, 1H), 6.29 (d, J = 11.7 Hz, 0.4H*), 5.51 – 5.44 (m, 1H), 5.43 – 5.36 (m, 0.4H*), 4.08 – 4.05 (m, 1H), 4.04 – 3.98 (m, 0.4H*), 2.78 – 2.70 (m, 1H), 2.53 – 2.36 (m, 4H), 1.96 – 1.90 (m, 1H), 1.88 (d, J = 8.1 Hz, 1H*), 1.85 (d, J = 6.7 Hz, 3H), 0.85 (s, 9H), 0.83 (s, 4H*), 0.01 (s, 1H*), 0.00 (s, 3H), -0.12 (s, 3H), -0.13 (s, 1H*). 13C NMR (125 MHz, CDCl₃, *denotes minor-isomer): δ (ppm) = 152.92*, 150.32, 136.51, 127.07*, 127.04, 124.95, 123.18*, 122.47, 121.84*, 121.69*, 121.68, 121.64*, 121.59, 119.29, 119.26*, 119.06, 118.66, 118.50*, 117.49, 117.20*, 110.95*, 110.93, 43.06, 41.85*, 30.57*, 30.24*, 29.80, 27.28, 25.62, 25.61*, 18.69, 18.21, 18.17*, 14.93*, -4.10*, -4.15, -4.26. IR (cm⁻¹): 3417, 2955, 2928, 2855, 1655, 1620, 1456, 1361, 1252, 1092, 1011, 966, 836, 779. HRMS (M + H)⁺ = 354.2248 calculated for C₂₂H₃₂NOSi; experimental = 354.2245.
8.6.2 Synthetic Procedures for α-Hydroxy Silylenol Ethers

Synthesis of 2-((tert-butyldimethylsilyl)oxy)-3-methyl-1-(prop-1-en-2-yl)cyclopent-2-en-1-ol

(6.10)

Ketone 6.9 (1.50 g, 6.63 mmol) was dissolved in CH₂Cl₂. Isopropenylmagnesium bromide (14.6 mL, 0.5 M in THF) was then added slowly. Upon completion, the reaction was quenched with half saturated NaHCO₃ (50 mL) and extracted (50 mL x 3) with CH₂Cl₂. The combined organic layers were then dried over sodium sulfate, and concentrated under vacuum. The crude mixture was purified using a 2% TEA buffer in hexanes for the solid phase, while the mobile phase consisted of 100 : 0.1 hexanes : TEA → 99 : 1 : 0.1 hexanes : Et₂O : TEA → 98 : 2 : 0.1 hexanes : Et₂O : TEA → 95 : 5 : 0.1 hexanes : Et₂O : TEA. Product 6.10 was isolated in 66% yield as a yellow oil (1.17 g, 4.36 mmol).

¹H NMR (400 MHz) δ = 5.03-5.02 (m, 1H), 4.83-4.82 (m, 1H), 2.30-2.22 (m, 1H), 2.15-2.06 (m, 2H), 1.89-1.82 (m, 2H), 1.71-1.70 (m, 3H), 1.61 (s, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). ¹³C NMR (100 MHz) δ = 146.98, 132.31, 132.23, 131.55, 128.55, 128.45, 110.43, 98.93, 83.79, 35.89, 32.27, 25.77, 18.66, 18.45, -3.20, -3.39. IR f (cm⁻¹) = 3464, 2955, 2929, 2895, 2856, 1688, 1644, 1472, 1462, 1442, 1381, 1361, 1328, 1252, 1216, 1164, 1103, 1078, 1036, 1006, 988, 967, 940, 919, 898, 860, 838, 781, 678, 641, 601, 578, 543. HRMS (M + Na)⁺ = 291.1751 calculated for C₁₅H₂₈O₂NaSi; 291.1745 experimental.
Synthesis of 2-((tert-butyldimethylsilyl)oxy)-3-methyl-1-(1-phenylvinyl)cyclopent-2-enol

(6.15a)

Magnesium turnings (160 mg, 6.64 mmol) was added in an oven-dried, three-neck round bottom flask, which was attached with a reflux condenser and an addition funnel. Dry THF (4.0 mL) was added, followed by bromoethane (34 mg, 0.309 mmol) as a solution in dry THF (1.0 mL). After stirring for 10 min, iodine (9 mg, 0.070 mmol) was added as solid. Afterwards, α-bromostyrene (1.20 g, 6.64 mmol) dissolved in dry THF (10 mL) was added dropwise over 30 min via an addition funnel. The resulting reaction mixture was then warmed to reflux for 2 hours. After cooling to 0ºC, ketone 6.9 (1.0 mg, 4.42 mmol) as a solution in dry THF (2 mL) was added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was cooled to 0ºC and then quenched with H₂O (15 mL). Solid precipitate was filtered through the pad of celite. The aqueous layer was then extracted with CH₂Cl₂ (3 x 40 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 2% TEA) with 98 : 2 hexanes : Et₂O to give product 6.15a in 82% yield (1.20 g, 3.63 mmol) as colorless oil.

¹H NMR (400 MHz, CDCl₃): δ (ppm) = 7.43 – 7.35 (m, 2H), 7.35 – 7.27 (m, 3H), 5.43 (d, J = 1.7 Hz, 1H), 5.18 (d, J = 1.6 Hz, 1H), 2.32 – 2.16 (m, 2H), 2.02 – 1.94 (m, 1H), 1.94 (bs, 1H), 1.84 – 1.77 (m, 1H), 1.64 (s, 3H), 1.02 (s, 9H), 0.24 (s, 3H), 0.24 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) = 152.51, 147.30, 140.60, 128.36, 127.61, 126.99, 116.77, 113.53, 85.35,
Ketone 6.9 (250 mg, 1.11 mmol) was dissolved in CH$_2$Cl$_2$ (2.8 mL) and cooled to 0ºC. Allylmagnesium bromide (2.2 mL, 1 M solution in THF) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was cooled to 0ºC and then quenched with H$_2$O (15 mL). Solid precipitate was filtered through the pad of celite. The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 2% TEA) with 98 : 2 hexanes : Et$_2$O to give product 6.15b in 53% yield (150 mg, 0.589 mmol) as colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) = 5.92 (dd, J = 17.3, 10.7 Hz, 1H), 5.25 (dd, J = 17.3, 1.4 Hz, 1H), 5.07 (dd, J = 10.7, 1.4 Hz, 1H), 2.27 – 2.18 (m, 1H), 2.15 – 2.04 (m, 2H), 1.94 – 1.85 (m, 1H), 1.80 (bs, 1H), 1.61 (s, 3H), 0.94 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm) = 148.15, 141.70, 115.39, 112.33, 83.02, 36.39, 29.71, 25.93, 18.39, 12.92, -3.59, -3.63. IR (cm$^{-1}$): 2929, 2856, 1686, 1326, 1251, 1216, 1069, 992, 938, 920, 858, 836, 779. HRMS (M - OH)$^+$ = 237.1675 calculated for C$_{14}$H$_{25}$OSi; experimental = 237.1676.
Synthesis of 2-((tert-butyldimethylsilyl)oxy)-3-methyl-1-(prop-1-en-1-yl)cyclopent-2-enol (6.15c)

Ketone 6.9 (250 mg, 1.11 mmol) was dissolved in CH$_2$Cl$_2$ (2.2 mL) and cooled to 0°C. 1-propenylmagnesium bromide (4.4 mL, 0.5 M solution in THF) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was cooled to 0°C and then quenched with H$_2$O (15 mL). Solid precipitate was filtered through the pad of celite. The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 2% TEA) with 98 : 2 hexanes : Et$_2$O to give product 6.15c in 54% yield as an inseparable 1:1 mixture of E/Z isomer (160 mg, 0.60 mmol) as colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) = 5.74 – 5.41 (m, 2H), 2.35 – 2.02 (m, 4H), 1.97 – 1.82 (m, 1H), 1.76 – 1.66 (m, 3H), 1.60 (s, 3H), 0.95 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, *denotes minor isomer): δ (ppm) = 149.32*, 148.64, 134.92*, 134.73, 126.08*, 123.34, 115.17*, 115.02, 82.78*, 82.55, 37.59*, 36.56, 29.99*, 29.71, 25.93, 25.89*, 18.43*, 17.65, 13.90, 13.90*, 12.94, 12.81*, -3.59, -3.61*, -3.70, -3.92*. IR (cm$^{-1}$): 2957, 2928, 2856, 1686, 1472, 1462, 1382, 1326, 1250, 1215, 1073, 859, 837. HRMS (M - OH)$^+$ = 251.1826 calculated for C$_{15}$H$_{27}$OSi; experimental = 251.1836.
Synthesis of 2-((tert-butyldimethylsilyl)oxy)-3-phenyl-1-(prop-1-en-2-yl)cyclopent-2-en-1-ol (6.15d)

Ketone S-8 (100 mg, 0.343 mmol, 1 equiv) was dissolved in a 3:1 mixture of toluene and EtOH (4 mL) in a pressure vessel. Phenyl boronic neopentyl ester (131 mg, 0.687 mmol) and K$_2$CO$_3$ (142 mg, 1.029 mmol) were then added, followed by Pd(PPh$_3$)$_4$ (20 mg, 0.02 mmol). The reaction mixture was then warmed to 85°C. Upon completion, the reaction was quenched with H$_2$O (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over Na$_2$SO$_4$ and concentrated under vacuum. The crude mixture was purified using 100% hexanes $\rightarrow$ 98 : 2 hexanes : Et$_2$O giving S-9 in 83% yield as pale yellow crystals (82 mg, 0.284 mmol).

$^1$H NMR (500 MHz) $\delta$ = 7.93-7.90 (2H, m), 7.44-7.35 (m, 3H), 2.87-2.85 (m, 2H), 2.49-2.47 (m, 2H), 0.97 (s, 9H), 0.25 (s, 6H). $^{13}$C NMR (125 MHz) $\delta$ =203.24, 149.19, 144.82, 134.46, 129.27, 128.26, 127.33, 31.48, 25.87, 23.71, 18.56, -3.59. IR f (cm$^{-1}$) =2954, 2929, 2895, 2857, 1702, 1609, 1573, 1495, 1471, 1446, 1408, 1369, 1336, 1316, 1249, 1231, 1142, 1103, 1078, 1055. HRMS (M + H)$^+$ = 289.1618 calculated for C$_{17}$H$_{25}$O$_2$Si; 289.1619 experimental.

Ketone S-9 (82 mg, 0.284 mmol) was dissolved in CH$_2$Cl$_2$ and cooled to 0°C. Isopropenylmagnesium bromide (0.63 mL, 0.5 M in THF) was then added slowly. Upon
completion, the reaction was quenched with saturated NaHCO\(_3\) (10 mL) and extracted with CH\(_2\)Cl\(_2\) (2 x 20 mL). The combined organic layers were then dried over Na\(_2\)SO\(_4\) and concentrated under vacuum. The crude mixture was purified using a 2% TEA buffer in hexanes for the solid phase, while the mobile phase consisted of 100% hexanes \(\rightarrow\) 98 : 2 hexanes : Et\(_2\)O \(\rightarrow\) 95 : 5 hexanes : Et\(_2\)O \(\rightarrow\) 90 : 10 hexanes : Et\(_2\)O to give compound 6.15d in 43% yield (40 mg, 0.122 mmol) as a pale yellow oil.

\(^1\)H NMR (500 MHz) \(\delta = 7.49\) (d, \(J = 8.3\) Hz, 1H), 7.31 (t, \(J = 7.7\) Hz, 2H), 7.20 (t, \(J = 7.5\) Hz, 1H), 5.08 (s, 1H), 4.91 (s, 1H), 2.80 (ddd, \(J = 14.8, 8.9, 3.6\) Hz, 1H), 2.44 (ddd, \(J = 14.5, 8.6, 5.7\) Hz, 1H), 2.23 (ddd, \(J = 13.4, 8.5, 3.7\) Hz, 1H), 1.97 (ddd, \(J = 14.0, 8.6, 5.6\) Hz, 1H), 1.83 (s, 3H), 0.90 (s, 9H), 0.06 (s, 3H), -0.11 (s, 3H). \(^{13}\)C NMR (125 MHz) \(\delta = 149.97, 147.68, 136.53, 126.90, 127.67, 126.41, 118.45, 110.00, 86.22, 35.99, 28.59, 26.01, 18.98, 18.49, -3.27, -3.49.\) IR \(f\) (cm\(^{-1}\)) = 3468, 2929, 2856, 1639, 1494, 1472, 1444, 1346, 1328, 1251, 1164, 1102, 1069, 957, 906, 837, 781, 760, 695, 628, 593, 533, 491. HRMS (M – H\(_2\)O\(^+\)) = 313.1982 calculated for C\(_{20}\)H\(_{29}\)OSi; 313.1982 experimental.

Synthesis of 2-((tert-butyldimethylsilyl)oxy)-3-(5-methylthiophen-2-yl)-1-(prop-1-en-2-yl)cyclopent-2-en-1-ol (6.15e)
Ketone S-8 (100 mg, 0.343 mmol, 1 equiv) was dissolved in a 3:1 mixture of toluene and EtOH (4 mL) in a pressure vessel. 2-Thiophenyl boronic picolinic ester (169 \( \mu \)L, 0.687 mmol) and \( \text{K}_2\text{CO}_3 \) (142 mg, 1.029 mmol) were then added, followed by \text{Pd}(\text{PPh}_3)_4 \) (20 mg, 0.02 mmol). The reaction mixture was then warmed to 85°C. Upon completion, the reaction was quenched with H\(_2\)O (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were then dried over Na\(_2\)SO\(_4\) and concentrated under vacuum. The crude mixture was purified using 100% hexanes \( \rightarrow \) 98 : 2 hexanes : Et\(_2\)O giving S-10 in 58% yield as pale yellow crystals (62 mg, 0.201 mmol).

\(^1\text{H} \text{NMR} \ (500 \text{ MHz}) \ \delta = 7.25 \ (d, \ J = 3.7 \text{ Hz}, 1\text{H}), \ 6.79-6.78 \ (m, 1\text{H}), \ 2.83-2.81 \ (m, 2\text{H}), \ 2.55 \ (s, 3\text{H}), \ 2.48-2.46 \ (m, 2\text{H}), \ 1.03 \ (s, 9\text{H}), \ 0.32 \ (s, 6\text{H}). \ ^{13}\text{C} \text{NMR} \ (125 \text{ MHz}) \ \delta = 201.06, \ 146.27, \ 144.26, \ 140.74, \ 134.85, \ 127.12, \ 125.64, \ 31.68, \ 28.07, \ 23.57, \ 18.69, \ 15.63, -3.11. \ \text{IR} \ f (\text{cm}^{-1}) = 2954, 2929, 2896, 2857, 1704, 1610, 1462, 1409, 1372, 1316, 1250, 1144, 1078. \ \text{HRMS} \ (\text{M} + \text{H})^+ = 309.1339 \ \text{calculated for} \ C_{16}H_{25}O_2SSi; \ 309.1336 \ \text{experimental.}

Ketone S-10 (62 mg, 0.201 mmol) was dissolved in CH\(_2\)Cl\(_2\) and cooled to 0°C. Isopropenylmagnesium bromide (0.44 \( \mu \)L, 0.5 M in THF) was then added slowly. Upon completion, the reaction was quenched with saturated NaHCO\(_3\) (10 mL) and extracted with CH\(_2\)Cl\(_2\) (2 x 20 mL). The combined organic layers were then dried over Na\(_2\)SO\(_4\) and concentrated under vacuum. The crude mixture was purified using a 2% TEA buffer in hexanes for the solid phase, while the mobile phase consisted of 100% hexanes \( \rightarrow \) 98 : 2 hexanes : Et\(_2\)O \( \rightarrow \) 95 : 5 hexanes : Et\(_2\)O \( \rightarrow \) 90 : 10 hexanes : Et\(_2\)O to give compound 6.15e in 32% yield (23 mg, 0.064 mmol) as a pale yellow oil.

\(^1\text{H} \text{NMR} \ (500 \text{ MHz}) \ \delta = 7.75-7.70 \ (m, 1\text{H}), \ 7.52-7.43 \ (m, 1\text{H}), \ 5.06 \ (dd, \ J = 1.6, 0.8 \text{ Hz}, 1\text{H}), \ 4.90 \ (t, \ J = 1.5 \text{ Hz}, 1\text{H}), \ 2.61 \ (ddd, \ J = 15.1, 9.2, 3.6 \text{ Hz}, 1\text{H}), \ 2.47 \ (ddd, \ J = 15.0, 8.7, 5.4}
Hz, 1H), 2.23 (ddd, J = 13.6, 8.7, 3.6 Hz, 1H), 1.99 (ddd, J = 13.6, 9.2, 5.4 Hz, 1H), 1.91 (s, 1H), 1.73 (dd, J = 1.5, 0.8 Hz, 3H), 1.93 (s, 3H), 0.96 (s, 3H), 0.31 (s, 3H), 0.27 (s, 3H). $^{13}$C NMR (125 MHz) $\delta =$ 149.97, 147.68, 136.53, 127.90, 127.67, 126.41, 118.45, 110.00, 86.22, 35.99, 28.59, 26.01, 18.98, 18.49, -3.27, -3.59. IR $f$ (cm$^{-1}$) = 3478, 2955, 2928, 2856, 1686, 1643, 1516, 1462, 1438, 1346, 1292, 1250, 1166, 1101, 963, 904, 839, 785, 749, 716. HRMS (M – H$_2$O)$^+$ = 333.1703 calculated for C$_{19}$H$_{29}$OSSi; 333.1702 experimental.

**Synthesis of 2-((tert-butylidemethylsilyl)oxy)-1-(prop-1-en-1-yl)cyclopent-2-enol (6.15f)**

Ketone 4.28 (100 mg, 0.472 mmol) was dissolved in CH$_2$Cl$_2$ (2.4 mL) and cooled to 0°C. 1-propenylmagnesium bromide (1.9 mL, 0.5 M solution in THF) was then added dropwise, and the mixture was allowed to warm to room temperature. After stirring for 1 hour, the reaction was cooled to 0°C and then quenched with H$_2$O (10 mL). Solid precipitate was filtered through the pad of celite. The aqueous layer was then extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and then concentrated under vacuum. The crude material was purified with flash column chromatography (buffered with 2% TEA) with 97:3 hexanes: diethyl ether to give product 6.15f as an inseparable 1:1 mixture of E/Z isomers in 66% yield (80 mg, 0.314 mmol) as colorless liquid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 5.71 – 5.44 (m, 3H), 4.69 (s, 1.5H), 2.35 – 1.89 (m, 8H), 1.77 (d, J = 6.7 Hz, 1.5H), 1.68 (d, J = 6.1 Hz, 3H), 0.92 (s, 6H), 0.91 (s, 9H), 0.16 (s, 4H), 0.14 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, * denotes minor isomer): $\delta$ (ppm) = 156.49*, 155.52, 134.25*, 134.15, 126.56*, 123.28, 102.44*, 102.40, 82.14*, 81.82, 37.72*, 36.67,

8.6.3 Synthetic Procedures for γ-Nucleophilic Addition

Synthesis of (E/Z)-N-(2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)propyl)aniline (6.17a)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). tert-Butylaniline (33 µL, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.025 mmol). The reaction was allowed to stir for 45 minutes. The crude mixture was then purified with 100% hexanes → 95 : 5 hexanes : Et₂O → 90 : 10 hexanes : Et₂O to give compound 6.17a in 73% yield in a 1:1 separable mixture of E : Z isomers as a yellow oil (47 mg, 0.136 mmol).

Z-Isomer: ¹H NMR (500 MHz) δ = 7.17-7.14 (2H, m), 6.57-6.54 (2H, m), 4.07 (2H, s), 2.75 (1H, s), 2.44-2.41 (2H, m), 2.23-2.21 (2H, m), 1.73 (3H, s), 1.68 (3H, s), 1.27 (9H, s), 0.96 (9H, s), 0.12 (6H, s). ¹³C NMR (125 MHz) δ = 148.06, 146.55, 139.23, 137.96, 125.99, 124.87, 119.74, 113.90, 112.40, 45.23, 39.16, 33.77, 31.58, 30.71, 27.39, 25.99, 25.93, 22.36, 18.83, 18.27, 14.39, 12.65, -3.71.

E-Isomer: ¹H NMR (500 MHz) δ = 7.21-7.18 (2H, m), 6.57-6.54 (2H, m), 3.63 (2H, s), 3.52 (1H, s), 2.53-2.50 (2H, m), 2.23-2.21 (2H, m), 1.97 (3H, s), 1.68 (3H, s), 1.27 (9H, s), 0.99 (9H, s), 0.09 (6H, s). ¹³C NMR (125 MHz) δ = 148.35, 146.53, 139.76, 137.68, 126.51, 125.89, 124.87, 119.74, 113.90, 112.40, 45.23, 39.16, 33.77, 31.58, 30.71, 27.39, 25.99, 25.93, 22.36, 18.83, 18.27, 14.39, 12.65, -3.94.
Combined: IR f (cm⁻¹) = 3420, 2954, 2929, 2904, 2857, 2332, 1689, 1638, 1614, 1518, 1471, 1462, 1384, 1361, 1333, 1304, 1251, 1213, 1193, 1094, 1007, 980, 927, 909, 838, 818, 779, 732, 684, 582, 549, 500. HRMS (M + H)⁺ = 400.3030 calculated for C₂₅H₄₂NOSi; 400.3032 experimental.

Synthesis of (E/Z)-tert-butyldimethyl((2-methyl-5-(1-(phenylthio)propan-2-ylidene)cyclopent-1-en-1-yl)oxy)silane (6.17b)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). Thiophenol (21 µL, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.025 mmol). The reaction was allowed to stir for 5 hours, and the crude mixture was then purified with 100% hexanes → 95 : 5 hexanes : Et₂O → 90 : 10 hexanes : Et₂O → 85 : 15 hexanes : Et₂O to give compound 6.17b in 62% yield as an inseparable 1:1 mixture of E : Z isomers as a colorless oil (42 mg, 0.116 mmol).

¹H NMR (500 MHz) δ = 7.38-7.32 (m, 4H), 7.29-7.23 (m, 1H), 7.20-7.15 (m, 4H), 7.11-7.08 (m, 1H), 4.09 (s, 2H), 3.57 (s, 2H), 2.38-2.31 (m, 4H), 2.14-2.0 (m, 4H), 2.03 (s, 3H), 1.76 (s, 3H), 1.65 (s, 3H), 1.61 (s, 3H), 0.99 (s, 9H), 0.97 (s, 9H), 0.10 (s, 6H), 0.09 (s, 6H). ¹³C NMR (125 MHz) δ = 148.28, 147.92, 139.10, 137.95, 137.53, 137.22, 130.24, 130.07, 128.62, 128.25, 126.17, 126.02, 125.59, 117.55, 116.96, 42.01, 37.43, 30.61, 27.51, 26.78, 25.95, 25.94, 25.92, 19.75, 18.25, 18.19, 17.59, 14.28, 14.26, -3.79, -3.94. IR f (cm⁻¹) = 2954, 2927, 2905, 2855, 1638, 1472, 1462, 1438, 1382, 1361, 1334, 1306, 1252, 1213, 1157, 1093, 1025, 1005, 932, 863.
836, 778, 736, 688, 475. HRMS (M + H)^+ = 361.2016 calculated for C_{21}H_{33}SO; 361.2007 experimental.

Synthesis of (E)-tert-butyl((5-(1-methoxypropan-2-ylidene)-2-methylcyclopent-1-en-1-yl)oxy)dimethylsilane (6.17c)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). Methanol (8 μL, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.025 mmol). The reaction was allowed to stir for 10 minutes. The crude mixture was then purified directly with 100% hexanes → 98 : 2 hexanes : Et_2O → 95 : 5 hexanes : Et_2O → 90 : 10 hexanes : Et_2O to give compound 6.17c in 59% yield as a colorless oil (31 mg, 0.109 mmol) as a single E isomer.

^1H NMR (400 MHz) δ = 4.92 (dt, J = 3.1, 0.9 Hz, 1H), 4.89 (dt, J = 3.9, 1.5 Hz), 3.16 (s, 3H), 2.41 (ddd, J = 14.9, 9.0, 3.8 Hz, 1H), 2.20 (ddd, J = 14.9, 9.0, 3.8 Hz, 1H), 2.00 (ddd, J = 13.7, 8.7, 3.8 Hz, 1H), 1.95 (dd, J = 1.5, 0.9 Hz, 3H), 1.73 (ddd, J = 13.7, 8.8, 5.4 Hz, 1H), 1.31 (s, 3H), 0.95 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H). ^13C NMR (125 MHz) δ = 148.90, 140.09, 119.87, 113.06, 85.78, 49.98, 31.05, 28.45, 26.17, 23.65, 22.44, 18.62, -2.71, -3.25. IR f(cm^{-1}) = 2956, 2930, 2897, 2857, 2822, 1630, 1462, 1361, 1332, 1293, 1252, 1188, 1171, 1122, 1086, 1065, 1007, 923, 906, 851, 836, 779, 732, 678. HRMS (M + K - TBS)^+ = 207.0782 calculated for C_{10}H_{16}KO_2; 207.0903 experimental.
Synthesis of (E)-tert-butyldimethyl((2-methyl-5-(1-(3-phenylpropoxy)propan-2-ylidene)cyclopent-1-en-1-yl)oxy)silane (6.17d)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). 3-Phenyl-1-propanol (28 µL, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.025 mmol). The reaction was allowed to stir for 45 minutes. The crude mixture was then purified directly with 100% hexanes → 95 : 5 hexanes : Et₂O → 90 : 10 hexanes : Et₂O → 85 : 15 hexanes : Et₂O to give compound 6.17d in 97% yield as a colorless oil (70 mg, 0.180 mmol) as a single E isomer.

¹H NMR (500 MHz) δ = 7.29-7.26 (m, 2H), 7.20-7.16 (m, 3H), 4.91 (dd, J = 2.4, 1.2 Hz, 1H), 4.89 (dd, J = 4.0, 1.5 Hz, 1H), 3.38 (dddd, J = 8.9, 6.4, 6.4, 2.3 Hz, 1H), 3.31 (dt, J = 8.9, 6.6 Hz, 1H), 2.69 (t, J = 7.7 Hz), 2.37 (ddd, J = 14.8, 8.7, 5.0 Hz, 1H), 2.19 (ddd, J = 14.8, 8.8, 4.4 Hz, 1H), 1.94 (t, J = 1.2 Hz, 3H), 1.90-1.85 (m, 2H), 1.32 (s, 3H), 0.95 (s, 9H), 0.22 (s, 3H), 0.15 (s, 3H). ¹³C NMR (125 MHz) δ = 149.87, 142.25, 140.15, 128.38, 128.26, 125.67, 119.16, 112.99, 85.33, 61.78, 32.69, 32.14, 31.96, 28.32, 26.23, 25.69, 23.30, 22.49, 18.62, -2.57, -3.51. IR f (cm⁻¹) = 2953, 2930, 2857, 1687, 1632, 1472, 1462, 1389, 1361, 1332, 1293, 1251, 1223, 1185, 1123, 1089, 924, 855, 839, 781, 745, 698, 682. HRMS (M + H)⁺ = 387.2714 calculated for C₂₄H₃₉O₂Si; 387.2707 experimental.
Synthesis of (E)-tert-butyldimethyl((2-methyl-5-(1-(2,4,6-trimethoxyphenyl)propan-2-ylidene)cyclopent-1-en-1-yl)oxy)silane (6.17e)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). 1,3,5-trimethoxybenzene (34 mg, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.025 mmol). The reaction was allowed to stir for 45 minutes. The crude mixture was then purified directly with 90 : 10 hexanes : CH$_2$Cl$_2$ → 75 : 25 hexanes : CH$_2$Cl$_2$ → 50 : 50 hexanes : CH$_2$Cl$_2$ to give compound 6.17e in 60% yield as a colorless oil (47 mg, 0.112 mmol) as a single Z isomer.

$^1$H NMR (500 MHz) $\delta = 6.11$ (s, 2H), 3.79 (s, 3H), 3.77 (s, 2H), 3.79 (s, 6H), 2.37-2.34 (m, 2H), 2.17-2.15 (m, 2H), 1.67 (s, 3H), 1.41 (s, 3H), 0.98 (s, 9H), 0.14 (s, 6H).

$^{13}$C NMR (125 MHz) $\delta = 159.50$, 158.98, 149.37, 133.97, 122.28, 121.63, 111.21, 90.78, 55.64, 55.25, 30.88, 27.63, 26.06, 25.73, 18.69, 18.28, 14.14, 1.02, -3.83.

IR $\nu$ (cm$^{-1}$) = 2996, 2931, 2855, 2838, 1602, 1459, 1418, 1383, 1333, 1303, 1251, 1205, 1151, 1126, 1092, 1067, 1044, 1008, 950, 927, 872, 839, 817, 780, 682. HRMS (M + H)$^+$ = 419.2612 calculated for C$_{24}$H$_{39}$O$_4$Si; 419.2600 experimental.
Synthesis of (E)-2-(2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)propyl)-1H-pyrrole (6.17f)

Alcohol 6.10 (50 mg, 0.186 mmol) was dissolved in toluene (0.93 mL). Pyrrole (14 µL, 0.205 mmol) was then added, followed by pyridinium triflate (4 mg, 0.025 mmol). The reaction was allowed to stir for 15 minutes. The crude mixture was then purified with 100% hexanes → 98 : 2 hexanes : Et₂O → 95 : 5 hexanes : Et₂O → 90 : 10 hexanes : Et₂O to give compound 6.17f in 89% yield as a yellow oil (52 mg, 0.165 mmol) as a single Z isomer.

¹H NMR (400 MHz) δ = 8.20 (bs, 1H), 6.65-6.63 (m, 1H), 6.07 (q, J = 2.9 Hz, 1H), 5.91-5.90 (m, 1H), 3.67 (s, 2H), 2.42-2.39 (m, 2H), 2.21-2.18 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 0.97 (s, 9H), 0.16 (s, 6H). ¹³C NMR (125 MHz) δ = 148.11, 134.91, 131.77, 125.32, 120.53, 116.17, 107.53, 105.40, 31.05, 30.57, 27.15, 26.06, 25.95, 20.62, 18.35, 14.54, -3.58. IR f (cm⁻¹) = 3420, 2954, 2928, 2906, 2856, 1638, 1566, 1472, 1442, 1382, 1361, 1333, 1304, 1252, 1213, 1158, 1090, 1024, 1007, 957, 928, 909, 837, 778, 731, 706, 685, 648, 578, 534. HRMS (M + H)⁺ = 318.2248 calculated for C₁₉H₃₂NOSi; 318.2248 experimental.

Synthesis of (Z)-3-(2-(2-((tert-butyldimethylsilyl)oxy)-3-methylcyclopent-2-en-1-ylidene)propyl)-1H-indole (6.11)
Compound 6.17c (70 mg, 0.246 mmol) was dissolved in toluene (1.23 mL). Indole (32 mg, 0.271 mmol) was then added, followed by pyridinium triflate (20 mg, 0.088 mmol). The reaction was allowed to stir for 3 hours, and the mixture was purified directly using 100% hexanes → 95 : 5 hexanes : Et\(_2\)O → 90 : 10 hexanes : Et\(_2\)O to give compound 6.11 in 74% yield as a colorless oil (67 mg, 0.182 mmol).

8.7 Synthesis and Characterization of Novel Chapter 7 Compounds

8.7.1 Synthetic Procedures for Carbazole Annulation

Synthesis of 1,4-dimethyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole (7.16a)

Alcohol 7.11 (50 mg, 0.186 mmol) was dissolved in CH\(_2\)Cl\(_2\) (0.37 mL). Indole (22 mg, 0.186 mmol) was then added, followed by camphorsulfonic acid (20 mg, 0.093 mmol). The reaction was allowed to stir for five hours, and the mixture was purified directly using 100% hexanes → 10% Et\(_2\)O in hexanes to give compound 7.16a in 99% yield as a colorless oil (44 mg, 0.184 mmol).

\(^1\)H NMR (500 MHz) \(\delta = 8.01\) (d, \(J = 7.8\) Hz, 1H), 7.85 (bs, 1H), 7.42 (d, \(J = 7.9\) Hz, 1H), 7.36 (ddd, \(J = 8.1, 7.0, 1.2\) Hz, 1H), 7.21-7.17 (m, 1H), 3.62 (ddd, \(J = 20.4, 6.9, 6.9\) Hz, 1H), 3.09-3.03 (m, 1H), 2.95-2.89 (m, 1H), 2.50-2.44 (m, 1H), 2.42 (s, 3H), 1.87-1.81 (m, 1H), 1.45 (d, \(J = 7.0\) Hz, 3H). \(^{13}\)C NMR (125 MHz) \(\delta = 141.18, 139.61, 134.57, 125.37, 124.37, 123.75, 122.57, 119.93, 118.54, 110.52, 38.14, 34.01, 30.67, 20.06, 19.35. IR \(f(\text{cm}^{-1}) = 3422, 2925, 2859, 1696, 1613, 1490, 1456, 1437, 1377, 1326, 1305, 1245, 1220, 1171, 1140, 1090, 1017,

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907, 861, 802, 733, 646, 591, 568, 537, 439. HRMS (M + H)$^+$ = 236.1434 calculated for C$_{17}$H$_{18}$N; 236.1437 experimental.

Synthesis of 1,4,7-trimethyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole (7.16b)

![Chemical structure diagram]

Alcohol 7.11 (50 mg, 0.186 mmol) was dissolved in CH$_2$Cl$_2$ (0.37 mL). 5-Methylindole (24 mg, 0.186 mmol) was then added, followed by camphorsulfonic acid (20 mg, 0.093 mmol). The reaction was allowed to stir for five hours. The reaction was allowed to stir for 5 hours, and the mixture was purified directly using 100% hexanes → 10% Et$_2$O in hexanes → 20% Et$_2$O in hexanes → 30% Et$_2$O in hexanes to give compound 7.16b in 97% yield as a colorless oil (42 mg, 0.180 mmol).

$^1$H NMR (500 MHz) δ = 7.81 (s, 1H), 7.75 (bs, 1H), 7.68 (s, 1H), 7.31 (d, $J$ = 8.1 Hz, 1H), 7.19 (dd, $J$ = 8.3, 1.6 Hz, 1H), 3.61 (ddd, $J$ = 20.3, 7.0, 7.0 Hz, 1H), 3.06 (ddd, $J$ = 15.3, 9.0, 6.1 Hz, 1H), 2.92 (ddd, $J$ = 15.2, 9.0, 5.8 Hz, 1H), 2.52 (s, 3H), 2.48-2.44 (m, 1H), 2.42 (s, 3H), 1.86-1.82 (m, 1H), 1.45 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (125 MHz) δ = 140.96, 137.86, 134.92, 129.13, 128.35, 126.27, 125.10, 123.92, 122.47, 119.92, 118.47, 110.17, 38.14, 34.01, 30.66, 21.43, 20.04, 19.35. IR (cm$^{-1}$) = 3423, 2951, 2860, 1677, 1620, 1492, 1447, 1374, 1346, 1295, 1249, 1219, 1186, 1112, 1018, 907, 861, 798, 731, 649, 595, 438. HRMS (M + H)$^+$ = 250.1590 calculated for C$_{18}$H$_{20}$N; 250.1594 experimental.
Synthesis of 7-methoxy-1,4-dimethyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole (7.16c)

Alcohol 7.11 (50 mg, 0.186 mmol) was dissolved in CH$_2$Cl$_2$ (0.37 mL). 5-Methoxyindole (36 mmol, 0.186 mmol) was then added, followed by camphorsulfonic acid (20 mg, 0.093 mmol). The reaction was allowed to stir for five hours. The reaction was allowed to stir for 5 hours, and the mixture was purified directly using 100% hexanes → 10% Et$_2$O in hexanes → 20% Et$_2$O in hexanes → 30% Et$_2$O in hexanes to give compound 7.16c in 60% yield as a colorless oil (35 mg, 0.112 mmol).

$^1$H NMR (500 MHz) $\delta$ = 7.71 (bs, 1H), 7.67 (s, 1H), 7.51 (d, $J = 2.5$ Hz, 1H), 7.31 (d, $J = 8.7$ Hz, 1H), 7.01 (dd, $J = 8.7$, 2.5 Hz), 3.93 (s, 3H), 3.60 (ddd, $J = 13.9$, 13.7, 7.1), 3.06 (ddd, $J = 15.3$, 8.9, 6.2 Hz, 1H), 2.92 (ddd, $J = 15.2$, 9.0, 5.8 Hz, 1H), 2.49-2.43 (m, 1H), 2.42 (s, 3H), 1.89-1.81 (m, 1H), 1.44 (d, $J = 7.0$ Hz). $^{13}$C NMR (125 MHz) $\delta$ = 153.71, 141.16, 135.46, 134.55, 129.30, 125.03, 124.24, 122.63, 118.43, 114.02, 111.18, 102.98, 56.02, 38.13, 33.98, 30.68, 20.00, 19.34. IR $f$ (cm$^{-1}$) = 3424, 2951, 2861, 1698, 1633, 1492, 1459, 1295, 1258, 1213, 1168, 1131, 1107, 1031, 859, 839, 803, 769. HRMS (M + H)$^+$ = 266.1539 calculated for C$_{18}$H$_{20}$NO; 288.1530 experimental.
Synthesis of 8-chloro-1,4-dimethyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole (7.16d)

Alcohol 7.11 (50 mg, 0.186 mmol) was dissolved in CH₂Cl₂ (0.37 mL). 6-Chloroindole (28 mg, 0.186 mmol) was then added, followed by camphorsulfonic acid (20 mg, 0.093 mmol). The reaction was allowed to stir for five hours, and the mixture was purified directly using 100% hexanes → 10% Et₂O in hexanes → 20% Et₂O in hexanes → 30% Et₂O in hexanes to give compound 7.16d in 67% yield as a colorless oil (34 mg, 0.125 mmol).

¹H NMR (500 MHz) δ = 7.89 (d, J = 8.3 Hz, 1H), 7.86 (bs, 1H), 7.66 (s, 1H), 7.39 (d, J = 1.9 Hz, 1H), 7.16 (dd, J = 8.3, 1.9 Hz, 1H), 3.64-3.57 (m, 1H), 3.06 (ddd, J = 15.3, 9.0, 6.2 Hz, 1H), 2.92 (ddd, J = 15.9, 8.9, 5.7 Hz), 2.50-2.44 (m, 1H), 2.42 (s, 3H), 1.90-1.82 (m, 1H), 1.44 (d, J = 7.0 Hz, 3H). ¹³C NMR (125 MHz) δ = 141.61, 140.05, 134.78, 130.49, 129.38, 125.96, 122.37, 121.95, 120.65, 119.68, 118.46, 110.60, 38.08, 33.96, 30.67, 20.04, 19.34. IR [cm⁻¹] = 3433, 2953, 2862, 1677, 1612, 1482, 1450, 1432, 1373, 1324, 1304, 1277, 1241, 1221, 1146, 1064, 919, 843, 804. HRMS (M + H)⁺ = 270.1044 calculated for C₁₇H₁₇CN; 270.1022 experimental.

Synthesis of 7-bromo-1,4-dimethyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole (7.16e)
Alcohol 7.11 (50 mg, 0.186 mmol) was dissolved in CH₂Cl₂ (0.37 mL). 5-Bromoindole (36 0.186 mmol) was then added, followed by camphorsulfonic acid (20 mg, 0.093 mmol). The reaction was allowed to stir for five hours, and the mixture was purified directly using 100% hexanes → 10% Et₂O in hexanes → 20% Et₂O in hexanes → 30% Et₂O in hexanes to give compound 7.16e in 84% yield as a colorless oil (49 mg, 0.156 mmol).

^1H NMR (500 MHz) δ = 8.11 (d, J = 2.0 Hz, 1H), 7.87 (bs, 1H), 7.65 (s, 1H), 7.43 (dd, J = 8.5, 2.0 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 3.60 (dt, J = 20.4, 6.9 Hz, 1H), 3.06 (ddd, J = 15.5, 9.0, 6.4 Hz, 1H), 2.92 (ddd, J = 15.3, 9.0, 6.0 Hz, 1H), 2.50-2.43 (m, 1H), 2.41 (s, 3H), 1.88-1.81 (m, 1H), 1.44 (d, J = 6.8 Hz, 3H). ^13C NMR (125 MHz) δ = 142.11, 138.17, 134.99, 129.36, 127.62, 125.95, 125.59, 122.70, 121.62, 118.66, 111.96, 111.94, 38.12, 33.96, 30.72, 20.04, 19.35. IR f (cm⁻¹) = 3440, 2953, 2863, 1677, 1628, 1486, 1456, 1375, 1282, 1242, 1223, 1051, 1015, 861. HRMS (M + H)^+ = 314.0539 calculated for C₁₁H₁₇Br; 314.0538 experimental.

Synthesis of methyl 1,4-dimethyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole-7-carboxylate (7.16f)

Alcohol 7.11 (50 mg, 0.186 mmol) was dissolved in CH₂Cl₂ (0.37 mL) in a pressure vessel. Methylindole-5-carboxylate (33 0.186 mmol) was then added, followed by camphorsulfonic acid (40 mg, 0.186 mmol). The reaction was warmed to 40°C and allowed to stir for seven hours, and the mixture was purified directly using 100% hexanes → 10% Et₂O in
hexanes $\rightarrow$ 20% Et$_2$O in hexanes $\rightarrow$ 30% Et$_2$O in hexanes to give compound 7.16f in 99% yield as a colorless oil (54 mg, 0.185 mmol).

$^1$H NMR (500 MHz) $\delta = 8.75$ (s, 1H), 8.12 (bs, 1H), 8.08 (dd, $J = 8.5$, 1.6 Hz, 1H), 7.56 (s, 1H), 7.41 (d, $J = 8.5$ Hz, 1H), 3.97 (s, 3H), 3.62 (dt, $J = 20.5$, 6.5 Hz, 1H), 3.06 (ddd, $J = 15.4$, 8.9, 6.3 Hz, 1H), 2.93 (ddd, $J = 15.3$, 9.0, 5.6 Hz, 1H), 2.50-2.44 (m, 1H), 2.43 (s, 3H), 1.86 (ddt, $J = 14.1$, 7.8, 4.3 Hz, 1H), 1.45 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (125 MHz) $\delta = 168.00$, 142.37, 142.10, 134.95, 129.53, 126.72, 126.41, 123.78, 123.49, 122.52, 122.49, 121.09, 118.86, 110.05, 51.87, 39.10, 33.98, 30.70, 20.11, 19.38. IR $f$(cm$^{-1}$) = 3336, 2951, 1692, 1613, 1436, 1350, 1267, 1240, 1221, 1196, 1131, 1089, 759. HRMS (M + H)$^+$ = 294.1489 calculated for C$_{19}$H$_{20}$NO$_2$; 294.1490 experimental

Synthesis of 1,4-dimethyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole-6-carbonitrile (7.16g)

Alcohol 7.11 (50 mg, 0.186 mmol) was dissolved in CH$_2$Cl$_2$ (0.37 mL) in a pressure vessel. 4-Cyanoindole (26 $\square$, 0.186 mmol) was then added, followed by camphorsulfonic acid (40 mg, 0.186 mmol). The reaction was warmed to 40°C and allowed to stir for seven hours, and the mixture was purified directly using 100% hexanes $\rightarrow$ 10% Et$_2$O in hexanes $\rightarrow$ 20% Et$_2$O in hexanes $\rightarrow$ 30% Et$_2$O in hexanes to give compound 7.16f in 51% yield as a colorless oil (25 mg, 0.095 mmol).
\[^{1}\text{H}\text{ NMR (500 MHz)}\ \delta = 8.22\ (s, 1\text{H})\ 8.10\ (bs, 1\text{H}),\ 7.64\ (dd, \text{ }J = 8.2, 0.9\ \text{Hz}, 1\text{H}),\ 7.51\ (dd, \text{ }J = 7.5, 1.0\ \text{Hz}, 1\text{H}),\ 7.39\ (t, \text{ }J = 7.8\ \text{Hz}, 1\text{H}),\ 3.64\ (ddd, \text{ }J = 20.7, 7.0, 7.0\ \text{Hz}, 1\text{H}),\ 3.09\ (ddd, \text{ }J = 15.6, 9.0, 6.3\ \text{Hz}, 1\text{H}),\ 2.95\ (ddd, \text{ }J = 16.1, 9.0, 5.7\ \text{Hz}, 1\text{H}),\ 2.52-2.45\ (m, 1\text{H}),\ 2.45\ (s, 3\text{H}),\ 1.95-1.86\ (m, 1\text{H}),\ 1.45\ (d, \text{ }J = 6.9\ \text{Hz}, 3\text{H}).\]

\[^{13}\text{C}\text{ NMR (125 MHz)}\ \delta = 148.05,\ 143.59,\ 139.33,\ 135.19,\ 129.31,\ 126.86,\ 124.47,\ 124.43,\ 119.92,\ 115.02,\ 103.32,\ 38.15,\ 33.88,\ 30.88,\ 20.07,\ 19.38.\]

IR\ \text{f (cm}^{-1}\text{)} = 3320,\ 2954,\ 2927,\ 2865,\ 2219,\ 1702,\ 1685,\ 1627,\ 1498,\ 1440,\ 1374,\ 1320,\ 1291,\ 1238,\ 1162,\ 1141,\ 867,\ 790,\ 765,\ 738.\ HRMS (M + H)^{+} = 261.1386\ \text{calculated for}\ C_{18}H_{17}N_{2};\ 261.1381\ \text{experimental.}

Synthesis of 7-methoxy-1,4-dimethyl-1,2,3,12-tetrahydrobenzo[a]cyclopenta[i]carbazole (7.16h)

Alcohol 7.11 (50 mg, 0.186 mmol) was dissolved in CH$_2$Cl$_2$ (0.37 mL) in a pressure vessel. 5-Methoxybenz[g]indole (36 $\mu$g, 0.186 mmol) was then added, followed by camphorsulfonic acid (20 mg, 0.093 mmol) and warmed to 40°C. The reaction was allowed to stir for eight days, and the mixture was purified directly using 100% hexanes $\rightarrow$ 10% Et$_2$O in hexanes $\rightarrow$ 20% Et$_2$O in hexanes $\rightarrow$ 30% Et$_2$O in hexanes to give compound 7.16h in 48% yield as a colorless oil (25 mg, 0.079 mmol).

\[^{1}\text{H}\text{ NMR (500 MHz)}\ \delta = 8.40\ (d, \text{ }J = 8.4\ \text{Hz}, 1\text{H}),\ 8.34\ (bs, 1\text{H}),\ 8.10\ (d, \text{ }J = 8.2\ \text{Hz}, 1\text{H}),\ 7.71\ (s, 1\text{H}),\ 7.61\ (t, \text{ }J = 7.4\ \text{Hz}, 1\text{H}),\ 7.52\ (t, \text{ }J = 7.9\ \text{Hz}, 1\text{H}),\ 7.43\ (s, 1\text{H}),\ 4.12\ (s, 3\text{H}),\ 3.74-3.67\ (m, 1\text{H}),\ 3.12-3.06\ (m, 1\text{H}),\ 2.99-2.92\ (m, 1\text{H}),\ 2.54-2.48\ (m, 1\text{H}),\ 2.46\ (s, 3\text{H}),\ 1.92-1.85\ (m, 1\text{H}),\ 1.52\ (d, \text{ }J = 7.0\ \text{Hz}, 3\text{H}).\]

\[^{13}\text{C}\text{ NMR (125 MHz)}\ \delta = 149.96,\ 140.03,\ 133.94,\ 129.69,\]
126.04, 125.61, 124.92, 124.28, 123.85, 123.51, 121.86, 120.16, 118.07, 117.84, 97.18, 55.95,
38.24, 34.03, 30.67, 20.21, 19.48. IR \( f (\text{cm}^{-1}) = 3461, 2951, 2862, 1689, 1628, 1598, 1525, 1470,
1447, 1377, 1336, 1273, 1248, 1211, 1158, 1117, 1094, 1037, 987, 945, 908, 857, 831. \) HRMS \( (M + H)^+ = 316.1696 \) calculated for \( \text{C}_{22}\text{H}_{22}\text{NO} \); 316.1692 experimental.

Synthesis of 1,5-dimethyl-2,3,4,11-tetrahydro-1H-benzo[\( \alpha \)]carbazole (7.17a)

\[
\begin{align*}
\text{TBSO} & \quad \text{Me} \\
\text{Me} & \quad \text{OH} \\
7.15 & \quad \text{CSA} \\
\text{CH}_2\text{Cl}_2, 40^\circ\text{C} & \quad \text{Me} \\
\text{Me} & \quad \text{N} \\
\text{7.17a} & \quad \text{H}
\end{align*}
\]

Alcohol 7.15 (50 mg, 0.186 mmol) was dissolved in \( \text{CH}_2\text{Cl}_2 \) (0.35 mL) in a pressure vessel. Indole (21 \( \square \), 0.186 mmol) was then added, followed by camphorsulfonic acid (41 mg, 0.186 mmol). The reaction was warmed to 40\( ^\circ \)C and allowed to stir for 22 hours, and the mixture was purified directly \( 100\% \) hexanes \( \rightarrow \) 10% Et\( _2 \)O in hexanes \( \rightarrow \) 20% Et\( _2 \)O in hexanes \( \rightarrow \) 30% Et\( _2 \)O in hexanes to give compound 7.17a in 71% yield as a colorless oil (32 mg, 0.126 mmol).

\( ^1\text{H} \) NMR (500 MHz) \( \delta = 8.02 \) (d, \( J = 7.8 \) Hz, 1H), 7.74 (bs, 1H), 7.44 (d, \( J = 8.1 \) Hz, 1H), 7.37 (ddt, \( J = 8.2, 7.1, 1.3 \) Hz, 1H), 7.23-7.19 (m, 1H), 3.34-3.28 (m, 1H), 2.91-2.86 (m, 1H), 2.71-2.64 (m, 1H), 2.40 (s, 3H), 2.07-1.94 (m, 3H), 1.87-1.83 (m, 1H), 1.44 (d, \( J = 7.2 \) Hz, 3H).

\( ^{13}\text{C} \) NMR (125 MHz) \( \delta = 139.30, 136.90, 132.74, 128.03, 124.84, 124.25, 123.80, 120.42,
119.87, 119.09, 118.41, 110.45, 29.48, 28.56, 27.37, 20.57, 20.14, 18.11. \) IR \( f (\text{cm}^{-1}) = 3430, 2960, 2927, 2862, 1610, 1491, 1457, 1434, 1421, 1377, 1336, 1296, 1247, 1226, 1187, 1146,
1016, 907, 865, 841, 774, 734. \) HRMS \( (M + H)^+ = 250.1590 \) calculated for \( \text{C}_{18}\text{H}_{20}\text{N} \); 250.1601 experimental.
Synthesis of 1,5,8-trimethyl-2,3,4,11-tetrahydro-1H-benzo[a]carbazole (7.17b)

![Chemical structure of 7.17b](image)

Alcohol 7.15 (50 mg, 0.177 mmol) was dissolved in CH\(_2\)Cl\(_2\) (0.35 mL) in a pressure vessel. 5-Methylindole (23 mg, 0.177 mmol) was then added, followed by camphorsulfonic acid (41 mg, 0.177 mmol). The reaction was warmed to 40°C and allowed to stir for 22 hours, and the mixture was purified directly using 100% hexanes → 10% Et\(_2\)O in hexanes → 20% Et\(_2\)O in hexanes → 30% Et\(_2\)O in hexanes to give compound 7.17b in 63% yield as a colorless oil (30 mg, 0.111 mmol).

\(^1\)H NMR (400 MHz) \(\delta = 7.80 (s, 1H), 7.77 (bs, 1H), 7.69 (s, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.18 (dd, \(J = 8.2, 1.6\) Hz, 1H), 3.33-3.25 (m, 1H), 2.90-2.84 (m, 1H), 2.70-2.61 (m, 1H), 2.52 (s, 3H), 2.38 (s, 3H), 2.03-1.91 (m, 3H), 1.86-1.81 (m, 1H), 1.43 (d, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (125 MHz) \(\delta = 137.55, 137.25, 132.53, 128.30, 127.76, 126.16, 124.21, 123.98, 120.31, 119.86, 118.36, 110.09, 29.50, 28.56, 27.37, 21.44, 20.53, 20.14, 18.12. IR (cm\(^{-1}\)) = 3433, 2960, 2929, 2863, 1616, 1493, 1446, 1377, 1295, 1254, 1226, 1190, 1038, 908, 862, 799, 734, 597, 584, 439. HRMS (M + H\(^+\)) = 264.1747 calculated for C\(_{19}\)H\(_{22}\)N; 264.1752 experimental.

Synthesis of 8-methoxy-1,5-dimethyl-2,3,4,11-tetrahydro-1H-benzo[\(\square\)]carbazole (7.17c)

![Chemical structure of 7.17c](image)
Alcohol 7.15 (50 mg, 0.177 mmol) was dissolved in CH₂Cl₂ (0.35 mL) in a pressure vessel. 5-Methoxyindole (26 µg, 0.177 mmol) was then added, followed by camphorsulfonic acid (41 mg, 0.177 mmol). The reaction was warmed to 40°C and allowed to stir for 22 hours, and the mixture was purified directly using 100% hexanes → 10% Et₂O in hexanes → 20% Et₂O in hexanes → 30% Et₂O in hexanes to give compound 7.17c in 76% yield (38 mg, 0.135 mmol).

¹H NMR (500 MHz) δ = 7.72 (bs, 1H), 7.67 (s, 1H), 7.48 (d, J = 2.5 Hz, 1H), 7.33 (d, J = 8.7 Hz, 1H), 7.00 (dd, J = 8.2, 2.6 Hz, 1H), 3.92 (s, 3H), 3.31-3.25 (m, 1H), 2.89-2.84 (m, 1H), 2.68-2.61 (m, 1H), 2.37 (s, 3H), 2.03-1.91 (m, 4H), 1.55 (s, 3H). ¹³C NMR (125 MHz) δ = 153.71, 137.79, 134.26, 132.76, 127.70, 124.40, 124.28, 120.49, 118.31, 113.94, 111.11, 102.92, 56.05, 29.49, 28.55, 27.38, 20.50, 20.13, 18.10. IR (cm⁻¹) = 3427, 2928, 2864, 2829, 1709, 1629, 1483, 1460, 1292, 1264, 1213, 1188, 1173, 1137, 1107, 1030, 859, 838, 802, 770, 737, 610, 438. HRMS (M + H)⁺ = 280.1696 calculated for C₁₀H₂₂NO; 280.1704 experimental

Synthesis of 9-chloro-1,5-dimethyl-2,3,4,11-tetrahydro-1H-benzo[a]carbazole (7.17d)

Alcohol 7.15 (50 mg, 0.177 mmol) was dissolved in CH₂Cl₂ (0.35 mL) in a pressure vessel. 6-Chloroindole (27 µg, 0.177 mmol) was then added, followed by camphorsulfonic acid (41 mg, 0.177 mmol). The reaction was warmed to 40°C and allowed to stir for 20 hours, and the mixture was purified directly using 100% hexanes → 10% Et₂O in hexanes → 20% Et₂O in
hexanes $\rightarrow$ 30% Et$_2$O in hexanes to give compound 7.17d in 88% yield as a colorless oil (44 mg, 0.156 mmol).

$^1$H NMR (400 MHz) $\delta = 7.89$ (s, 1H), 7.87 (s, 1H), 7.67 (s, 1H), 7.41 (s, 1H), 7.16 (d, $J = 8.3$ Hz, 1H), 3.28 (ddd, $J = 16.4$, 8.0, 7.9 Hz, 1H), 2.90-2.84 (m, 1H), 2.69-2.60 (m, 1H), 2.38 (s, 3H), 2.03-1.91 (m, 3H), 1.83-1.81 (m, 1H), 1.42 (d, $J = 7.1$ Hz, 3H). $^{13}$C NMR (100 MHz) $\delta = 139.74$, 137.13, 133.20, 130.40, 128.67, 124.46, 120.62, 119.67, 118.30, 110.56, 29.38, 28.50, 27.35, 20.58, 20.13, 18.02. IR $f$(cm$^{-1}$) = 3437, 2959, 2929, 2862, 1610, 1454, 1427, 1287, 1243, 1065, 924, 805. HRMS (M + H)$^+$ = 284.1201 calculated for C$_{18}$H$_{19}$ClN; 284.1200 experimental.

Synthesis of 8-bromo-1,5-dimethyl-2,3,4,11-tetrahydro-1H-benzo[a]carbazole (7.17e)

Alcohol 7.15 (50 mg, 0.177 mmol) was dissolved in CH$_2$Cl$_2$ (0.35 mL) in a pressure vessel. 5-Bromoindole (35 mg, 0.177 mmol) was then added, followed by camphorsulfonic acid (41 mg, 0.177 mmol). The reaction was warmed to 40°C and allowed to stir for 20 hours, and the mixture was purified directly using 100% hexanes $\rightarrow$ 10% Et$_2$O in hexanes $\rightarrow$ 20% Et$_2$O in hexanes $\rightarrow$ 30% Et$_2$O in hexanes to give compound 7.17e in 90% yield as a colorless oil (53 mg, 0.160 mmol).

$^1$H NMR (500 MHz) $\delta = 8.10$ (d, $J = 1.8$ Hz, 1H), 7.88 (bs, 1H), 7.66 (s, 1H), 7.43 (dd, $J = 8.5$, 1.9 Hz, 1H), 7.30 (d, $J = 8.6$ Hz, 1H), 3.31-3.25 (m, 1H), 2.90-2.84 (m, 1H), 2.65 (ddd, $J = 17.1$, 10.7, 6.5 Hz, 1H), 2.37 (s, 3H), 1.99-1.91 (m, 3H), 1.42 (d, $J = 7.1$ Hz, 3H). $^{13}$C NMR
(125 MHz) \( \delta = 137.85, 137.33, 133.68, 128.61, 127.48, 125.62, 124.45, 122.62, 119.48, 118.44, 111.91, 111.87, 29.38, 28.52, 27.38, 20.55, 20.13, 18.00. \) IR \( f (\text{cm}^{-1}) = 3442, 2961, 2930, 2864, 1490, 1459, 1418, 1284, 1244, 861. \) HRMS \( (M + H)^{+} = 328.0695 \) calculated for \( C_{18}H_{19}NBr; 328.0695 \) experimental.

Synthesis of methyl 1,5-dimethyl-2,3,4,11-tetrahydro-1H-benzo[a]carbazole-8-carboxylate (7.17f)

Alcohol 7.15 (50 mg, 0.177 mmol) was dissolved in \( \text{CH}_2\text{Cl}_2 \) (0.35 mL) in a pressure vessel. methyl-5-Carboxylate indole (31 mg, 0.177 mmol) was then added, followed by camphorsulfonic acid (41 mg, 0.177 mmol). The reaction was warmed to 40°C and allowed to stir for 20 hours, and the mixture was purified directly using 100% hexanes \( \rightarrow 10\% \) Et\(_2\)O in hexanes \( \rightarrow 20\% \) Et\(_2\)O in hexanes \( \rightarrow 30\% \) Et\(_2\)O in hexanes to give compound 7.17f in 29% yield as a colorless oil (16 mg, 0.051 mmol).

\(^1\text{H} \) NMR (500 MHz) \( \delta = 8.74 \) (s, 1H), 8.11 (bs, 1H), 8.08 (dd, \( J = 8.5, 1.6 \) Hz, 1H), 7.77 (s, 1H), 7.43 (d, \( J = 8.5 \) Hz, 1H), 3.96 (s, 1H), 3.33-3.28 (m, 1H), 2.90-2.85 (m, 1H), 2.69-2.62 (m, 1H), 2.69 (t, \( J = 6.7 \) Hz, 1H), 2.40-2.35 (m, 2H), 1.99-1.94 (m, 3H), 1.43 (dd, \( J = 7.2 \) Hz, 3H). \(^{13}\text{C} \) NMR (125 MHz) \( \delta = 167.98, 142.02, 137.31, 133.67, 129.11, 126.59, 124.58, 123.54, 122.47, 121.08, 120.40, 118.65, 109.98, 51.87, 30.30, 29.35, 28.50, 20.68, 20.18, 17.98. \) IR \( f (\text{cm}^{-1}) = 3351, 2926, 2856, 1693, 1609, 1584, 1494, 1435, 1393, 1323, 1302, 1261, 1225, 1197, 1163, \)
1113, 1089, 1016, 985, 907, 865, 803, 770, 730, 683, 648, 596, 496, 440. HRMS (M + H)$^+$ = 308.1645 calculated for C$_{20}$H$_{22}$NO$_2$; 308.1644 experimental.

Synthesis of 8-methoxy-1,5-dimethyl-2,3,4,13-tetrahydro-1H-dibenzo[a,i]carbazole (7.17h)

Alcohol 7.15 (50 mg, 0.177 mmol) was dissolved in CH$_2$Cl$_2$ (0.35 mL) in a pressure vessel. 5-Methoxy benz[g]indole (34 mg, 0.177 mmol) was then added, followed by camphorsulfonic acid (41 mg, 0.177 mmol). The reaction was warmed to 40°C and allowed to stir for eight days, and the mixture was purified directly using 100% hexanes $\rightarrow$ 2% Et$_2$O in hexanes $\rightarrow$ 5% Et$_2$O in hexanes $\rightarrow$ 10% Et$_2$O in hexanes $\rightarrow$ 20% Et$_2$O in hexanes to give compound 7.17h in 43% yield as a colorless oil (28 mg, 0.085 mmol).

$^1$H NMR (500 MHz) $\delta$ = 8.40 (d, $J$ = 8.4 Hz, 1H), 8.33 (bs, 1H), 8.12 (d, $J$ = 8.2 Hz, 1H), 7.73 (s, 1H), 7.62 (d, $J$ = 7.3 Hz, 1H), 7.53-7.50 (m, 1H), 7.42 (s, 1H), 4.12 (s, 3H), 3.47-3.42 (m, 1H), 2.92-2.88 (m, 1H), 2.73-2.66 (m, 1H), 2.42 (s, 3H), 2.06-1.96 (m, 3H), 1.90-1.86 (m, 1H), 1.51 (d, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (125 MHz) $\delta$ = 149.92, 136.18, 131.59, 129.16, 128.24, 126.00, 124.84, 124.72, 124.21, 123.50, 121.81, 121.68, 120.14, 118.03, 117.76, 97.11, 55.94, 29.51, 28.60, 27.33, 20.76, 20.24, 18.17. IR $f$(cm$^{-1}$) = 3463, 2930, 2863, 2830, 1626, 1597, 1525, 1471, 1446, 1431, 1378, 1290, 1271, 1246, 1209, 1189, 1157, 1125, 1111, 1096, 1032, 985, 858, 830, 758, 737, 701, 431. HRMS (M + H)$^+$ = 330.1852 calculated for C$_{23}$H$_{24}$NO; 330.1589 experimental.
Synthesis of 1-allyl-4-methyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole (7.19a)

Alcohol 7.18a (51 mg, 0.1173 mmol) was dissolved in dichloromethane (0.350 mL). Indole (20 \text{ mg}, 0.173 mmol) was then added, followed by camphorsulfonic acid (20 mg, 0.087 mmol). The reaction was allowed to stir for 5 hours, and the mixture was purified directly using 100% hexanes $\rightarrow$ 5% Et$_2$O in hexanes $\rightarrow$ 10% Et$_2$O in hexanes $\rightarrow$ 20% Et$_2$O in hexanes to give compound 7.19a in 51% yield as a colorless oil (25 mg, 0.096 mmol).

$^1$H NMR (500 MHz) $\delta$ = 8.01 (d, $J$ = 7.8 Hz, 1H), 7.98 (bs, 1H), 7.72 (s, 1H), 7.41 (dt, $J$ = 8.1, 0.9 Hz, 1H), 7.36 (ddd, $J$ = 8.2, 7.0, 1.2 Hz, 1H), 7.19 (ddd, $J$ = 8.0, 7.1, 1.2 Hz, 1H), 5.96 (dddd, $J$ = 13.8, 10.1, 6.9, 6.9 Hz, 1H), 5.20 (dq, $J$ = 17.1, 1.6 Hz, 1H), 5.14 (dt, $J$ = 10.4, 1.1 Hz, 1H), 3.62 (ddd, $J$ = 13.0, 8.0, 5.0 Hz, 1H), 3.04 (ddd, $J$ = 16.0, 7.8, 7.8 Hz, 1H), 2.92 (ddd, $J$ = 16.0, 8.9, 4.7 Hz, 1H), 2.66-2.20 (m, 1H), 2.47-2.43 (m, 1H), 2.42 (s, 3H), 2.42-2.33 (m, 1H), 2.02 (ddd, $J$ = 12.9, 12.9, 4.6 Hz, 1H). $^{13}$C NMR (125 MHz) $\delta$ = 141.67, 139.56, 137.78, 134.70, 127.49, 125.32, 124.99, 122.58, 119.92, 119.13, 118.77, 116.60, 110.54, 99.97, 43.66, 38.91, 31.35, 30.59, 19.37. IR $f$ (cm$^{-1}$) = 3418, 2928, 2856, 1703, 1636, 1614, 1491, 1458, 1438, 1329, 1304, 1247, 1222, 913, 842, 744, 439. HRMS (M + H)$^+$ = 262.1590 calculated for C$_{19}$H$_{20}$N; 262.1593 experimental.
Synthesis of 4-methyl-1-nonyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole (7.19b)

Alcohol 7.18b (31 mg, 0.081 mmol) was dissolved in CH₂Cl₂ (0.20 mL). Indole (9.5 mg, 0.081 mmol) was then added, followed by camphorsulfonic acid (9.4 mg, 0.041 mmol). The reaction was allowed to stir for 96 hours, and the mixture was purified directly using 100% hexanes → 10% Et₂O in hexanes to give compound 7.19b in 74 % yield as a colorless oil (20.8 mg, 0.060 mmol).

¹H NMR (500 MHz) δ = 8.01 (d, J = 7.7 Hz, 1H), 7.82 (s, 1H), 7.70 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 3.51 (tt, J = 8.7, 4.5 Hz, 1H), 3.04 (dt, J = 15.9, 7.7 Hz, 1H), 2.91 (ddd, J = 13.8, 8.9, 4.8 Hz, 1H), 2.42 (s, 3H), 2.37 (m, 1H), 1.95 (ddddd, J = 23.5, 13.0, 8.5, 4.5 Hz, 2H), 1.66 – 1.54 (m, 3H), 1.35-1.20 (sm, 20H), 0.88 (t, J = 6.7 Hz, 5H). ¹³C NMR (125 MHz) δ = 141.43, 139.56, 134.71, 128.35, 125.35, 124.94, 123.78, 122.51, 119.91, 119.11, 118.52, 110.51, 43.86, 34.73, 31.89, 31.18, 30.77, 30.05, 29.71, 29.64, 29.33, 27.92, 22.68, 19.40, 14.11. IR f(cm⁻¹) = 3424, 2921, 2851, 1708, 1613, 1490, 1458, 1438, 1377, 1303, 1259, 1089, 1015, 863, 798, 734. HRMS (M + H)⁺ = 348.2686 calculated for C₁₇H₁₈N; 348.2696 experimental.
Synthesis of 1-methyl-4-phenyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole (7.19c)

Alcohol 7.18c (50 mg, 0.151 mmol) was dissolved in dichloromethane (0.300 mL). Indole (18 mg, 0.151 mmol) was then added, followed by camphorsulfonic acid (18 mg, 0.08 mmol). The reaction was allowed to stir for 24 hours, and the mixture was purified directly using 100% hexanes $\rightarrow$ 10% Et₂O in hexanes $\rightarrow$ 20% Et₂O in hexanes $\rightarrow$ 30% Et₂O in hexanes to give compound 7.19c in 63% yield (29 mg, 0.096 mmol).

$^1$H NMR (500 MHz) $\delta$ = 8.05 (d, $J = 7.8$ Hz, 1H), 7.97 (bs, 1H), 7.93 (s, 1H), 7.55 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.45 (t, $J = 2.7$ Hz, 1H), 7.42-7.38 (m, 1H), 7.36-7.33 (m, 2H), 7.24-7.21 (m, 1H), 3.70-3.63 (m, 1H), 3.20 (ddd, $J = 15.5, 8.9, 6.3$ Hz, 1H), 3.04 (ddd, $J = 15.6, 8.5, 5.9$ Hz, 1H), 2.46-2.39 (m, 1H), 1.88-1.81 (m, 1H), 1.51 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (125 MHz) $\delta$ = 142.35, 140.85, 139.83, 135.49, 130.87, 129.88, 128.97, 128.15, 126.28, 125.43, 123.69, 122.93, 120.12, 119.49, 118.91, 110.66, 38.09, 34.70, 31.89, 19.72. IR $\nu$ (cm⁻¹) = 3424, 3389, 3377, 3057, 3038, 2953, 2928, 2889, 2867, 1694, 1670, 1612, 1576, 1490, 1471, 1451, 1436, 1375, 1353, 1326, 1306, 1284, 1244, 1117, 1100, 1074, 1031, 1016, 931, 878, 864, 839, 767, 739, 701, 585, 491, 439. HRMS (M + H)$^+$ = 298.1590 calculated for C$_{22}$H$_{20}$N; 298.1584 experimental.
Synthesis of tert-butyl 3-(4-methyl-1,2,3,10-tetrahydrocyclopenta[a]carbazol-1-yl)-1H-indole-1-carboxylate (7.19d)

Alcohol 7.18d (68 mg, 0.145 mmol) was dissolved in dichloromethane (0.290 mL). Indole (17 □□, 0.145 mmol) was then added, followed by camphorsulfonic acid (15 mg, 0.072 mmol). The reaction was allowed to stir for 19 hours, and the mixture was purified directly using 100% hexanes → 10% Et2O in hexanes → 20% Et2O in hexanes → 30% Et2O in hexanes to give compound 7.19d in 43% yield as a white solid (27 mg, 0.063 mmol).

$^1$H NMR (500 MHz) $\delta$ = 8.09 (d, $J$ = 8.5 Hz, 1H), 7.99 (d, $J$ = 7.4 Hz, 1H), 7.78 (s, 1H), 7.61 (d, $J$ = 3.8 Hz, 1H), 7.47 (d, $J$ = 1.8 Hz, 1H), 7.27-7.23 (m, 2H), 7.15-7.12 (m, 3H), 6.49 (d, $J$ = 3.8 Hz, 1H), 4.76 (t, $J$ = 8.5 Hz, 1H), 3.20 (ddd, $J$ = 15.8, 9.0, 3.1 Hz, 1H), 3.04 (dt, $J$ = 16.5, 8.4 Hz, 1H), 2.84-2.78 (m, 1H), 2.50 (s, 3H), 2.22-2.14 (m, 1H), 1.67 (s, 9H). $^{13}$C NMR (125 MHz) $\delta$ = 200.36, 149.76, 142.11, 139.44, 138.86, 134.90, 131.08, 126.95, 125.20, 124.84, 123.41, 122.66, 119.89, 119.83, 119.05, 118.97, 115.57, 110.65, 107.25, 83.73, 50.49, 37.52, 31.58, 28.18, 19.41. IR $\nu$ (cm$^{-1}$) = 3454, 3411, 2975, 2931, 2858, 1731, 1631, 1613, 1579, 1536, 1491, 1468, 1458, 1440, 1372, 1347, 1332, 1305, 1247, 1218, 1161, 1130, 1083, 1040, 1024, 852, 820, 766, 734, 632, 574, 487, 439, 421. HRMS (M + H)$^+$ = 437.2224 calculated for C$_{29}$H$_{29}$N$_2$O$_2$; 437.2221 experimental.
Synthesis of 4-methyl-1-phenyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole (7.19e)

Alcohol 7.18e (55 mg, 0.166 mmol) was dissolved in dichloromethane (0.330 mL). Indole (19 mg, 0.166 mmol) was then added, followed by camphorsulfonic acid (19 mg, 0.083 mmol). The reaction was allowed to stir for 19 hours, and the mixture was purified directly using 100% hexanes → 10% Et₂O in hexanes → 20% Et₂O in hexanes → 30% Et₂O in hexanes to give compound 7.19e in 92% yield as a yellow solid (46 mg, 0.153 mmol).

¹H NMR (500 MHz) δ = 8.00 (d, J = 7.8 Hz, 1H), 7.78 (s, 1H), 7.37-7.27 (m, 6H), 7.20-7.14 (m, 2 H), 7.12 (bs, 1H), 4.67 (t, J = 8.4 Hz, 1H), 3.18 (ddd, J = 15.8, 9.0, 3.3 Hz, 1H), 3.03 (dt, J = 16.5, 8.5 Hz, 1H), 2.82-2.75 (m, 1H), 2.49 (s, 3H), 2.20-2.13 (m, 1H). ¹³C NMR (125 MHz) δ = 144.45, 142.13, 139.45, 134.81, 128.92, 127.89, 126.79, 126.55, 125.21, 124.91, 123.42, 119.87, 119.03, 110.5850.53, 37.04, 31.55, 19.40. IR ν (cm⁻¹) = 3456, 3025, 2928, 2855, 1701, 1632, 1612, 1490, 1456, 1439, 1372, 1326, 1306, 1245, 1218, 1141, 1077, 1016, 908, 841, 792, 761, 745, 732, 701, 651, 613, 574, 554, 518, 495, 438. HRMS (M + H)⁺ = 298.1590 calculated for C₂₂H₂₀N; 298.1581 experimental.

Synthesis of 1-methyl-1,2,3,10-tetrahydrocyclopenta[a]carbazole (7.19g)
Alcohol 7.18g (100 mg, 0.393 mmol) was dissolved in CH$_2$Cl$_2$ (0.80 mL). Indole (46

□□, 0.393 mmol) was then added, followed by camphorsulfonic acid (46 mg, 0.197 mmol). The reaction was allowed to stir for 4 days, and the mixture was purified directly using 100% hexanes $\rightarrow$ 10% Et$_2$O in hexanes $\rightarrow$ 20% Et$_2$O in hexanes to give compound 7.19g in 70% yield as a colorless oil (61 mg, 0.276 mmol).

$^1$H NMR (500 MHz) δ = 8.04 (d, $J = 7.7$ Hz, 1H), 7.93 (s, 1H), 7.89 (d, $J = 7.9$ Hz, 1H), 7.44 (d, $J = 8.1$ Hz, 1H), 7.38 (ddd, $J = 8.2$, 7.1, 1.2 Hz, 1H), 7.22 (ddd, $J = 8.0$, 7.1, 1.1 Hz, 1H), 7.13 (d, $J = 7.9$ Hz, 1H), 3.61 (x, $J = 13.8$, 6.9 Hz, 1H), 3.17 (ddd, $J = 15.7$, 8.5, 6.3 Hz, 1H), 3.02 (ddd, $J = 15.3$, 8.7, 6.0 Hz, 1H), 2.46 (ddd, $J = 12.5$, 8.7, 8.0, 6.2 Hz, 1H), 1.85 (ddt, $J = 12.4$, 8.5, 5.7 Hz, 1H), 1.46 (d, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (125 MHz) δ = 142.03, 139.48, 136.15, 129.59, 125.16, 123.87, 122.21, 120.00, 119.37, 118.50, 116.30, 110.56, 37.90, 34.52, 31.92, 19.88. IR $\nu$(cm$^{-1}$) = 3422, 3057, 2952, 2923, 2848, 1687, 1610, 1493, 1458, 1421, 1323, 1303, 1259, 1223, 1015, 907, 803, 734, 553. HRMS (M + H)$^+$ = 222.1277 calculated for C$_{16}$H$_{16}$N; 222.1277 experimental.

Synthesis of 1-methyl-2,3,4,11-tetrahydro-1H-benzo[a]carbazole (7.19h)

![Synthesis of 1-methyl-2,3,4,11-tetrahydro-1H-benzo[a]carbazole](attachment)

In a pressure vessel, alcohol 7.18h (50 mg, 0.212 mmol) was dissolved in dichloromethane (0.350 mL). Indole (25 □□, 0.212 mmol) was then added, followed by camphorsulfonic acid (41 mg, 0.212 mmol). The reaction was allowed to stir for 20 hours at 40°C, and the mixture was purified directly using 100% hexanes $\rightarrow$ 10% Et$_2$O in hexanes $\rightarrow$
20% Et₂O in hexanes → 30% Et₂O in hexanes to give compound 7.19h in 62% yield (31 mg, 0.132 mmol).

\(^1\)H NMR (500 MHz) \(\delta = 8.02\) (d, \(J = 7.8\) Hz, 1H), 7.94 (bs, 1H), 7.82 (d, \(J = 7.8\) Hz, 1H), 7.45 (d, \(J = 8.1\) Hz, 1H), 7.37 (ddd, \(J = 8.2, 7.1, 1.2\) Hz, 1H), 7.23-7.19 (m, 1H), 6.98 (d, \(J = 8.0\) Hz, 1H), 3.32-3.27 (m, 1H), 3.00-2.89 (m, 2H), 2.06-1.95 (m, 2H), 1.88-1.83 (m, 2H), 1.43 (d, \(J = 7.2\) Hz, 3H). \(^1\)C NMR (125 MHz) \(\delta = 139.20, 138.26, 134.05, 124.96, 124.25, 123.89, 121.18, 120.83, 119.91, 119.30, 117.58, 110.50, 30.29, 29.91, 28.30, 20.69, 18.46. IR \(f(\text{cm}^\text{-1}) = 3430, 2929, 1608, 1459, 1423, 1329, 1305, 1237, 772, 739.\) HRMS (M + H)\(^+\) = 236.1434 calculated for \(\text{C}_{17}\text{H}_{17}\text{N}; 236.1430\) experimental.

8.7.2 Synthetic Procedures for Starting Material Formation

Synthesis of 2-((tert-butyldimethylsilyl)oxy)-3-methyl-1-vinylcyclohex-2-en-1-ol (7.18h)

Starting ketone S-11 (500 mg, 2.08 mmol) was dissolved in dichloromethane (10 mL). Vinylmagnesium bromide (3.12 mL, 3.12 M solution in THF) was then slowly added. After five minutes, the reaction was quenched with water. The aqueous layer was extracted twice with ethyl acetate, and collected organic layers were dried over sodium sulfate. Crude product was concentrated under vacuum and purified with 1% TEA buffered flash column chromatography 100% hexanes → 2% Et₂O in hexanes → 5% Et₂O in hexanes to give product 7.18h in 56% yield (315 mg, 1.17 mmol).
$^1$H NMR (400 MHz) $\delta = 5.96$ (dd, $J = 21.8, 13.4$ Hz, 1H), 5.24 (dd, $J = 21.7, 1.5$ Hz, 1H), 5.13 (dd, $J = 13.4, 1.5$ Hz, 1H), 2.15 (s, 1H), 2.11-1.90 (m, 3H), 1.64-1.57 (m, 4H), 0.94 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H). $^{13}$C NMR (125 MHz) $\delta = 144.14, 143.41, 114.58, 113.53, 73.70, 38.15, 31.23, 26.30, 18.88, 18.66, 17.35, -3.31, -3.34$. IR $f$ (cm$^{-1}$) = 3475, 2930, 2857, 2833, 1671, 1628, 1472, 1462, 1441, 1407, 1388, 1360, 1332, 1311, 1251, 1195, 1171, 1140, 1121, 1087, 1038, 1005, 991, 950, 921, 866, 828, 777, 672, 592, 559, 531, 510, 443, 419. HRMS (M + H)$^+$ = 291.1751 calculated for C$_{15}$H$_{28}$NaO$_2$Si; 291.1753 experimental.

Synthesis of 2-((tert-butyldimethylsilyl)oxy)-3-(5-methylfuran-2-yl)-1-(prop-1-en-2-yl)cyclopent-2-en-1-ol (7.18a)

![Chemical Reaction Diagram]

In a pressure vessel, starting ketone S-8 (300 mg, 1.03 mmol), allylttributyltin (350 $\mu$L, 1.13 mmol), and lithium chloride (218 mg, 5.15 mmol) was dissolved in THF (7mL). The reaction was degassed with nitrogen for thirty minutes, and Pd(PPh$_3$)$_4$ (119 mg, 0.103 mmol) was added. The reaction was then heated to reflux for 18 hours. The reaction was then diluted with DI water (20 mL) and extracted (3 x 15 mL) with ethyl acetate. Organic layers were dried over sodium sulfate and concentrated under vacuum. Crude product was purified with flash column chromatography 100% hexanes $\rightarrow$ 10% Et$_2$O in hexanes $\rightarrow$ 20% Et$_2$O in hexanes give product S-12 in 79% yield (206 mg, 0.816 mmol).
\(^1\)H NMR (500 MHz) \(\delta = 5.79\) (ddt, \(J = 16.8, 9.9, 6.7\) Hz, 1H), 5.15-5.09 (m, 2H), 3.13 (d, \(J = 6.9\) Hz, 2H), 2.42-2.40 (m, 2H), 2.34-2.30 (m, 2H), 0.095 (s, 9H), 0.20 (s, 6H). \(^{13}\)C NMR (125 MHz) \(\delta = 203.11, 151.97, 149.24, 133.20, 117.28, 33.24, 32.18, 25.72, 24.54, 18.33, -4.06.\)

IR \(\nu (\text{cm}^{-1}) = 2955, 2928, 2857, 1713, 1639, 1366, 1251, 1112, 856, 841, 785.\) HRMS (M + H)\(^+\) = 253.1618 calculated for C\(_{14}\)H\(_{25}\)O\(_2\)Si; 253.1620 experimental.

Starting ketone S-12 (88 mg, 0.349 mmol) was dissolved in dichloromethane (5 mL). Isopropenylmagnesium bromide (2.09 mL, 0.5 M solution in THF) was then slowly added. After one hour, the reaction was quenched with DI H\(_2\)O. The aqueous layer was extracted with ethyl acetate (3 x 15 mL), and collected organic layers dried over sodium sulfate. Crude product was concentrated under vacuum and purified with buffered 2% triethylamine flash column chromatography 100% hexanes \(\rightarrow\) 5% Et\(_2\)O in hexanes \(\rightarrow\) 10% Et\(_2\)O in hexanes to give product 7.18a in 50% yield (51 mg, 0.173 mmol).

\(^1\)H NMR (500 MHz) \(\delta = 5.74\) (ddt, \(J = 16.8, 10.1, 6.6\) Hz, 1H), 5.06-4.99 (m, 3H), 4.84 (ddd, \(J = 3.1, 1.6, 1.6\) Hz, 1H), 2.87-2.78 (m, 2H), 2.28-2.24 (m, 1H), 2.14-2.09 (m, 2H), 1.87-1.83 (m, 1H), 1.72 (s, 3H), 0.92 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H). \(^{13}\)C NMR (125 MHz) \(\delta = 148.42, 147.93, 135.42, 117.54, 115.54, 109.54, 85.57, 35.85, 31.52, 27.65, 25.80, 18.89, 18.38, -3.54, -3.83.\) IR \(\nu (\text{cm}^{-1}) = 3469, 2954, 2929, 2857, 1680, 1640, 1472, 1361, 1336, 1250, 1184, 1064, 993, 958, 899, 838, 781, 678, 630, 577.\) HRMS (M – H\(_2\)O\(^+\)) = 277.1982 calculated for C\(_{17}\)H\(_{29}\)OSi; 277.1997 experimental.
Synthesis of 2-((tert-butyldimethylsilyl)oxy)-3-nonyl-1-(prop-1-en-2-yl)cyclopent-2-en-1-ol (7.18b)

Ketone S-12 (200 mg, 0.792 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL). 1-Octene (445 µL, 3.96 mmol) was then added, followed by Grubbs second-generation catalyst (20 mg, 0.024 mmol). The reaction was heated to reflux and allowed to stir for 2 days. The reaction was concentrated in vacuo and purified directly using 100% hexanes → 10% Et$_2$O in hexanes → 20% Et$_2$O in hexanes to give product S-13 as an inseparable mixture of isomers (E/Z : 5.7:1) in 47% yield as a colorless oil (124 mg, 0.370 mmol).

$^1$H NMR (500 MHz) δ = 5.52 (dtt, $J = 15.0, 6.7, 1.7$ Hz, 1H), 5.37 (dtt, $J = 15.0, 6.8, 1.5$ Hz, 1H), 3.12 (d, $J = 7.5$ Hz, 0.4 H), 3.05 (d, $J = 6.7$ Hz, 1.7 H), 2.80 – 2.78 (m, 1.3 H), 2.49 – 2.47 (m, 1.3 H), 2.38 (m, 2H), 2.30 (m, 2H), 2.08 (q, $J = 7.1$ Hz, 0.4 H), 2.00 (q, $J = 6.6$ Hz, 1.7 H), 1.39 – 1.21 (m, 9H), 0.97 (s, 5H), 0.94 (s, 8H), 0.90 – 0.83 (m, 4H), 0.22 (s, 3.6H), 0.18 (s, 6H). $^{13}$C NMR (125 MHz) δ = 203.00, 198.24, 153.10, 151.78, 148.87, 135.73, 133.67, 132.92, 124.30, 123.70, 33.95, 32.45, 32.14, 32.12, 32.06, 31.70, 31.66, 29.82, 29.45, 29.30, 28.93, 28.76, 27.82, 27.31, 26.87, 26.79, 25.73, 25.55, 24.55, 24.45, 22.58, 18.32, 18.29, 17.50, 14.01,
Ketone S-13 (85 mg, 0.253 mmol) and activated palladium on carbon (8.0 mg, 0.076 mmol) were dissolved in ethyl acetate (1.3 mL). Hydrogen gas was bubbled through reaction for 6 hours, and crude reaction was filtered over Celite pad, concentrated in vacuo, and purified directly using 100% hexanes → 2.5% Et₂O in hexanes to give product S-14 in 48% yield as a colorless oil (41 mg, 0.121 mmol).

\( ^1\)H NMR (400 MHz) \( \delta = 2.44 - 2.22 \) (m, 6H), 1.49 (t, \( J = 7.4 \) Hz, 2H), 1.33 – 1.22 (m, 13H), 0.95 (s, 9H), 0.88 (t, \( J = 6.6 \) Hz, 3H), 0.19 (s, 6H). \( ^13\)C NMR (125 MHz) \( \delta = 203.10, 155.40, 149.16, 32.14, 31.85, 29.65, 29.47, 29.38, 29.25, 28.71, 26.98, 25.75, 24.73, 22.65, 18.34, 14.07, -4.05. \) IR \( f(\text{cm}^{-1}) = 2926, 2854, 1710, 1639, 1462, 1409, 1374, 1248, 1113, 858, 839, 783, 684, 572, 492. \) HRMS (M + H)\(^+ \) = 339.2714 calculated for C\(_{20}\)H\(_{39}\)O\(_2\)Si; 339.2720 experimental.

Starting ketone S-14 (41 mg, 0.121 mmol) was dissolved in CH\(_2\)Cl\(_2\) (0.60 mL). Isopropenylmagnesium bromide (1.1 mL, 0.5 M solution in THF) was then slowly added. After two hours, the reaction was quenched with DI H\(_2\)O. The aqueous layer was extracted with ethyl acetate (3 x 15 mL), and collected organic layers dried over sodium sulfate. Crude product was concentrated under vacuum and purified with a buffered 2% triethylamine flash column chromatography 100% hexanes to give product 7.18b in 67% yield as a colorless oil (31 mg, 0.081 mmol).

\( ^1\)H NMR (500 MHz) \( \delta = 5.03 - 5.01 \) (d, \( J=1.4 \) Hz, 1H), 4.83 (t, \( J = 1.6 \) Hz, 1H), 2.15-2.08 (m, 3H), 1.99- (dt, \( J = 14.2, 7.4 \) Hz, 1H), 1.89 – 1.80 (m, 1H), 1.71 (s, 3H), 1.35-1.24 (m, Hz, 21
H, 0.96 (s, 3H), 0.93 (s, 9H), 0.88 (t, J = 6.8 Hz, 5H), 0.14 (d, J = 3.0 Hz, 6H). \(^{13}\)C NMR (125 MHz) \(\delta = 148.18, 147.38, 120.33, 109.42, 85.64, 35.91, 31.89, 30.32, 29.69, 29.58, 29.51, 29.31, 27.65, 27.56, 26.92, 25.87, 22.68, 18.94, 18.43, 14.10, -3.51, -3.80. IR (cm\(^{-1}\)) = 3478, 2925, 2854, 1681, 1462, 1360, 1250, 1070, 897, 859, 837, 780, 677. HRMS (M + Na\(^+\)) = 403.3003 calculated for C\(_{23}\)H\(_{44}\)NaO\(_2\)Si; 403.2989 experimental.

Synthesis of tert-butyl 3-(2-((tert-butyldimethylsilyloxy)-3-hydroxy-3-(prop-1-en-2-yl)cyclopent-1-en-yl)-1H-indole-1-carboxylate (7.18d)

\[
\begin{align*}
\text{S-8} &+ \text{K}_2\text{CO}_3, \text{Pd(PPh}_3\text{)}_4, \text{Toluene, EtOH} \rightarrow \text{S-15} \\
\text{S-15} \rightarrow \text{MeMgBr, CH}_2\text{Cl}_2, \text{rt} \rightarrow 7.18d
\end{align*}
\]

In a pressure vessel, starting ketone S-8 (153 mg, 0.525 mmol) was dissolved in toluene/ethanol (12 : 4mL). Potassium carbonate (218 mg, 1.58 mmol) and boronic ester (361 mg, 1.05 mmol) was then added, followed by Pd(PPh\(_3\))\(_4\) (30 mg, 0.026 mmol). The reaction was then heated to 80\(^\circ\)C for 18 hours. The reaction was then diluted with DI water (20 mL) and extracted (3 x 15 mL). Organic layers were dried over sodium sulfate and concentrated under vacuum. Crude product was purified with buffered flash column chromatography 100% hexanes \(\rightarrow\) 2% Et\(_2\)O in hexanes \(\rightarrow\) 5% Et\(_2\)O in hexanes \(\rightarrow\) 10% Et\(_2\)O in hexanes \(\rightarrow\) 20% Et\(_2\)O in hexanes \(\rightarrow\) 30% Et\(_2\)O in hexanes to give product S-15 in 73% yield (163 mg, 0.381 mmol).
$^1$H NMR (500 MHz) $\delta = 8.20$ (d, $J = 1.2$ Hz, 1H), 7.93 (dd, $J = 8.8, 1.2$ Hz, 1H), 7.61 (d, $J = 3.5$ Hz, 1H), 6.59 (d, $J = 3.7$ Hz, 1H), 2.94-2.92 (m, 2H), 2.51-2.49 (m, 2H), 1.68 (s, 9H), 1.00 (s, 9H), 0.27 (s, 6H). $^{13}$C NMR (125 MHz) $\delta = 203.05$, 149.53, 148.55, 145.62, 135.54, 130.43, 129.15, 126.61, 123.73, 120.35, 114.80, 107.53, 83.97, 31.46, 28.16, 25.92, 24.00, 18.61, -3.56. IR $f$(cm$^{-1}$) = 2930, 2857, 1735, 1699, 1605, 1471, 1438, 1359, 1336, 1285, 1256, 1158, 1132 1084, 1058, 1041, 1022, 873, 841, 785, 766, 727, 688, 595, 528, 510, 422. HRMS (M + H)$^+$ = 428.2252 calculated for C$_{24}$H$_{34}$NO$_4$Si; 428.2259 experimental.

Starting ketone S-15 (163 mg, 0.381 mmol) was dissolved in dichloromethane (5 mL). Isopropenylmagnesium bromide (0.833 mL, 0.5 M solution in THF) was then slowly added. After thirty minutes, the reaction was quenched with DI water (20 mL). The aqueous layer was extracted twice with ethyl acetate (2 x 20 mL), and collected organic layers were dried over sodium sulfate. Crude product was concentrated under vacuum and purified with buffered 2% triethylamine flash column chromatography 100% hexanes $\rightarrow$ 2% Et$_2$O in hexanes $\rightarrow$ 5% Et$_2$O in hexanes $\rightarrow$ 10% Et$_2$O in hexanes $\rightarrow$ 20% Et$_2$O in hexanes $\rightarrow$ 30% Et$_2$O in hexanes to give product 7.18d in 38 % yield (68 mg, 0.145 mmol).

$^1$H NMR (500 MHz) $\delta = 8.06$ (d, $J = 7.4$ Hz, 1H), 7.69 (d, $J = 1.0$ Hz, 1H), 7.56 (d, $J = 2.9$ Hz, 1H), 7.46 (dd, $J = 8.6, 1.2$ Hz, 1H), 6.52 (d, $J = 3.7$ Hz, 1H), 5.10 (s, 1H), 4.91 (t, $J = 1.6$ Hz, 1H), 2.86 (ddd, $J = 15.5, 8.9, 3.7$ Hz, 1H), 2.48 (ddd, $J = 14.2, 8.5, 5.5$ Hz, 1H), 2.24 (ddd, $J = 13.2, 8.5, 3.7$ Hz, 1H), 1.99 (ddd, $J = 13.9, 8.9, 5.5$ Hz, 1H), 1.85 (s, 3H), 1.67 (s, 9H), 0.91 (s, 9H), 0.04 (s, 3H), -0.14 (s, 3H). $^{13}$C NMR (125 MHz) $\delta = 149.74$, 149.25, 147.88, 133.82, 131.11, 130.28, 126.04, 124.11, 120.08, 118.70, 114.51, 109.95, 107.27, 86.31, 83.54, 35.96, 28.95, 28.20, 26.06, 19.04, 18.51, -3.26, -3.54. IR $f$(cm$^{-1}) = 3522, 3154, 2954, 2930, 2856, 1965,
1734, 1686, 1639, 1574, 1540, 1471, 1438, 1368, 1337, 1282, 1250, 1195, 1157, 1135, 1100, 1083, 1041, 1022, 960, 939, 903, 839, 781, 766, 726, 680, 648, 592, 543, 523, 486, 436. HRMS (M – H$_2$O)$^+$ = 452.2615 calculated for C$_{27}$H$_{38}$NO$_3$Si; 452.2619 experimental.
CHAPTER 9: REFERENCES


68. CCDC 879960 (compound 7e) contains the supplementary crystallographic data for this compound, which can be obtained via http://www.ccdc.cam.ac.uk/data_request/cif.


73. Hemantha, H. P.; Sureshbabu, V. V., Synlett 2008, 496.


75. Andres Villalpando, M. S., Thomas Tugwell, Rendy Kartika, Stereoselective Chlorination of Acyclic Aliphatic 1,3-Anti vs. 1,3-Syn Diols with Triphosgene-Pyridine Activation. Organic letters 2015, Manuscript Submitted.


120. Rueping, M.; Kuenkel, A.; Atodiresei, I., Chiral Bronsted acids in enantioselective carbonyl activations - activation modes and applications. *Chemical Society Reviews* 2011, 40 (9), 4539-4549.


147. pKa of pyridinium ion in H2O is 5.14

148. pKa of a-CH3 substituent is ~25, with a-phenyl substituent is ~20


150. Reported yield was 97%; Our experimental yields were <10%.


170. Catalyst equivalents lowered to 10 mol %.


176. The N-value of 2-methylthiophene is calculated at 1.4.


184. Isopropanol also failed to generate desired alcohol adduct.


214. Luo, J.; Jiang, Q.; Chen, H.; Tang, Q., Catalyst-free formation of 1,4-diketones by addition of silyl enolates to oxyallyl zwitterions in situ generated from alpha-haloketones. RSC Adv. 2015, 5 (83), 67901-67908.


APPENDIX A: COPYRIGHT RELEASES

Title: Chlorination of Aliphatic Primary Alcohols via Triphosgene–Triethylamine Activation

Author: Caitlan E. Ayala, Andres Villalpando, Alex L. Nguyen, et al

Publication: Organic Letters

Publisher: American Chemical Society

Date: Jul 1, 2012

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Title: Bronsted Acid Catalyzed α'-Functionalization of Silylenol Ethers with Indoles
Author: Caitlan E. Ayala, Nitin S. Dange, Frank R. Fronczek, Rendy Kartika
Publication: Angewandte Chemie International Edition
Publisher: John Wiley and Sons
Date: Feb 18, 2015
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United States  
Attn: Caitlan Ayala |
APPENDIX B: NMR SPECTRA

CHAPTER 2 NMR SPECTRA
Cl–N–Boc
2.11a
CHAPTER 5 NMR SPECTRA
5.21a
5.27
CHAPTER 6 NMR SPECTRA
No $-H_b$ signal
No $-H_b$ signal
No $-H_b$ signal

$-H_a$  $-H_b$
No -Hb signal
No $-H_b$ signal

$-H_a$

$-H_b$
-Hₐ

-Hₐ

-Hₐ

No -Hₐ signal
No -Hb signal
6.16f
(E:Z = 3:1)
Z-6.17a

No -H_b signal

-H_a
-H_b
6.17d
No $-H_b$

$-H_a$

$-H_D$

No $-H_b$ signal
VITA

Caitlan Ayala grew up in the Northern Illinois area, and she stayed close to home for her undergraduate studies in chemistry at Northern Illinois University. She discovered her interests in research in her Senior year of her studies. Caitlan completed her Bachelor’s Degree of Science in Chemistry, summa cum laude in May 2011, and she enrolled in the LSU Graduate School for the Department of Chemistry in the following Fall 2011 semester. She is a candidate to receive her doctorate degree in May 2016.