NEW MECHANISMS FOR TURNOVER AND FUNCTIONALIZATION IN THE
PLATINUM INITIATED CYCLIZATION OF POLYENES

Michael J. Geier

A dissertation submitted to the faculty at the University at the North Carolina at Chapel Hill
in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the
Department of Chemistry.

Chapel Hill
2014

Approved by:
Michel Gagné
Joseph Templeton
Maurice Brookhart
Cynthia Schauer
David Nicewicz
ABSTRACT

Michael J. Geier: New Mechanisms for Turnover and Functionalization in the Platinum Initiated Cyclization of Polyenes
(Under the direction of Michel Gagné)

The replication of nature’s ability to convert acyclic polyenes to polyeycles has long been the target of synthetic chemists. Progress has been made through manipulation of both substrate and initiator to achieve products of increasing complexity. While significant advances have been made, the abilities of the synthetic chemist pale in comparison to that of nature.

In an effort to bridge this gap, several areas have been explored. Current synthetic methods for the synthesis of C3-oxygenated polycycles rely upon pre-installation of the oxygen functionality. Development of a catalytic scheme for the generation of several C3-oxygenated polycycles using molecular oxygen as the oxygen source has been achieved. This scheme proceeds through a unique Pt(III) intermediate which undergoes homolytic cleavage of the Pt-C bond before interception of the alkyl radical.

Application of a (CNC)Pt$^{2+}$ pincer complex to the cyclization of polyene substrates has resulted in a remarkably efficient cycloisomerization. Where phosphine ligated Pt complexes have proven remarkably stable toward oxidation, rapid Pt-alkyl protodemetallation was observed. This complex was particularly effective in initiating cyclization of the more challenging alkene terminating substrates, forming up to four rings and five stereocenters in a single step.
Extension of this cycloisomerization methodology to substrates which proceed through secondary carbocations has allowed for a unique opportunity to study the nature of polycyclization reactions experimentally. Through selective substrate demethylation, a concerted yet highly asynchronous process was uncovered, revealing a process highly dependent on the stability of the A ring.

En route to exploration of new methods for oxygenation of the C-3 position, an opportunity for the fundamental study of reductive elimination from Pt(IV) complexes arose. Under standard conditions, reactions of a Pt(II) organometallic complex with electrophilic halonium reagents resulted in stereoretentive reductive elimination. Addition of the appropriate anion to these reactions resulted in a switch in the mechanism of reductive elimination, forming the invertive halogenation products.
ACKNOWLEDGEMENTS

First and foremost I’d like to thank Mike for giving me the opportunity to work in his lab. The freedom to explore new ideas (both good and bad) is something I’ll always appreciate. Knowing that Mike’s door was always open and having support when I needed it has made these 5 years much easier.

I’d also like to thank Steve Westcott (Mount Allison University) for pointing me in this direction and continuing to provide guidance along the way.

I’d like to thank Gagné group members both past and present. In particular, Joe Sokol who put up with my endless questions and Laura Adduci for helping with every problem I’ve had in lab.
# TABLE OF CONTENTS

TABLE OF CONTENTS ........................................................................................................ VI
LIST OF TABLES .................................................................................................................. VIII
LIST OF FIGURES .............................................................................................................. IX
LIST OF ABBREVIATIONS ................................................................................................... XIV

## CHAPTER 1: INTRODUCTION ......................................................................................... 1

Enzyme Catalyzed Terpene Cyclization ........................................................................... 1
Biomimetic Approaches to Cascade Cyclization ................................................................. 7
Biomimetic Cyclization of Polyenes .................................................................................. 16
Secondary Carbocations in Biomimetic Cyclization Reactions ........................................... 19
Electrophilic Pt-initiated Cyclization of Polyenes ............................................................... 23
Oxidative Functionalization of M-C Bonds ......................................................................... 28
Research Objectives .......................................................................................................... 36
References ......................................................................................................................... 38

## CHAPTER 2: STOICHIOMETRIC HALOGENATION OF PT-C BONDS .................... 45

Introduction ....................................................................................................................... 45
Results ............................................................................................................................... 46
Discussion ......................................................................................................................... 55
Experimental Section ......................................................................................................... 58
References ......................................................................................................................... 62
LIST OF TABLES

Table 2.1: Fluorination in the presence of TBAOAc .......................................................... 50
Table 2.2: Fluorination in the presence of TBAB ............................................................... 52
Table 2.3: Bromination in the presence of TBAB ............................................................... 54
Table 3.1: Additive effect in photochemical oxygenation reactions ..................................... 67
Table 3.2: Halogenation of Pt-alkyl with CuX₂ ................................................................. 68
Table 3.3: Optimization of oxygenation of Pt-alkyl ............................................................ 71
Table 3.4: Solvent effect on oxygenation of Pt-alkyl ........................................................... 72
Table 3.5: Additive effect on oxygenation of Pt-alkyl ......................................................... 73
Table 3.6: Re-oxidation of Cu(OTf)₂ ................................................................................... 74
Table 3.7: Substrate scope ................................................................................................. 76
Table 3.8: Oxidant screen .................................................................................................. 77
Table 4.1: Optimization of proton shuttle loading .............................................................. 89
Table 4.2: Substrate scope ................................................................................................. 90
# LIST OF FIGURES

Figure 1.1: Enzymatic cyclization of squalene .......................................................... 2
Figure 1.2: A stepwise illustration of the conversion of squalene to hopene .......... 3
Figure 1.3: Comparison of conformation in squalene and oxidosqualene ....................... 3
Figure 1.4: Intermediates in squalene cyclization .......................................................... 5
Figure 1.5: Intermediates in the formation of lanosterol ............................................ 6
Figure 1.6: Concerted C ring expansion and D ring formation ................................. 7
Figure 1.7: Humulyl cation intermediate in the formation of pentalenene .................... 7
Figure 1.8: Stork-Eschenmoser postulate .................................................................... 8
Figure 1.9: Johnson’s pentacyclization reaction ................................................................. 9
Figure 1.10: Johnson’s synthesis of 11α-hydroxyprogesterone ..................................... 9
Figure 1.11: Initiation by chiral acetal opening ............................................................. 10
Figure 1.12: Yamamoto’s chiral Brønsted Lewis Acid cyclization ................................. 10
Figure 1.13: Corey’s chiral Brønsted Lews acid cyclization ........................................ 11
Figure 1.14: Corey’s synthesis of dehydroabietic acid ......................................................... 11
Figure 1.15: Corey’s synthesis of 4-epipodocarpic acid ............................................... 11
Figure 1.16: Halonium induced polycyclization ............................................................... 12
Figure 1.17: Carreira’s total synthesis of asperolide C ................................................... 13
Figure 1.18: Toste’s gold catalyzed polycyclization ...................................................... 13
Figure 1.19: Products derived from 2,3-oxidosqualene ............................................... 14
Figure 1.20: Biomimetic cyclization of 2,3-oxidosqualene ......................................... 15
Figure 1.21: van Tamelen’s synthesis of allopregnolone ................................................. 15
Figure 1.22: Corey’s Al mediated bicyclization ............................................................. 15
Figure 1.23: Cyclization of propargylic alcohol substrate ................................................................. 16
Figure 1.24: Mercury initiated cyclization ............................................................................................ 17
Figure 1.25: Bi(OTf)₃ catalyzed bicyclization and rearrangement ......................................................... 18
Figure 1.26: Formation of multiple products in Bi(OTf)₃ catalyzed cyclization ..................................... 18
Figure 1.27: Cyclization of secondary alkene containing substrates ..................................................... 20
Figure 1.28: Tetracyclization of secondary alkene containing substrate ............................................. 20
Figure 1.29: Vinyl and isopropenyl terminating substrates ................................................................. 21
Figure 1.30: Step-wise vs. concerted tetracyclization ......................................................................... 22
Figure 1.31: Fluorine stabilization of 6-membered C-ring .................................................................... 23
Figure 1.32: Metal activation of alkenes ............................................................................................... 23
Figure 1.33: Palladium catalyzed cyclization ......................................................................................... 24
Figure 1.34: Platinum pincer mediated cyclization .............................................................................. 24
Figure 1.35: Formation of enantiomerically enriched bicyclopropanes ............................................. 25
Figure 1.36: Catalytic polycyclization via β-hydride elimination ....................................................... 26
Figure 1.37: Catalytic cyclization/fluorination ....................................................................................... 27
Figure 1.38: Stoichiometric polyene cyclization .................................................................................. 28
Figure 1.39: Wagner-Meerwein rearrangement of 5-exo terminating substrate ................................. 28
Figure 1.40: Catalytic polyene cyclization ............................................................................................ 28
Figure 1.41: Shilov cycle ....................................................................................................................... 29
Figure 1.42: Reductive elimination of ethane from 5 coordinate intermediate ..................................... 30
Figure 1.43: Reductive elimination pathways ....................................................................................... 30
Figure 1.44: Stereoretentive C-F reductive elimination ....................................................................... 31
Figure 1.45: Stereoretentive C-Cl reductive elimination ...................................................................... 31
Figure 1.46: Stereoretentive C-I reductive elimination from Rh(III) ........................................ 32
Figure 1.47: Bromination of Pd and Hg-bonds ........................................................................ 33
Figure 1.48: Donor effects on the oxidation of Pt(II) compounds ........................................ 34
Figure 1.49: Inner and outer sphere one electron oxidation of organostannanes .......... 34
Figure 1.50: Single electron oxidation of Pd pincer complex ................................................ 36
Figure 2.1: Possible C-X reductive elimination pathways......................................................... 46
Figure 2.2: Stereoretentive C-X bond forming reductive elimination ..................................... 47
Figure 2.3: Mechanism of stereoretentive C-X bond formation ............................................. 48
Figure 2.4: Possible reductive elimination pathways with XeF$_2$ and TBAOAc .................. 51
Figure 2.5: Possible reductive elimination pathways with XeF$_2$ and TBAB ..................... 53
Figure 2.6: Possible reductive elimination pathways with NBS and TBAB ......................... 55
Figure 2.7: Reductive elimination from 5-coordinate complex .............................................. 56
Figure 2.8: Sanford’s C-F reductive elimination from Pd(IV) ................................................. 56
Figure 2.9: Possible paths to stereoinvertive reductive elimination ..................................... 57
Figure 2.10: Comparison of possible intermediates ............................................................. 58
Figure 3.1: Insertion of singlet oxygen to Pt-Me bond ............................................................ 65
Figure 3.2: Goldberg’s insertion of O$_2$ into Pd-Me bond ....................................................... 66
Figure 3.3: Proposed mechanism for halogenation of 3.1 with CuX$_2$ reagents .................. 68
Figure 3.4: Mechanism of oxygenation of Pt-C bond ........................................................... 69
Figure 3.5: Russell disproportionation of alkyl radical ........................................................... 70
Figure 3.6: Oxygenation catalytic cycle ................................................................................. 75
Figure 4.1: Desired ligand framework .................................................................................... 86
Figure 4.2: Limbach’s Pt-catalyzed hydrovinylation ............................................................... 86
Figure 4.3: Reaction of 4.1 with 4.2 ................................................................. 87
Figure 4.4: Polyene cycloisomerization mechanism ......................................... 88
Figure 4.5: Isomerization of trisubstituted alkene to tetrasubstituted alkene .......... 91
Figure 4.6: Abnormal Claisen rearrangement of aryl ether .............................. 92
Figure 4.7: Rearrangement of substrate 4.16 .................................................... 93
Figure 4.8: Wagner-Meerwein rearrangements of 4.20 and oxidosqualene .......... 94
Figure 5.1: Concerted formation of rings A, B and C of hopene ......................... 119
Figure 5.2: Tetracyclization of 1 ........................................................................ 120
Figure 5.3: 2,3-oxidosqualene and analogs ....................................................... 120
Figure 5.4: Synthesis of 5.1 .............................................................................. 121
Figure 5.5: Attempted synthesis of secondary alkene ....................................... 122
Figure 5.6: One pot vinylation/Claisen rearrangement ...................................... 122
Figure 5.7: Library of penta-ene substrates ....................................................... 123
Figure 5.8: Cyclization of 5.4 ............................................................................ 124
Figure 5.9: Cyclization of 5.3 ............................................................................ 125
Figure 5.10: Cyclization of 5.5 .......................................................................... 126
Figure 5.11: Relative rates for concerted, synchronous cyclization .................... 126
Figure 5.12: Reaction coordinate for a concerted, synchronous reaction ............. 127
Figure 5.13: Relative rates for step-wise cyclization .......................................... 128
Figure 5.14: Reaction coordinate diagram from concerted, asynchronous reaction ... 131
Figure A.1: Cyclization by (terpy)Pt$^{2+}$ ........................................................... 158
Figure A.2: Cyclization by P$_3$PPt$^{2+}$ ............................................................... 159
Figure A.3: Cyclization by P$_2$CPr$^{2+}$ ............................................................... 160
Figure B.1: Tricyclization of secondary alkene containing substrate.......................... 162

Figure B.2: Cyclization of tetrasubstituted alkene containing substrate......................... 163
**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>α</td>
<td>alpha</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>atm</td>
<td>atmospheres</td>
</tr>
<tr>
<td>β</td>
<td>beta</td>
</tr>
<tr>
<td>BF₄⁻</td>
<td>tetrafluoroborate</td>
</tr>
<tr>
<td>nBuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>BLA</td>
<td>Brønsted Lew's acid</td>
</tr>
<tr>
<td>bpy</td>
<td>bipyridine</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>δ</td>
<td>delta – change from standard value</td>
</tr>
<tr>
<td>CD₂Cl₂</td>
<td>deuterated dichloromethane</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>CD₃CN</td>
<td>deuterated acetonitrile</td>
</tr>
<tr>
<td>CD₃NO₂</td>
<td>deuterated nitromethane</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>endo</td>
<td>endocyclic</td>
</tr>
<tr>
<td>eq</td>
<td>equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>GCMS</td>
<td>gas chromatography/mass spectroscopy</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>J</td>
<td>three bond H-H coupling constant</td>
</tr>
<tr>
<td>Kcal</td>
<td>kilocalorie</td>
</tr>
<tr>
<td>L</td>
<td>liter</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>M</td>
<td>molarity</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>mL</td>
<td>milliliter</td>
</tr>
<tr>
<td>mM</td>
<td>millimole</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>mes</td>
<td>mesityl</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mol %</td>
<td>mole percent</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge</td>
</tr>
<tr>
<td>NBS</td>
<td>n-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>n-chlorosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Meaning</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>OTf</td>
<td>triflate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PF₆</td>
<td>hexafluorophosphate</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPP</td>
<td>bis(2-diphenylphosphinoethyl)phenylphosphine</td>
</tr>
<tr>
<td>PTFE</td>
<td>polytetrafluoroethylene</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tol</td>
<td>toluene</td>
</tr>
<tr>
<td>triphos</td>
<td>bis(2-diphenylphosphinoethyl)phenylphosphine</td>
</tr>
<tr>
<td>Ts</td>
<td>p-toluenesulfonate</td>
</tr>
</tbody>
</table>
CHAPTER 1: INTRODUCTION

Enzyme Catalyzed Terpene Cyclization

Nature’s ability to mediate the formation of a variety of complex products is unmatched by current synthetic methods. This remarkable capacity for chemical manipulation is perhaps best exemplified in the enzyme catalyzed terpene cyclization reactions.\(^1\) These reactions provide complex polycyclic products with full stereocontrol from simple achiral polyene substrates.

A number of these polycyclic compounds are the products of multiple enzyme catalyzed reactions, ultimately derived from the substrate squalene.\(^2\) In bacteria, squalene is converted to hopene by squalene-hopene cyclase, while plants, animals and fungi first enantioselectively epoxidize squalene to (3\(S\))-2,3-oxidosqualene with squalene epoxidase and molecular oxygen.\(^{1b,1d,e}\) Cyclization of 2,3-oxidosqualene leads to products with a 6,6,6,5 framework and an alcohol moiety at C3 and are known as the sterol family of compounds which includes lanosterol and cycloartenol (Figure 1.1).\(^{1a,3}\) These compounds are the precursors to a wide variety of better known natural products including cholesterol and testosterone.
Figure 1.1: Enzymatic cyclization of squalene

The fundamental chemical process that underpins terpene cyclization chemistry is the cation-olefin reaction, where transiently generated carbocations\(^4\) rapidly react with alkenes which have been pre-organized within the enzyme to make a C-C bond and regenerate the carbocation. This process, which converts long chain polyenes to predominantly saturated polycyclic compounds is thermodynamically favorable due to the conversion of C-C double bonds to C-C single bonds, all while converting double bonds to rings.\(^5\)

The cyclization of squalene to hopene by squalene hopene cyclase represents a comparatively simple transformation. Squalene is held in an all chair conformation within the enzyme. Protonation of the 2,3-alkene from an acidified aspartic acid residue initiates the cascade and a series of five cation olefin reactions ensues, to be terminated by an elimination of the final exocyclic tertiary carbocation to form the E-ring isopropenyl group (Figure 1.2).
Figure 1.2: A stepwise illustration of the conversion of squalene to hopene

The oxidosqualene cyclases are believed to have evolved from the squalene hopene cyclase.\textsuperscript{1c} While squalene hopene cyclase is able to accommodate several different substrates, the oxidosqualene cyclases are more substrate selective, and possess the ability to distinguish between (3\textit{S}) and (3\textit{R})-2,3-oxidosqualene. In contrast to the all chair conformation of squalene enforced by squalene cyclase, 2,3-oxidosqualene cyclase induces a \textit{chair-boat-chair} conformation (Figure 1.3), resulting in significant alteration of the framework.\textsuperscript{1d} Cyclization of 2,3-oxidosqualene is initiated by protonation of the epoxide. A series of cation olefin reactions and skeletal rearrangements generates a tertiary carbocation at the junction of rings B and C which eliminates to the tetrasubstituted alkene product.\textsuperscript{1d}

Figure 1.3: Comparison of conformation in squalene and oxidosqualene.
The concerted nature of the enzyme mediated polycyclization of triterpene substrates has long been debated,\textsuperscript{1d} with several studies suggesting stepwise processes involving formation of discrete carbocationic intermediates\textsuperscript{6} while others have suggested a more concerted process with several transformations occurring without the formation of intermediates.\textsuperscript{7}

Much of the theoretical work in this area has benefited from the report of Schulz in which an X-ray structure of 2-azasqualene was obtained within the hopene cyclase enzyme.\textsuperscript{8} The conformation in which the squalene derivative was held within the enzyme provided a starting point for many of the calculations used to assess the nature of the cyclization.

Several computational investigations by Hess on a variety of truncated squalene models revealed the concerted but highly asynchronous formation of the A,B and C rings of hopene. It was shown that full closure of the A ring is observed prior to significant engagement of the B and C rings.\textsuperscript{9} While the A and B rings form via a cation-olefin reaction that generates the most favorable $3^\circ$ carbocations (6-endo ring closures), the C-ring closes by a kinetically controlled 5-exo cyclization to generate a $3^\circ$ carbocation rather than the $2^\circ$ carbocation that a 6-endo regiochemistry would have required. Such a process requires little substrate reorganization relative to the structure obtained by Schulz.\textsuperscript{7b,9} This exocyclic carbocation is then believed to undergo concerted C-ring expansion and D ring formation, a process that is then repeated for D ring expansion and E ring formation (Figure 1.4).\textsuperscript{10}
Figure 1.4: Intermediates in squalene cyclization

The enzymatic cyclization of oxidosqualene to lanosterol is believed to proceed in a similar fashion with concerted formation of the A, B and C rings, proceeding by an alternative chair-boat-chair conformation (Figure 1.5). Recent calculations have shown the process to be highly asynchronous, with nearly full closure of the A ring prior to any significant interaction between the developing carbocation and the sequence that forms the B and C rings. The formation of these three rings has been shown to release 39 kcal/mol, slightly less than formation of the A-B and C rings of hopene (48 kcal/mol), a difference which has been attributed to the boat conformation of the B ring in lanosterol.
Figure 1.5: Intermediates in the formation of lanosterol

The cyclizations of squalene and oxidosqualene have been calculated to proceed strictly through tertiary carbocation intermediates.\textsuperscript{1d} These calculations have shown that the intermediacy of high energy secondary carbocations along the reaction path can be avoided by allowing several transformations to occur in concert. In both cyclizations, initial formation of the 6-6-5 skeleton occurs, and is followed by concerted C ring expansion and D ring formation. These two transformations occur in tandem to avoid what would otherwise be a secondary carbocation formed in a step-wise process following C ring expansion (Figure 1.6).\textsuperscript{7a}
Nature’s aversion to the formation of secondary carbocationic intermediates is not ubiquitous. Several calculations have revealed that secondary carbocations can exist as intermediates, their structures, however, are highly stabilized within the enzyme. The enzymatic stabilization of these secondary carbocations has allowed for anti-Markovnikov selectivity to be observed in the biosynthesis of several natural products. The humulyl cation has been shown by computational methods to be an intermediate in the conversion of farnesyl diphosphate to pentalenene (Figure 1.7).

![Figure 1.6: Concerted C ring expansion and D ring formation](image)

**Figure 1.6: Concerted C ring expansion and D ring formation**

Biomimetic Approaches to Cascade Cyclization

The unique selectivity displayed by cyclase enzymes has prompted a variety of biomimetic approaches to the construction of similar polycyclic frameworks. These methods are generally initiated solely from the alkene or epoxide terminus and suffer from a lack of pre-organization of substrate found within the cyclase enzymes. This limitation often
necessitates nucleophilic terminating groups and can result in incomplete cyclization and a lack of selectivity.

\[
\begin{align*}
\text{cis} & \quad \Rightarrow \quad \text{trans} \\
\end{align*}
\]

**Figure 1.8: Stork-Eschenmoser postulate**

Vital to synthetic approaches to replicate these reactions is the Stork-Eschenmoser postulate. Stork and Eschenmoser postulated a relationship between the alkene geometry of the acyclic substrate and the geometry of the ring junction in systems related to terpene cyclization. The hypothesis states that a *cis* ring junction is formed from the cyclization of *Z* alkenes, while a *trans* ring junction is formed by cyclization of *E* alkenes (Figure 1.8).\textsuperscript{1c,16} This hypothesis allows for stereochemical control of ring junctions based upon the alkene geometry of the starting material, and explicitly requires some degree of concertedness in the cyclizations.

A variety of approaches has been devised to synthesize bio-like polycyclic frameworks. Many of these methods rely upon Brønsted or Lewis acids to mimic enzymatic substrate protonation, while some more recent approaches have turned to electrophilic halonium sources and transition metal catalysis to initiate cyclization.\textsuperscript{1c}

W.S. Johnson was a major contributor to the field of biomimetic cyclization.\textsuperscript{17} His approaches generally relied upon carbocation formation by reaction with Brønsted or Lewis
acids to initiate the cascade. Early work began with the generation of simple mono and bicyclic products in formic acid solution, confirming the Stork-Eschenmoser postulate. Much later, he would become the first to report a non-enzymatic pentacyclization reaction toward the total synthesis of sophoradiol (Figure 1.9). Johnson’s contributions to selectivity in polyene cyclizations have also been remarkable. In his total synthesis of 11α-hydroxyprogesterone, he reported that the inclusion of a chiral centre in the polyene substrate led to diastereoselectivity in the cyclized product (Figure 1.10). His later use of chiral acetal opening to initiate cyclization resulted in a remarkably selective tetracyclization, making use of a cation stabilizing fluorine atom to assist in the cyclization (Figure 1.11).
More recent work from Yamamoto has made use of chiral Brønsted Lewis Acids which were able to initiate an enantioselective cascade cyclization. These initiators were able to deliver a proton in an enantioselective fashion as a result of the enhanced acidity of the BINOL from complexation of the Lewis acidic tin tetrachloride (Figure 1.12). While diastereoselectivities were high, enantioselectivities were moderate. These reactions also suffered from the requirement of an excess of chiral initiator, nucleophilic terminating groups, and were plagued by premature termination of the cascade in the case of aryl terminating groups, requiring additional steps and reagents to achieve full cyclization.

E.J. Corey has made a number of contributions to the field of polycyclizations over the years, including the total synthesis of scalarenedial. A more recent report disclosed an improved variant of Yamamoto’s chiral Brønsted Lewis Acids. Use of the larger and more Lewis acidic antimony in place of tin, along with the more Brønsted acidic dichloro-BINOL
derivative allowed for a more active and enantioselective cyclization initiator when compared to that of Yamamoto, reporting enantiomeric excesses of up to 92% (Figure 1.13).\textsuperscript{24} More recently, this approach has been extended to the selective activation of internal olefins for predictably controlled cyclizations. This method was applied to these substrates en route to the synthesis of dehydroabietic acid (Figure 1.14) and 4-epipodocarpic acid (Figure 1.15).\textsuperscript{25}

**Figure 1.13:** Corey’s chiral Brønsted Lews acid cyclization

**Figure 1.14:** Corey’s synthesis of dehydroabietic acid

**Figure 1.15:** Corey’s synthesis of 4-epipodocarpic acid
Notably, Ishihara has disclosed an enantioselective halocyclization of polyprenoids by delivering I⁺ or Br⁺ from a chiral phosphoramidite to form the C3-halogenated product with high enantioselectivity. Enantiomeric excesses of up 99% were reported with moderate yields. These reactions generated unique C3-functionalized products, however, they too were plagued by premature termination of the cyclization, requiring additional steps to form polycyclic products (Figure 1.16). More recently, a catalytic variant was reported in which the stoichiometric chiral phosphoramidite was replaced with a catalytic amount of a phosphate-urea catalyst, unfortunately, this catalytic variant was unable to provide the same enantioselectivity, resulting in only a 2% ee.

Figure 1.16: Halonium induced polycyclization

Carreira has reported a highly enantioselective cyclization in which an allylic alcohol moiety can be activated by the combination of a Lewis acid and a chiral iridium catalyst with both aryl and heteroaryl terminating groups being tolerated. Yields of up to 93% and enantiomeric excesses of >99.5% were reported in several cases. This system was effective at initiating bicyclization reactions, however, tricyclization reactions resulted in a combination of bi and tricyclized products. This system has recently been applied in the total synthesis of (+)-Asperolide C (Figure 1.17). Toste has also reported an enantioselective polycyclization reaction catalyzed by gold. Activation of a terminal alkyne initiates the cascade while both aryl and heteroatom based nucleophiles were tolerated, producing yields and ee’s in the 90’s (Figure 1.18).
A subset of the polyolefin cascade cyclization reactions are those that result in C3-oxygenated products, similar to those derived from 2,3-oxidosqualene. This includes the sterol family of natural products such as lanosterol and cholesterol as well as the steroid family which includes testosterone. Synthetically, these products have been formed exclusively by pre-installation of the oxygen at the C3-position in the polyene substrate, often in the form of an epoxide where cyclization can be initiated by epoxide opening (Figure 1.19).
Much of the early work in this subset of products was performed by Van Tamelen.\textsuperscript{31} Biomimetic reactions on oxidosqualene-like substrates revealed remarkable rearrangements, indicating that much of the skeletal changes observed in nature are in fact not enzyme dependent, suggesting the enzyme functions solely to protect the substrate from premature termination during rearrangement.\textsuperscript{32} Attempted cyclization of oxidosqualene with SnCl\(_4\) produced several partially cyclized products, among them, a tricyclic product, the result of formation of the 5-membered C-ring without subsequent ring expansion and cyclization. Termination occurred with a hydride and methyl shift, similar to rearrangements observed in nature (Figure 1.20).
Figure 1.20: Biomimetic cyclization of 2,3-oxidosqualene

Formation of the desired 6,6,6,5 sterol skeleton in biomimetic reactions has proved challenging due to the preferential formation of 5-membered C-rings arising from 5-exo Markovnikov ring closure to form the more favorable tertiary carbocation. This problem was overcome by design of an alkyne terminating substrate by van Tamelen in which methyl group placement allowed for Lewis acid initiated tetracyclization, forming the sterol allopregnanolone with the desired 6,6,6,5 framework (Figure 1.21).

Figure 1.21: van Tamelen’s synthesis of allopregnanolone

Figure 1.22: Corey’s Al mediated bicyclization

E.J. Corey has utilized epoxide opening to initiate a variety of cascade cyclization reactions. Early work reported the synthesis of simple bicyclic compounds promoted by Lewis acidic aluminum reagents (Figure 1.22). Application of chiral epoxide starting
materials has allowed for the stereocontrolled total synthesis of a remarkable number of C3 oxygenated natural products including β-amyрин,\textsuperscript{36} oleanolic acid,\textsuperscript{36} erythodiol,\textsuperscript{36} lanosterol,\textsuperscript{37} dammarenediol,\textsuperscript{38} serratenediol,\textsuperscript{39} onocerin\textsuperscript{40} and germanicol.\textsuperscript{41} Recent work has involved the indium catalyzed cyclization of a series of chiral propargylic alcohols and silyl ethers to form polycyclic structures in good yield and enantioselectivity. In these cases, activation was achieved by coordination of the indium catalyst to a terminal alkyne, while enantiomeric excesses in the 90’s resulted from pre-installation of the chiral propargyl alcohol or silyl ether (Figure 1.23).\textsuperscript{42}

**Figure 1.23: Cyclization of propargylic alcohol substrate**

**Biomimetic Cyclization of Polyenes**

A second, much less explored area of the biomimetic cascade cyclization reactions are those that utilize strictly polyene containing substrates. In contrast to those methods which benefit from the enhanced nucleophilicity of heteroatom terminating substrates, or those that are aided by cation-pi stabilization in the case of arene terminating substrates, alkene terminating groups provide a significantly more challenging target. Alkene terminating groups suffer from a lack of nucleophilicity, the required formation of discrete carbocations, as well as the loss of H-bond assistance in heteroatom terminating cyclizations, making these substrates much slower to cyclize and prone to incomplete or unselective cyclization.
Early work in the cyclization of polyene substrates employed mercury salts as initiators. These proved effective at activating alkenes, however they suffered from a lack of selectivity, as mercury is unselective in its alkene preference. These methods also required a stoichiometric amount of mercury. More recently, Nishizawa has reported the cyclization of a number of substrates including several alkene terminating substrates. These substrates resulted in several different products, including those arising from incomplete cyclization (Figure 1.24); stoichiometric mercury is still required.

![Figure 1.24: Mercury initiated cyclization](image)

More recent work from the Dunach group has focused on the use of Bi(OTf)$_3$ to promote cyclization of polyene substrates. While Bi(OTf)$_3$ was added as the catalyst, it has been proposed that a Lewis acid assisted Brønsted acid type of activation may be responsible for the activation, further supported by the ability of triflic acid to promote reactivity. Reactions proceeded rapidly, but required elevated temperatures (100°C) and often provide the products as a mixture of diastereomers (Figure 1.25). In several cases, Wagner Meerwein rearrangements were observed. These carbocation rearrangements can involve 1,2 migration of a hydride, alkyl or aryl group between neighboring carbons.
Figure 1.25: Bi(OTf)$_3$ catalyzed bicyclization and rearrangement

Computation and further experimental studies allowed for the identification of several possible intermediates. Lowering of the temperature from 100°C to 0°C allowed for formation of two previously unobserved products. While the Wagner-Meerwein rearranged product remained the predominant species at room temperature, a product arising from elimination from the initially formed tertiary cabocation as well as a mixture of monocyclized products appeared in the reaction mixture (Figure 1.26). Subjecting these products to initial cyclization conditions resulted in formation of the Wagner-Meerwein rearranged product.\(^47\)

Figure 1.26: Formation of multiple products in Bi(OTf)$_3$ catalyzed clylization
Secondary Carbocations in Biomimetic Cyclization Reactions

The synthetic viability of secondary carbocations in catalytic biomimetic cyclization reactions has remained relatively unexplored. Substrates currently employed in these reactions have been carefully crafted, controlling ring size and termination geometry by strategic positioning of methyl groups within the substrate. This approach has allowed for predictable cyclization reactions, however, it has left an important area of biomimetic cyclization reactions relatively untouched.

The majority of recent efforts to study the involvement of secondary carbocations in such cyclizations have been calculations on the enzyme mediated transformations. Early experimental work from W.S. Johnson has reported several reactions containing secondary alkenes, while some of his later work has detailed the stabilization of secondary carbocations in polyene cyclization reactions.

Johnson and others have reported several different approaches to initiate polyene cyclizations under substrate control. The addition of a stoichiometric amount of stannic chloride to induce acetal opening has proven to be effective for the tricyclization of substrates containing secondary alkenes. Remarkably, this method was also effective for inducing tricyclization of a substrate containing two disubstituted alkenes, albeit in lower yield and longer reactions times (Figure 1.27).

14
15
48
49
50
Extension of this protocol to tetracyclization reactions also proved effective, with stannic chloride in pentane furnishing the tetracyclic product, setting 7 stereocenters, providing only 2 of a possible 64 stereoisomers (Figure 1.28).

The generation of allylic carbocations through several means has also been effective in initiating cyclizations that proceed through disubstituted alkenes. Formation of cyclohexenyl, cyclopentenyl and tetramethylallylic cations have been used to induce cyclization. Particularly noteworthy are several examples in which direct comparisons between secondary and tertiary carbocations can be drawn. Cyclization of vinyl terminating and isopropenyl terminating substrates were compared, noting a larger proportion of tetracyclized products arising from the isopropenyl terminating substrates, likely due to its
enhanced nucleophilicity arising from the stability of the terminal carbocation (Figure 1.29).\textsuperscript{54}

![Chemical structures](image)

**Figure 1.29: Vinyl and isopropenyl terminating substrates**

A second example once again draws comparison between vinyl and isopropenyl terminating groups. In the case of the vinyl terminating substrate, a *cis* ring junction was observed in the tetracyclized product. This unexpected outcome was proposed to arise from an initial tricyclization and elimination from the tertiary carbocation. Protonation of this alkene and D ring formation led to a *cis* ring junction in this stepwise process. Meanwhile, cyclization of the isopropenyl terminating substrate provided the anticipated *trans* ring junctions in the tetracyclized product, indicating a more concerted tetracyclization, once again, attributed to the enhanced nucleophilicity of the terminating group (Figure 1.30).\textsuperscript{55}
Johnson has also reported the application of fluorine to stabilize secondary carbocations that ensue during the course of a cascade cyclization.\textsuperscript{56} This approach has enabled the previously mentioned pentacyclization\textsuperscript{19} reaction and the total synthesis of several natural products.\textsuperscript{21,57} The use of fluorine has also overcome the regiospecificity problem during biomimetic C-ring formation. The anti-Markovnikov C-ring closure observed in the enzyme mediated cyclization (ie lanosterol, hopene) has been difficult to replicate due to the preference for formation of tertiary over secondary carbocations and the aversion to C-ring expansion.\textsuperscript{32} This results in 5-exo C-ring closure followed by elimination to form tricyclic products. Strategic positioning of the fluorine atom to stabilize the secondary carbocation allowed for the desired 6-membered C-ring (Figure 1.31).\textsuperscript{58}
Electrophilic Pt-initiated Cyclization of Polyenes

The use of transition metals to activate unsaturation has long been exploited in catalysis. Coordination of an alkene to a metal centre generates an electrophilic carbon centre, prone to nucleophilic attack (Figure 1.32). In the case of polyunsaturated compounds, Pt and Pd will preferentially coordinate the least substituted alkene, allowing for selective activation.\(^{59}\)

This unique tendency of Pd and Pt has been used in the Gagné lab for the cyclization of polyene substrates by selective placement of a monosubstituted alkene at the terminus of the polyene. This assures that the catalyst will initiate at the desired position and start the cation-olefin cascade at the position favored by enzymes. Initial studies employing a Pd catalyst and an oxidant allowed for catalytic cyclization of polyene substrates with heteroatom terminating groups. Initiation at the monosubstituted alkene led to a polycyclic organopalladium species which underwent rapid and unselective $\beta$-hydride elimination to form several alkene isomers of the products (Figure 1.33).\(^{60}\)
A more selective variant of these cyclization reactions employed tridentate ligands on both Pd and Pt initiators. The tridentate ligand creates a coordinatively saturated organometallic species upon cyclization, which prevented β-hydride elimination, resulting in a series of remarkably stable Pt-alkyl compounds. As a result of the bulk of the group 10 metal initiators, these reactions provided excellent diastereoselectivity due to the metal’s preference for equatorial disposition (Figure 1.34).61

Application of the (triphos)Pt catalyst to 1,6 and 1,7 diene systems produced a catalytic cycloisomerization reaction that initiates with a cation-olefin reaction but turns over through rearrangement that forms bicyclop propane products.62 Deconstruction of the tridentate triphos ligand to a combination of a chiral bidentate and a monodentate ligand allowed for easy access to chiral catalysts. This ligand alteration allowed for enantioselective cycloisomerization reactions63 (Figure 1.35) as well as a stoichiometric, enantioselective polyene cyclization.64
The cyclization of polyenes with tridentate and deconstructed tridentate phosphine ligands was effective in stoichiometric reactions, forming stable Pt organometallics, however, these complexes proved remarkably stable toward acid, undergoing protonolysis only under strongly acidic conditions. The triphos ligands proved significantly more vulnerable to protodemetalation than their P$_2$P counterparts, an observation rationalized by the relief of torsional strain created by the tridentate ligand.$^{65}$ While protonolysis was accelerated by increasing the electron density on the triphos ligand, this significantly shifted the equilibrium constant toward the uncyclized starting material.$^{66}$

While tridentate phosphine ligands made for effective initiators, their stability to β-hydride elimination prevented catalytic turnover. This situation stimulated development of several new turnover mechanisms. In lieu of the previously used tridentate ligands, Pt catalysts with bidentate phosphine ligands provide Pt-R intermediates with a vacant coordination site. Activation and cyclization thus leads to an organometallic species which was prone to β-hydride elimination. This led to a 2,3-unsaturated polycyclic product and a Pt-hydride species which could be re-activated through hydride abstraction to turn over the catalytic cycle (Figure 1.36).$^{67}$
Figure 1.36: Catalytic polycyclization via β-hydride elimination

Oxidation of the stable divalent (triphos)Pt⁺-R organometallic compounds by electrophilic fluorinating reagents led to the product of a stereoretentive C3-fluorination of the R group. These reactions are believed to proceed by initial two electron oxidation of the Pt organometallic by F⁺ to give a Pt(IV) fluoride intermediate which underwent rapid and stereoretentive C-F bond forming reductive elimination.⁶⁸ Replacement of the triphos ligand in this system with a bulky bisphos ligand slowed beta hydride elimination enough that catalytic cyclization/fluorination scheme for polyene substrates could be developed. These reactions produced fluorinated products in good yields and enantioselectivities with the xylyl-phanephos ligand (Figure 1.37).⁶⁹
Heteroatom terminating substrates were efficiently cyclized in both stoichiometric and catalytic schemes, however, the more challenging alkene terminating substrates remained untested. Stoichiometric cyclization of these substrates proved significantly more challenging, long reactions times were observed despite optimized conditions that required two equivalents of substrate and multiple equivalents of base. Under these conditions, a variety of substrates would be cyclized, including those that terminate in both a 6-endo and a 6-exo fashion (Figure 1.38). In the 5-exo terminating case, a Wagner-Meerwein rearranged product was observed, the result of a hydride and methyl shift to form a more thermodynamically stable tetrasubstituted alkene (Figure 1.39).
Attempts to shift these polyene substrates into a catalytic manifold proved challenging as slow and incomplete reactions were the norm. Optimization of conditions produced reactions which consumed starting material, but formed multiple isomers of products resulting in low isolated yields (Figure 1.40).\(^{70}\)

Oxidative Functionalization of M-C Bonds

The introduction of new functional groups in transition metal catalyzed pathways often relies upon oxidation of the metal centre. The bond forming reductive elimination from
higher oxidation species remains one of the most common and effective method for derivatizing M-C bonds. While oxidative addition has been the subject of intense study and generally proceeds via an $S_N2$ mechanism, the reductive elimination of C-X bonds proceeds by the microscopic reverse, involving dissociation from an 18 electron species prior to $S_N2$-type attack to reduce the metal and liberate the product.  

![Shilov cycle diagram]

**Figure 1.41: Shilov cycle**

Much of the mechanistic work on reductive elimination has been performed on Pt complexes as their slow rates of ligand exchange simplify mechanistic study. Early work involved study of the Shilov cycle in which both C-O and C-Cl bond forming reductive elimination from Pt(IV) are possible (Figure 1.41). In a thorough mechanistic study, Bercaw reported that both the formation of methanol and methyl chloride are the result of $S_N2$ type attack upon the methyl group. This was shown experimentally as C-Cl reductive elimination from Pt-alkyl model compounds led to an inversion of configuration at carbon.

It has previously been reported that reductive elimination from L$_2$PtMe$_2$X yielded exclusively ethane, the result of C-C reductive elimination from the Pt(IV) complex. In this case, use of monodentate phosphine ligands allowed for initial phosphine dissociation, prior
to C-C reductive elimination from the 5-coordinate complex (Figure 1.42). While addition of excess iodide had no effect, addition of phosphine significantly slowed the reaction.

Replacement of the monodentate phosphines with bidentate dppe, yielded a vastly different system. In this case, phosphine dissociation was limited by the chelate effect, allowing for competitive dissociation of iodine, which could subsequently attack a methyl group, resulting in MeI formation. The reverse reaction, oxidative addition of MeI to (dppe)PtMeI was possible, thus setting up an equilibrium. The reversible nature of the reductive elimination of MeI was verified by the addition of NaI, which inhibited the formation of ethane. Over time, the Pt(IV) species was converted to (dppe)PtMeI, the result of the reductive elimination of ethane from the same 5-coordinate intermediate (Figure 1.43).[^77a]

![Image of chemical reactions](image_url)

Figure 1.42: Reductive elimination of ethane from 5 coordinate intermediate

Seminal work on the reductive elimination of C-X bonds from Pt(IV) was performed by Goldberg in the mid 90’s.[^77]
The majority of studies have supported the $S_N2$ type reductive elimination from 5-coordinate complexes, however, notable exceptions have been observed with Rh$^{78}$ and Pt.

We have recently reported the C-F bond forming reductive elimination from Pt organometallic compounds. Oxidation of the Pt(II) alkyl species with XeF$_2$ resulted in formation of a Pt(II)-F and the stereoretentive fluorinated product, likely the result of a direct reductive elimination from a Pt(IV)-F (Figure 1.44).$^{68}$ While no Pt(IV) intermediates were observed in these reactions, several similar Pt(IV) fluorides have been isolated.$^{79}$

![Figure 1.44: Stereoretentive C-F reductive elimination](image)

The direct reductive elimination of C-Cl from Pt(IV) has also been observed.

Oxidation of the doubly cyclometalated Pt(II) complex formed a mixture of cis and trans isomers of the Pt(IV) complex. While the trans isomer proved relatively stable, warming a solution of the cis isomer resulted in the formation of a new Pt(II) species. This proved to be the result of the reductive elimination of C-Cl which then datively bonds to the Pt centre. Once again, the reaction rate proved independent of additional chloride, suggesting a direct reductive elimination (Figure 1.45).$^{80}$

![Figure 1.45: Stereoretentive C-Cl reductive elimination](image)

In the case of Rh, oxidative addition of methyl iodide to a Rh(I) pincer complex resulted in formation of a stable, five coordinate Rh(III)-alkyl complex. Placing this complex under an atmosphere of CO resulted in highly steric dependent reactivity. When the
phosphine groups contained isopropyl substituents, addition of CO formed a pair of six coordinate Rh(III) complexes. However, when the isopropyl substituents were replaced with t-butyl groups, addition of CO resulted in reductive elimination of methyl iodide and formation of the Rh(I) carbonyl complex (Figure 1.46). Addition of tetrabutylammonium iodide to the reaction left the reaction rate unchanged, making an $S_N2$-type mechanism unlikely.$^{78}$

![Chemical structure](image)

**Figure 1.46: Stereoretentive C-I reductive elimination from Rh(III)**

Functionalization of metal carbon bonds via 2-electron oxidation mechanisms has been well studied and applied across a broad range of metals. Much less common, is the functionalization of metal carbon bonds which occurs by a single electron oxidation of the metal. While reports of this type have varied in both metal and ligand selection, single electron oxidation has often resulted in the formation of a carbon centered radical which can undergo further reaction to form halogenated, oxygenated or further reduced organic species depending on the choice of oxidant and atmosphere.

Early work involving the generation of alkyl radicals from organometallic complexes was performed by Kochi with several different metals. Formation of alkyl bromides from the reaction of mercury, palladium and zirconium organometallic complexes with copper (II) bromide was studied and revealed a mechanism involving homolytic cleavage of the metal.
alkyl bond in all cases. The involvement of a radical mechanism was confirmed by the stereochemical scrambling observed in the formation of the alkyl bromide, a result of the reaction of the free radical with copper (II) bromide (Figure 1.47). 

\[
\begin{array}{c}
\text{AcO} \quad \text{M} \\
\xrightarrow{\text{CuBr}_2} \\
\text{AcO} \quad \text{Br}
\end{array}
\]

\[
\text{M} = \text{Pd(diphos)Cl, HgCl}
\]

**Figure 1.47: Bromination of Pd and Hg-bonds**

In the case of Pt(II) organometallic compounds, an in depth study revealed an oxidative process highly dependent upon the donating ability of both ligand and alkyl group. Several dialkyl(bisphosphine)platinum(II) complexes were oxidized in the presence of hexachloroiridate and produced products resulting from single and double electron oxidation of the Pt centre. In the case of methyl groups, oxidation of \(\text{Me}_2\text{Pt(PMe}_2\text{Ph)}_2\) produced Pt(IV) compounds. Replacement of the dimethylphenylphosphine ligands with triphenylphosphine resulted in competitive formation of Pt(IV) compounds and methylplatinum (II) compounds accompanied by MeCl - the result of homolytic cleavage of a Me-Pt bond and interception of the Me radical by hexachloroiridate. Replacement of the methyl groups with ethyl groups in both the dimethylphenylphosphine and triphenylphosphine complex allowed for a clean single electron oxidation, producing EtCl and monoethylplatinum (II) (Figure 1.48). While both reactions provided the same products, the rate of oxidation of the triphenylphosphine complex was slower than that of the dimethylphenylphosphine complex. The involvement of alkyl radicals was confirmed by spin trapping and oxygen scavenging experiments.
Figure 1.4: Donor effects on the oxidation of Pt(II) compounds

Later studies on the single electron oxidation of lead, tin and mercury compounds focused on the oxidation event itself. The oxidation was probed using a series of trisphenanthroline iron(III) complexes which varied in reduction potential according to their substitution. Oxidation of the lead, tin and mercury organometallic complexes with these coordination complexes of iron revealed a second order rate constant which was linearly dependent upon the reduction potential of the oxidant, showing no deviation for steric effects. These data suggested a strictly outer-sphere oxidation process. In contrast to the iron(III) oxidants, application of hexachloroiridate as the oxidant in the same reactions, revealed significantly faster oxidations than those predicted solely based upon their reduction potential. Oxidations with the hexachloroiridate also proved sensitive to steric effects, pointing toward an inner sphere electron transfer process. While the iron complexes also served to oxidize the subsequently formed radical, the hexachloroiridate provided the alkyl chloride product (Figure 1.49).83

\[
\begin{align*}
\text{PhMe}_2\text{P}^\text{Me} & \quad \text{PhMe}_2\text{P}^\text{Me} \quad \text{IrCl}_6^{2-} \quad \text{CH}_3\text{CN} & \quad \text{Me}_2\text{Pt}^{IV}(\text{PPh}_3)_2\text{X}_2 & \quad \text{MePt}^{III}(\text{PPh}_3)_2\text{X} & + & \text{MeCl} \\
\text{Ph}_3\text{P}^\text{Me} & \quad \text{Ph}_3\text{P}^\text{Me} \quad \text{IrCl}_6^{2-} \quad \text{CH}_3\text{CN} & \quad \text{Me}_2\text{Pt}^{IV}(\text{PPh}_3)_2\text{X}_2 & \quad 54\% & \quad \text{MePt}^{III}(\text{PPh}_3)_2\text{X} & + & \text{MeCl} \\
\text{L} & \quad \text{Pt}^\text{Me} & \quad \text{IrCl}_6^{2-} \quad \text{CH}_3\text{CN} & \quad \text{EtPt}^{III}\text{L}_2(\text{CH}_3\text{CN})^+ & + & \text{EtCl} \\
\text{L} = \text{PPh}_3, \text{PMe}_2\text{Ph}
\end{align*}
\]

Figure 1.49: Inner and outer sphere one electron oxidation of organostannanes
Baird has also studied the single electron oxidation of both iron\textsuperscript{84} and ruthenium\textsuperscript{85} complexes. In the case of iron, two possible reaction pathways could be followed. Oxidation with copper (II) halides resulted in formation of an ion paired complex, the fate of which was dependent upon the alkyl group. In the case of methyl and benzyl substituents, single electron oxidation with a copper (II) halide resulted in the breakdown of the ion pair via an SN2 type attack of halide upon the alpha carbon, generating MeX or PhCH\textsubscript{2}X with inversion of configuration. When the alkyl group was n-Bu or Me\textsubscript{3}CCH\textsubscript{2}CH\textsubscript{2} the ion pair broke down via homolytic cleavage of the iron carbon bond, the alkyl radical then reacts with the copper (II) halide to form the alkyl halide.\textsuperscript{84}

Oxidation of ruthenium organometallics with copper (II) halides provided the organic radical which was once again halogenated with excess copper halide. Electrochemical studies revealed that the ruthenium complexes were more challenging to oxidize and reacted accordingly. Reaction of the ruthenium complexes with mercury (II) halides resulted in a transmetallation reaction, forming the organomercury complexes in quantitative yield.\textsuperscript{85}

Trogler has also reported the chemical and electrochemical single electron oxidation of palladium organometallic compounds.\textsuperscript{86} A series of dialkyl palladium compounds underwent single electron oxidation and homolytic Pd-C bond cleavage induced either electrochemically or chemically with ferrocenium. A PCP pincer palladium methyl complex was also studied, revealing selective homolytic cleavage of the palladium methyl bond (Figure 1.50). Electrochemical studies of the Pd complexes revealed that despite the uphill electron transfer process between Pd and ferrocenium, the irreversible nature of the process allowed for facile electron transfer.
Research Objectives

Biomimetic approaches to the cyclization in acyclic polyene substrates have struggled to replicate the complexity observed in their enzyme mediated counterparts. These reactions have long suffered from a lack of selectivity, premature termination and an inability to duplicate the structural rearrangements observed in nature. This gap between nature and synthetic approaches has prompted the design of elaborate systems to overcome the inherent problems observed in the laboratory.

Of particular interest is the synthesis of C3-oxygenated polycycles. This structural motif is commonly observed in nature and has as its source the oxygen of oxidosqualene. While effective methods exist for their synthesis, installation of the oxygen moiety has occurred exclusively prior to cyclization, generally in the form of an epoxide. This has necessitated the synthesis of chiral substrates in to achieve selectivity in the products, making catalyst controlled cyclization and subsequent installation of the C3-oxygen an attractive alternative.

Our previous efforts in the cyclization of polyene substrates have proven effective for the stoichiometric synthesis of C3 platinated organometallic complexes from both heteroatom and alkene terminating substrates. Catalytic variants of these reactions have been limited by the formation of complex mixtures of products and in several cases, a limited substrate scope.
We present herein, efforts toward the development of new methods for the post-cyclization oxygenation and halogenations of polycycles under catalyst control. We also report the development and application of a versatile catalyst for the cyclization of polyenes, designed to enable the atom economical cycloisomerization of a wide range of polyene substrates.
References


CHAPTER 2: STOICHIOMETRIC HALOGENATION OF PT-C BONDS*

Introduction

When considering the reductive elimination of C-X bonds from high valent metal centres, two modes of reactions are possible: stereoretentive reductive elimination in which configuration is retained, and S_N2 type reductive elimination in which an inversion of configuration is observed. The majority of studies on C-X bond forming reductive elimination have involved formation Me-X bonds, a process in which the stereochemical information is lost since both retentive and S_N2-type reductive elimination mechanisms form the same identical product.

The stability of (triphos)Pt-R^+ complexes toward acid has allowed for the isolation of unique Pt alkyl compounds where the alkyl is a complex multicyclic structure. Formation of the diastereomerically pure Pt-alkyl compounds generated from a polyene cyclization, provide ideal subjects for study of C-X bond forming reductive elimination. In contrast to the reductive elimination of MeX bonds, the stereogenicity of the carbon center and the diastereomeric purity of this compound allows for the generation of two different and distinguishable diastereomeric products depending upon the mechanism of reductive elimination (Figure 2.1).

*Portions of this chapter were adapted with permission from Geier, M.J.; Gagné, M.R. Organometallics, 2013, 32, 380 and Geier, M.J.; Gagné, M.R., in preparation.
We have previously reported the first stereoretentive C-F bond forming reductive elimination from a proposed Pt(IV) intermediate.\textsuperscript{1} While this stereochemical outcome was surprising, as C-X reductive elimination generally proceeds in a step-wise stereoinvertive fashion,\textsuperscript{2} the poor nucleophilicity of fluoride was thought to perhaps contribute to this phenomenon.

The successful fluorination\textsuperscript{1} and β-hydride elimination\textsuperscript{3} reactions of polycyclic Pt-alkyl compounds led us to the explore the possibility of developing new Pt-C bond functionalizing reactions and turnover mechanisms through mechanistic studies on pre-isolated Pt-alkyl intermediates. With this long-term goal in mind, further exploration of the reductive elimination from the Pt-alkyl complex was undertaken.

**Results**

We began our studies by investigating the chlorination, bromination and iodination of compound 2.1 to determine whether a stereoretentive (akin to the fluorination chemistry)\textsuperscript{1} or invertive reductive elimination process would be operative. Oxidation of compound 2.1 with two equivalents of a halosuccinimide reagent (n-bromosuccinimide and n-chlorosuccinimide) again - in analogy to the XeF\textsubscript{2} work - resulted in stereoretentive reductive elimination of the C-X bond. While C-F reductive elimination proceeded rapidly with XeF\textsubscript{2}, C-Cl and C-Br bond forming reductive elimination proved significantly slower, three hours in the case of the bromide and 18 hours for the chloride. While yields were a moderate 43\% for the chloride,
and 58% for the bromide, diastereoselectivity of the reaction was good, producing the products in greater than 10:1 dr. In the case of iodine (I$_2$), oxidation proceeded in less than five minutes, producing the stereoretentive iodide in 89% yield with greater than 10:1 dr (Figure 2.2). Despite convenient monitoring by $^{31}$P NMR spectroscopy, no intermediates were observed, suggesting slow oxidation of Pt(II) to Pt(IV) followed by rapid reductive elimination from the proposed Pt(IV) intermediate. In each case, the Pt-product was determined to be (triphos)Pt-X$^+$ (X = Cl, Br, I) as determined from 31P NMR spectroscopy. In each case, the coupling constant of the phosphine trans to the halide was $\sim$3 000 Hz, characteristic of a (triphos)PtX$^+$ complex.

Figure 2.2: Stereoretentive C-X bond forming reductive elimination

Starting from the four coordinate Pt(II) complex, oxidation with X$^+$ reagents is believed to generate a dicationic Pt(IV)-halide complex with a sixth coordination site left
vacant or occupied by solvent. This complex is likely to be highly unstable as the soft phosphine donor ligands struggle to stabilize hard, high-oxidation state metal complexes such as Pt(IV). As a consequence of its high reactivity, this complex will then undergo rapid, metal-based reductive elimination, resulting in the observed stereoretentive products (Figure 2.3). Given the electron deficient nature of a dicationic Pt(IV) complex it is perhaps not so surprising that $X^-$ loss (to a tricationic, formally four coordinate Pt(IV) species) and re-addition is not a competitive mechanism of reductive elimination. In most cases where the invertive/S$_N$2 mechanism is invoked for R-X reductive elimination the charge on the metal is such that the overall charge on the putative intermediate is not nearly so high.

While the aversion of F$^-$ to behave as a nucleophile in an S$_N$2-type reaction could explain the stereoretentive fluorination, the larger halides (Br$^-$, I$^-$) are known to be sufficiently nucleophilic to engage in such reactivity, making their C-X bond forming, stereoretentive reductive elimination that much more surprising. While stereoretentive C-Cl bond forming reductive elimination has recently been reported, these represent the first cases of stereoretentive C-Br and C-I bond forming reductive elimination from Pt(IV).

![Figure 2.3: Mechanism of stereoretentive C-X bond formation](image)

The use of halonium reagents as two electron oxidants proved effective for converting Pt(II) to Pt(IV) resulting in formation of the C3-halogenated products, however, we became interested in C3-oxygenated compounds, a structural motif found in numerous natural products. To access such products, we contemplated methods to achieve C-O bond forming
reductive elimination.\textsuperscript{8} Recent organometallic chemistry of high valent Pt and Pd complexes with electrophilic fluorinating reagents has proven to be quite complex,\textsuperscript{9} often involving competing reductive elimination processes.\textsuperscript{10} The significant kinetic barrier to C-F bond forming reductive elimination has made electrophilic fluorinating reagents an attractive by-standing oxidant, wherein F\textsuperscript{+} serves as the oxidant but does not participate in bond forming reductive elimination, an approach that has shown the ability to promote a variety of alternative reductive elimination processes.\textsuperscript{11}

We envisioned a process through which Pt oxidation with an electrophilic fluorinating reagent would produce a transient Pt(IV) complex, which, in the presence of a suitable oxygen nucleophile could undergo an S\textsubscript{N}2 type C-O bond forming reaction. Attempts to use XeF\textsubscript{2} in the role of by-standing oxidant to achieve selective C-O bond forming reductive elimination produced unexpected results. Addition of 3 eq. of XeF\textsubscript{2} to a solution of 2.1 and 10 eq. tetrabutylammonium acetate (TBAOAc) in acetonitrile consumed the starting material, however, the desired C3-acetate was not observed. In place of the acetate, we discovered that the invertive C3-fluorinated product was now the preferred product (Table 2.1). To better determine the role of acetate, its concentration was varied, at a single equivalent of TBAOAc, a slight preference for the stereoretentive product was observed (47\% to 36\%), while at 5 and 10 equivalents of TBAOAc, a strong preference for the invertive product (58\% to 5\% and 35\% to 3\% respectively), suggesting an important role for TBAOAc.
In the presence of acetate, the previously reported direct reductive elimination pathway\(^1\) from the five coordinate Pt(IV)-fluoride could be nearly shut off. Oxidation of the Pt(II)-alkyl complex by XeF\(_2\) results in formation of the five coordinate Pt(IV) fluoride, however, in the presence of acetate, we surmised that the five coordinate Pt(IV)-fluoride can be quickly trapped (more effectively at high TBAOAc concentrations) to form a 6-coordinate, cationic complex, preventing the previously reported stereoretentive reductive elimination. From this six coordinate complex, there are two possible pathways to arrive at the stereoinvertive product: path A: fluoride dissociation to form a five coordinate Pt-acetate and attack of the fluoride at C3, or path B: direct attack of fluoride (XeF\(_2\) serves as a kinetic source of F\(^+\) first and and F\(^-\) second)\(^12\) at C3 of the six coordinate complex (Figure 2.4).
Figure 2.4: Possible reductive elimination pathways with XeF$_2$ and TBAOAc
To further investigate this unexpected switch in reductive elimination mechanism, several similar processes were examined. Addition of tetrabutylammonium bromide in place of the tetrabutylammonium acetate allowed for formation of C3-brominated products. At one equivalent of tetrabutylammonium bromide, the stereoretentive C3-fluoride remained the major product at a 51% yield. At 2 equivalents TBAB, 32% of the retentive fluoride, 19% of the invertive bromide and 4% of the retentive bromide formed. At 5 equivalents TBAB 31% of the retentive fluoride, 31% of the invertive bromide and 21% of the retentive bromide formed. This data provide a clear indication that brominated products are preferred at higher loadings of TBAB.

Table 2.2: Fluorination in the presence of TBAB

<table>
<thead>
<tr>
<th>Equivalents TBAB</th>
<th>Total Yield</th>
<th>% 2.5</th>
<th>% 2.6</th>
<th>% 2.3</th>
<th>% 2.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59%</td>
<td>51%</td>
<td>3%</td>
<td>-</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>56%</td>
<td>32%</td>
<td>1%</td>
<td>4%</td>
<td>19%</td>
</tr>
<tr>
<td>5</td>
<td>83%</td>
<td>31%</td>
<td>-</td>
<td>21%</td>
<td>31%</td>
</tr>
</tbody>
</table>

*Yields determined by 1H NMR with 4-methylanisole as internal standard

While formation of the stereoretentive fluoride likely proceeds through the 5 coordinate complex, formation of the invertive bromide is most easily explained as proceeding through two different mechanisms. Attack of Br⁻ on the 5 coordinate complex (path A) or trapping of the five coordinate complex with Br⁻ to form the 6 coordinate complex, which could then undergo bromide attack (path B). Formation of the
Stereoretentive bromide could occur through two different mechanisms: from dissociation of fluoride from the 6-coordinate complex, which could then undergo stereoretentive C-Br reductive elimination, akin the reaction of 2.1 with NBS (Figure 2.5), or conversion of Br⁻ to Br⁺ through reaction with XeF₂.

Figure 2.5: Possible reductive elimination pathways with XeF₂ and TBAB
The kinetic barrier to C-F bond forming reductive elimination is known to allow competing processes to occur with electrophilic fluorinating reagents.\textsuperscript{9,11} With this in mind, we explored the use of NBS as oxidant to ascertain if this mechanistic switch occurred exclusively with electrophilic fluorinating reagents. Use of N-bromosuccinimide as oxidant and tetrabutylammonium bromide (TBAB) as the nucleophile also produced a mixture of invertive and retentive bromides. At 1 equivalent of TBAB, equal amounts of invertive and retentive bromide were formed at 19% a piece. At 2 equivalents 2 TBAB, the ratio remained similar, however, both were formed in greater yield, 33% of the retentive and 27% of the invertive. At 5 equivalents of TBAB, the invertive product was favored by nearly a 2:1 ratio at 23% to 12%. While the variations in yield were unexpected, the increasing amounts of the invertive product suggest a link between formation of the invertive and the concentration of TBAB.

Table 2.3: Bromination in the presence of TBAB

<table>
<thead>
<tr>
<th>Equivalents TBAB</th>
<th>Total Yield\textsuperscript{a}</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38%</td>
<td>19%</td>
<td>19%</td>
</tr>
<tr>
<td>2</td>
<td>61%</td>
<td>33%</td>
<td>27%</td>
</tr>
<tr>
<td>5</td>
<td>35%</td>
<td>12%</td>
<td>23%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}yields determined by \textsuperscript{1}H NMR with 4-methylanisole as internal standard

While the retentive bromide is likely produced from reductive elimination from the 5-coordinate complex, the invertive product can once again be produced in two different ways: bromide attack on a 5 coordinate (path A) or 6 coordinate (path B) complex (Figure 2.6).
While a 6-coordinate complex is likely to be favored at higher bromide concentrations, these data do not provide sufficient evidence for a 5 vs. 6 coordinate mechanism.

![Figure 2.6: Possible reductive elimination pathways with NBS and TBAB](image)

**Discussion**

This study has provided clear evidence that the process of reductive elimination from proposed Pt(IV) intermediates can proceed by two different mechanisms, each of which leads to a different favored diastereomer in the product. In the absence of suitable nucleophiles, formation of the stereoretentive products is likely the result of the instability of the 5 coordinate complex. While dissociation of $X^-$ and $S_N2$ type attack is generally favored in most late metal organometallic compounds, in this case, dissociation of $X^-$ would produce a
14 electron, 4-coordinate, tricationic Pt(IV) complex (Figure 2.6). The instability of such a putative intermediate would seem to reduce the likelihood of proceeding in this fashion.

![Figure 2.6: Electrification](image)

**Figure 2.6**

A mechanistically relevant process has recently been reported by Sanford et. al in which C-F bond forming reductive elimination from Pd(IV) produces an alkyl fluoride. The authors concluded that ligand (pyridine) dissociation from a 6 coordinate complex takes place prior to reductive elimination from a similar 5 coordinate complex. While the authors were unable to differentiate between invertive and retentive reductive elimination, they favored the retentive pathway due to the poor nucleophilicity of F⁻ and unlikely dissociation of F⁻ from the 5 coordinate complex. The observation of invertive F⁻ reductive elimination pathways in the present suggests that this possibility may indeed be feasible.

![Figure 2.7: Reductive elimination from 5-coordinate complex](image)

**Figure 2.7:** Reductive elimination from 5-coordinate complex

A mechanismically relevant process has recently been reported by Sanford et. al in which C-F bond forming reductive elimination from Pd(IV) produces an alkyl fluoride. The authors concluded that ligand (pyridine) dissociation from a 6 coordinate complex takes place prior to reductive elimination from a similar 5 coordinate complex. While the authors were unable to differentiate between invertive and retentive reductive elimination, they favored the retentive pathway due to the poor nucleophilicity of F⁻ and unlikely dissociation of F⁻ from the 5 coordinate complex. The observation of invertive F⁻ reductive elimination pathways in the present suggests that this possibility may indeed be feasible.

![Figure 2.8: Sanford’s C-F reductive elimination from Pd(IV)](image)

**Figure 2.8:** Sanford’s C-F reductive elimination from Pd(IV)
In the case of the stereoinvertive reductive eliminations, two different pathways are possible in each case: 1) nucleophilic attack on a 5 coordinate complex, or 2) nucleophilic attack on a 6 coordinate complex (Figure 2.9). While either or both processes may be operative, previous work by Goldberg, Puddephatt and others would suggest that reductive elimination proceeds by nucleophilic attack upon the 5 coordinate complex.\textsuperscript{2a,b,9,14}

\textbf{Figure 2.9: Possible paths to stereoinvertive reductive elimination}

While $X^-$ dissociation from a 5 coordinate complex is likely to be highly disfavored (see above), the coordination of a nucleophile ($\text{OAc}^-$, $\text{Br}^-$) is likely to provide sufficient electron density to allow for halide dissociation and $S_N2$ type reductive elimination. While in the absence of a nucleophile, dissociation would produce a 4 coordinate, tricationic Pt(IV) intermediate, the addition of a nucleophile would produce a more feasible 5-coordinate dicationic species.
The ability to manipulate the mechanism of reductive elimination from Pt(IV) has provided a means through which to control the diastereoselectivity of the halogenated product. This unexpected deviation from standard $S_N2$-type behavior has provided evidence that this process may be more complicated than previously believed. While we have been unable to determine the nature of the coordination sphere from which these reductive elimination mechanisms take place, study of their role in this process will provide valuable insight. While we have previously reported catalytic, stereoretentive cyclization/fluorination of polyenes,$^{15}$ we have thus far been unable to translate this to catalytic manifold, selectively proving the other fluoride diastereomer.

**Experimental Section**

All air and moisture sensitive procedures were performed using an MBraun glovebox or standard Schlenk line techniques. Commercially available reagents were used without further purification. Acetonitrile was distilled from CaH$_2$. NMR spectra were collected on a...
Bruker 600 MHz Avance spectrometer and referenced to residual solvent peaks. Compounds 2.1, 2.5\textsuperscript{1} and 2.7\textsuperscript{17} have been reported. HRMS was performed by Dr. Mee-Kyung Chung at the University of North Carolina at Chapel Hill.

**General Procedure for Oxidation Reactions**

The oxidant of choice was added to a stirring solution of 2.1 (8 mg, 0.04 mmol) in CD\textsubscript{3}CN (0.7 mL). For reactions involving tetrabutylammonium salts, the salt was added prior to the oxidant. NMR yields were determined in reference to an internal standard by \textsuperscript{1}H or \textsuperscript{19}F NMR (4-methylanisole for reactions with TBAB and 1-fluoro-3,5-dimethoxybenzene for reactions with TBAOAc)

**Compound 2.2:**

\[
\begin{align*}
\text{BF}_4^- & \quad \text{[Pt]} \\
\text{2 eq. NCS} & \quad \text{CH}_3\text{CN} \\
& \quad 18 \text{ hours}
\end{align*}
\]

43% isolated yield

2.2: \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): \(\delta\) 7.12 (m, 1H), 7.06 (m, 1H), 6.86 (m, 1H), 6.80 (m, 1H), 3.99 (m, 1H), 2.63 (m, 1H), 2.53 (m, 1H), 2.29 (br, 2H), 2.05 (m, 1H), 1.92 (m, 1H), 1.86 (m, 1H), 1.75 (m, 1H), 1.59 (m, 1H), 1.22 (s, 3H) ppm. \textsuperscript{13}C NMR (152 MHz, CDCl\textsubscript{3}): 153.4, 129.6, 127.7, 121.3, 120.2, 117.5, 75.7, 57.7, 40.1, 39.4, 38.9, 34.3, 28.9, 16.6 ppm. HRMS (ESI) C\textsubscript{14}H\textsubscript{17}ClO \([M+H]^+\)/z calc. 237.1041, found 237.1045.

**Compound 2.3:**


**2.3:** $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.10 (m, 1H), 7.02 (m, 1H), 6.84 (m, 1H), 6.78 (m, 1H), 4.08 (m, 1H), 2.60 (m, 1H), 2.50 (m, 1H), 2.36 (br, 2H), 2.00 (m, 2H), 1.90 (m, 1H), 1.60 (m, 2H) 1.21 (s, 3H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): 153.4, 129.6, 127.7, 121.3, 120.2, 117.5, 75.6, 48.9, 41.0, 40.5 40.0, 35.2, 28.8, 16.6 ppm. HRMS (ESI) $\text{C}_{14}\text{H}_{17}\text{BrO}$ [M+H]$^+$/z calc. 281.0536, found 281.0534.

**Compound 2.4:**

2.4: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.10 (m, 1H), 7.02 (m, 1H), 6.83 (m, 1H), 6.77 (m, 1H), 4.17 (m, 1H), 2.59 (br, 1H), 2.40-2.52 (m, 3H), 2.17 (m, 1H), 1.82-1.91 (m, 3H), 1.71 (m, 1H), 1.21 (s, 3H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): $\delta$ 153.3, 129.6, 127.7, 121.3, 120.16, 117.5, 75.6, 43.4, 42.1, 41.5, 37.6, 28.6, 25.5, 16.6 ppm. HRMS (ESI) $\text{C}_{14}\text{H}_{17}\text{IO}$ [M+H]$^+$/z calc. 329.0397, found 329.0395.

**Compound 2.6:**
2.6: $^1$H NMR (600 MHz, CD$_2$Cl$_2$): δ 7.11-7.06 (m, 2H), 6.84 (m, 1H), 6.77 (m, 1H), 4.90 (dm, 1H, J$_{H-F}$ = 48Hz), 2.62 (dd, 1H, J = 16.8 Hz, 5.4 Hz), 2.47 (dd, 1H, J = 16.8 Hz, 13.2 Hz), 2.25 (m, 1H), 2.15 (m, 2H), 2.00 (m, 1H) 1.83-1.65 (m, 2H), 1.46-1.33 (m, 1H), 1.17 (s, 3H) ppm. $^{13}$C NMR (152 MHz, CD$_2$Cl$_2$): δ 153.5, 129.5, 127.3, 121.9, 119.7, 117.1, 87.6 (d, J$_{C-F}$ = 168 Hz), 76.1, 34.7 (d, J$_{C-F}$ = 21.1 Hz), 33.4, 33.3, 28.5, 28.4 (d, J$_{C-F}$ = 21.1 Hz), 15.4 ppm. $^{19}$F NMR (565MHz, CD$_2$Cl$_2$): -182.2 ppm. HRMS (EI) C$_{14}$H$_{18}$FO [M + H]$^+$/z calc. 221.1336 found 221.1331.
References


(17) See Chapter 3
CHAPTER 3: ONE ELECTRON OXIDATION OF Pt-ALKYL COMPOUNDS*

Introduction

The two electron oxidation of platinum alkyl complexes with halonium reagents provided access to C3-halogenated compounds with controllable diastereoselectivity. Despite attempts to employ these halonium reagents as spectator oxidants, no oxygenated products were observed. In an attempt to access these desired C3-oxygenated compounds, several other oxidative routes were explored.

Recent work from the Goldberg\textsuperscript{1} and Britovsek\textsuperscript{2} groups disclosed the photochemical reaction of Pt and Pd-Me complexes with oxygen to generate the O\textsubscript{2} insertion products. These reactions have been proposed to proceed via two different mechanisms. In the case of the diaminoterpyridine Pt-Me complex, the complex itself has been shown to act as an oxygen sensitizer, converting triplet oxygen to the more reactive singlet oxygen, enabling insertion of O\textsubscript{2} to proceed.\textsuperscript{2} Continued exposure of the complex to light resulted in formation of formaldehyde and the platinum hydroxide complex (Figure 3.1).

\footnotesize{\textsuperscript{1} Portions of this chapter were adapted with permission from Geier, M.J.; Gagné, M.R. \textit{Organometallics}, \textbf{2013}, \textit{32}, 380}
Goldberg has reported a light dependent radical chain mechanism for the insertion of O\textsubscript{2} into a Pd-Me bond of (bpy)PdMe\textsubscript{2}.\textsuperscript{1b} Detailed mechanistic study revealed that initiation occurred by homolysis of the radical initiator AIBN to form an alkyl radical which was rapidly intercepted by oxygen. The alkyl peroxy radical then underwent a free radical substitution reaction with (bpy)PdMe\textsubscript{2} to liberate a methyl radical. Propagation then occurred by interception of this methyl radical by oxygen and reaction with a second equivalent of (bpy)PdMe\textsubscript{2} to form a five coordinate, Pd(III) complex which then liberated a methyl radical and formed the observed O\textsubscript{2} insertion product (Figure 3.2). These reports of Pt and Pd alkyl reactivity under photochemical conditions formed the starting point for the study described in this chapter.
Figure 3.2: Goldberg’s insertion of O₂ into Pd-Me bond

Stoichiometric Reactions

Initial studies focused on the photochemical reactivity of Pt-alkyl complex 3.1 under an atmosphere of oxygen. Consumption of starting material was monitored by \(^{31}\)P NMR and organic products were identified by gc/ms. Exposure of the complex to a compact fluorescent light (CFL) bulb under oxygen in acetonitrile resulted in formation of the desired C3-ketone 3.2 in a 60% yield. In contrast to the report of Britovsek\(^2\) in which the platinum hydroxide product was formed, extensive decomposition of the Pt complex was observed.

Reactions were slow, taking approximately 18 hours for complete consumption. Addition of the radical initiator AIBN resulted in slightly shorter reaction times and a small bump in yield to 67%, while the radical inhibitor BHT resulted in longer reaction times and a lower yield of the ketone product at 40%, mildly suggestive of a radical mechanism (Table 3.1). Despite formation of the desired oxygenated product in these reactions, decomposition
of the Pt initiator precluded development of a catalytic scheme for the cyclization/oxygenation of polyenes.

Table 3.1: Additive effect in photochemical oxygenation reactions

<table>
<thead>
<tr>
<th>Additive</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>60%</td>
</tr>
<tr>
<td>AIBN</td>
<td>67%</td>
</tr>
<tr>
<td>BHT</td>
<td>40%</td>
</tr>
</tbody>
</table>

Eager to explore milder conditions for generation of the C3 oxygenated product, chemical oxidants were explored following reports of Pt-Me$_3$ and Pd-Me$_{1b,4}$ bond homolysis from the $+3$ oxidation state. The radical initiators AIBN and benzoyl peroxide were first examined. Initiation of the reactions required elevated temperatures, multiple equivalents of the initiator and extended reaction times. Formation of the ketone product was once again observed, albeit in low yield. Once again, extensive decomposition of the Pt initiator was observed.

In an attempt to effect a cleaner oxidation reaction, metal oxidants were explored. Copper (II) chloride, commonly used to oxidize Pd(0) to Pd(II) in a stepwise fashion in the Wacker process was chosen as the single electron oxidant. Reaction of 3.1 with a single equivalent of CuCl$_2$ in acetonitrile resulted in 50% consumption of the starting material in under 5 minutes, extended reaction times provided no further reaction. Analysis of the organic products by gc-ms revealed a 1:1 ratio of the two C3-chloride diastereomers, with concominant formation of (triphos)PtCl$^+$. Reaction of 3.1 with two equivalents of CuCl$_2$ provided complete consumption of starting material, resulting in a 54% isolated yield of a 1:1 mixture of chloride diastereomers. Application of two equivalents of CuBr$_2$ as oxidant,
resulted in a 66% isolated yield of the C3-brominated product with a dr of 1.8:1 with a preference for the invertive brominated product as established by $^1$H NMR coupling constants (Table 3.2).

**Table 3.2: Halogenation of Pt-alkyl with CuX$_2$**

<table>
<thead>
<tr>
<th>Cmpd #</th>
<th>X</th>
<th>Time</th>
<th>Isolated Yield</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3</td>
<td>Cl</td>
<td>&lt;5 mins</td>
<td>54%</td>
<td>1:1</td>
</tr>
<tr>
<td>3.4</td>
<td>Br</td>
<td>&lt;5 mins</td>
<td>66%</td>
<td>1.8:1</td>
</tr>
</tbody>
</table>

The formation of a mixture of diastereomers suggested the involvement of a free radical process. The proposed mechanism involves initial one electron oxidation of the Pt(II)-alkyl to Pt(III), which initiates Pt-C bond homolysis, forming the (triphos)PtX$^+$ and a C3-radical. The C3 radical can then be intercepted in a non-diastereoselective fashion by a second equivalent of CuX$_2$ to form the C3-halide (Figure 3.3). Kochi has measured the rate constant for the interception of alkyl radicals by CuBr$_2$ to be $\sim4\times10^9$ M$^{-1}$s$^{-1}$, indicating rapid quenching of the free radical.

![Proposed mechanism for the halogenation of 3.1 with CuX$_2$ reagents](image-url)

**Figure 3.3: Proposed mechanism for the halogenation of 3.1 with CuX$_2$ reagents**
The successful generation of alkyl radicals suggested that oxygenation may indeed be possible (Figure 3.4). In an attempt to thwart the undesired bromination pathway, the reagents were combined under 2 atm of oxygen in acetonitrile. Analysis of the organic products by gc-ms revealed 37% of the C3-ketone, 49% of a mixture of diastereomers of the C3-alcohol and a 14% yield of the bromide diastereomers. Isolation of the oxygenated products resulted in a 63% yield with a ketone:alcohol ratio of 1:1. While initially confounded by the mixture of oxygenated products due to the observation of formaldehyde by Britovsek and the formation of the C3-ketone under photochemical conditions, the mixture can be explained by a simple free radical mechanism, first proposed by Russell\(^6\) to explain the reactivity of secondary radicals with \(O_2\), further supporting the proposed radical mechanism for halogenation.

Figure 3.4: Mechanism of oxygenation of Pt-C bond

Oxidation of the Pt(II)-alkyl by CuBr\(_2\) again results in eventual Pt-C bond homolysis, in this case, the alkyl radical can be intercepted by molecular oxygen in a non-diastereoselective fashion to form the alkylperoxy radical. Despite the comparable rate of
interception of free radicals by oxygen \((3-5\times10^9 \text{ M}^{-1}\text{s}^{-1})\)\(^7\) and CuBr\(_2\) \((\sim4\times10^9 \text{ M}^{-1}\text{s}^{-1})\),\(^5\) the increased pressure of \(O_2\) allowed for preferential oxygenation. Alkylperoxy radicals have been shown to undergo Russell disproportionation\(^6,8\) through a six membered transition state to generate one equivalent of ketone and one equivalent of the alcohol and \(^1\)O\(_2\) (Figure 3.5).

![Figure 3.5: Russell disproportionation of alkyl radical](image)

Use of copper halides as the single electron oxidant under an increased pressure of oxygen provided the desired organic product, however, formation of (triphos)PtX\(^+\) prevented any exploration of a catalytic variant as (triphos)PtX\(^+\) complexes are unable to initiate polyene cyclization. To solve this problem, we turned to Cu(OTf)\(_2\) in the hope that the weakly coordinating triflate may allow for catalytic reactions. Addition of 1 equivalent of Cu(OTf)\(_2\) to a solution of 3.1 in acetonitrile resulted in immediate consumption of starting material and a 53\% isolated yield of oxygenated products. Addition of two equivalents of Cu(OTf)\(_2\) under the same conditions resulted in a 33\% isolated yield of oxygenated products with a notable increase in the \(\beta\)-hydride elimination product. In order to maximize the yield of oxygenated products, the reaction of 3.1 with 1 equivalent of Cu(OTf)\(_2\) was performed under 2 atm of oxygen which provided an 80\% isolated yield of oxygenated products (Table
3.3). To confirm molecular oxygen as the source of oxygen, reactions performed with rigorous exclusion of oxygen resulted in exclusive formation of the product of net β-hydride elimination. This alkene product likely forms as a result of the oxidation of the alkyl radical by a second equivalent of Cu(OTf)₂. This reaction only occurs in the absence of copper halides and oxygen as the rate constant for oxidation of the alkyl radical by Cu(OTf)₂ is significantly slower at (∼2×10⁷ M⁻¹ s⁻¹).⁹ Importantly, oxidations using Cu(OTf)₂ provided clean formation of (triphos)Pt-NCMe²⁺. While (triphos)Pt-NCMe²⁺ is incapable of initiating cyclization, its formation suggested a simple change in solvent may regenerate the catalyst.

Table 3.3: Optimization of oxygenation of Pt-alkyl

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Time</th>
<th>Atmosphere</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 eq. Cu(OTf)₂</td>
<td>&lt;5 min</td>
<td>air</td>
<td>53%</td>
</tr>
<tr>
<td>2 eq. Cu(OTf)₂</td>
<td>&lt;5 min</td>
<td>air</td>
<td>33%</td>
</tr>
<tr>
<td>1 eq. Cu(OTf)₂</td>
<td>&lt;5 min</td>
<td>2 atm O₂</td>
<td>80%</td>
</tr>
</tbody>
</table>

Catalytic Studies

Initial work toward a catalytic sequence focused on a change in solvent from acetonitrile to something less coordinating. A dramatic solvent effect was quickly observed, as the stoichiometric oxidation reaction which takes seconds in acetonitrile did not proceed in the majority of solvents tested. This phenomenon can be explained by the higher redox potential of copper(II) triflate in acetonitrile, due to the thermodynamic stability of the product copper(I) tetrakis acetonitrile complex. Despite the lack of reactivity in nitroethane, a switch to nitromethane provided the desired oxidation, however, reaction times were
significantly slower than in acetonitrile, taking several hours to observe complete consumption of the Pt-alkyl (Table 3.4).

Table 3.4: Solvent effect on oxygenation of Pt-alkyl

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CN</td>
<td>&lt;5 mins</td>
</tr>
<tr>
<td>CD₃NO₂</td>
<td>~4 hours</td>
</tr>
<tr>
<td>EtNO₂</td>
<td>days</td>
</tr>
</tbody>
</table>

The rate of the oxidation reaction was impacted by the use of poorly coordinating ligands as additives. In nitromethane, stoichiometric oxidation of the Pt-alkyl required 4 hours for complete consumption of starting material. Addition of 2 equivalents of 1-hexene, designed to mimic the presence of an excess of polyene substrate, dropped the reaction time to less than three hours. Oxidation in the presence of pentafluorobenzonitrile, a poorly coordinating nitrile used previously in Pt catalyzed polyene cyclizations, further reduced reaction times to less the 1.5 hours (Table 3.5). These results, particularly the rate enhancement in the presence of 1-hexene, suggested that oxidation in a catalytic manifold should proceed at a faster rate than those performed in a stoichiometric fashion.
Table 3.5: Additive effect on oxygenation of Pt-alkyl

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Additive</th>
<th>Reaction Time</th>
<th>Major Pt Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>4 hours</td>
<td>Ph-P-Pt-OTf</td>
</tr>
<tr>
<td>1-hexene</td>
<td>&lt;3 hours</td>
<td>Ph-P-Pt-(\text{PPPh}_2)R</td>
</tr>
<tr>
<td>pentafluorobenzonitrile</td>
<td>&lt;1.5 hours</td>
<td>Ph-P-Pt-N=(\text{F}_2)</td>
</tr>
</tbody>
</table>

To test the feasibility of a catalytic variant, oxidation of the Pt-alkyl was carried out under 1 atm of \(\text{O}_2\), upon complete consumption of starting material (verified by \(^{31}\text{P}\) NMR), a second equivalent of substrate and a second equivalent of copper (II) triflate were added. Monitoring of the reaction over time revealed consumption of the second equivalent of starting material, suggesting continued activity of the initiator.

The use of copper(II) reagents as oxidants in organometallic chemistry has been especially fruitful. The remarkable ability of copper(II) reagents to reoxidize Pd(0) to Pd(II) while using molecular oxygen as the terminal oxidant has allowed the use of catalytic quantities of Cu in many cases. To test the ability of copper(II) triflate to engage in such a scheme, 0.4 eq. of Cu(OTf)_2 was added to the Pt-alkyl in acetonitrile under an atmosphere of air. Monitoring of the reaction revealed continued consumption of the starting material over
a period of several hours, reaching a maximum of 70% consumption, suggesting that despite slow and incomplete turnover, re-oxidation of Cu(OTf)$_2$ was occurring in air (Table 3.6).

**Table 3.6: Re-oxidation of Cu(OTf)$_2$**

<table>
<thead>
<tr>
<th>Time</th>
<th>% consumption of Pt-R</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mins</td>
<td>35%</td>
</tr>
<tr>
<td>2 hours</td>
<td>55%</td>
</tr>
<tr>
<td>4.5 hours</td>
<td>65%</td>
</tr>
<tr>
<td>6.5 hours</td>
<td>70%</td>
</tr>
<tr>
<td>1 day</td>
<td>70%</td>
</tr>
</tbody>
</table>

These stoichiometric reactions suggested a Pt(II)/Pt(III) catalytic cycle in which activation of the [(triphos)PtI]I precursor by halide abstraction with silver tetrafluoroborate would generate the catalyst. Cyclization would form the Pt-alkyl complex and oxidation by copper(II) triflate would form a Pt(III)-alkyl which would undergo Pt-C bond homolysis to regenerate the catalyst, forming an alkyl radical and copper(I) triflate. This radical could be quickly intercepted by oxygen and undergo Russell disproportionation to furnish the oxygenated products. Re-oxidation of copper(I) triflate to copper(II) triflate by molecular oxygen would allow the use of a substoichiometric amount of copper (Figure 3.6).
Conditions chosen for the catalytic scheme included a 20 mol % loading of the catalyst, 2 eq. of a piperidinomethyl polystyrene resin base to assist cyclization and remove acid formed upon cyclization, 1 eq. of copper(II) triflate and nitromethane as the solvent under a pressure of 2 atm of oxygen. Initial results with 6-endophenol substrate 3.6 were promising as product was being formed and starting material consumed. However, upon isolation of the products, only a 64% of oxygenated material was recovered with the mass balance unaccounted for. Attempts to cyclize the more challenging alkene terminating substrates 3.7 and 3.10 revealed a larger problem. While a 43% yield of oxygenated material was recovered in the case of substrate 3.7, no conversion of product was observed with substrate 3.10. While initially confounded by the complete lack of reactivity, analysis of the reaction mixture revealed formation of the Pt-alkyl complex, but no turnover (Figure 3.7). A literature search revealed what was likely a redox incompatibility within the system.
Carpentier has reported that alkene containing compounds are able to reduce copper(II) triflate, producing unidentified organic products, triflic acid and copper(I) triflate as determined by ESR. The decomposition of the organic substrate explained the lack of mass balance recovered, the production of triflic acid explained the amount of Brønsted acid catalyzed products observed and the reduction of copper(II) triflate explained the lack of turnover observed with compound 3.9.

Table 3.7: Substrate scope

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Products</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Structure of 3.6]</td>
<td>3.2 + 3.5</td>
<td>64% 54% (10 mol%)</td>
</tr>
<tr>
<td>[Structure of 3.7]</td>
<td>3.8 + 3.9</td>
<td>46%</td>
</tr>
<tr>
<td>[Structure of 3.10]</td>
<td>3.11 + 3.12</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Oxidant Screen**

The redox incompatibility of the above mentioned catalytic system led to exploration of alternative reagents and conditions to prevent substrate decomposition and allow for a more complete substrate scope. We hypothesized that this could be achieved through several
different approaches, the use of milder oxidants or through the design of a new catalyst more susceptible to oxidation.

To confirm this proposed redox incompatibility, several other oxidants were briefly explored. Oxidants spanning a range of redox potentials were chosen, many of which provided visible indication of the oxidation as reduction of several oxidants resulted in dramatic color changes. The oxidation potential of copper(II) triflate has been reported at 0.40 V (vs Fc),\textsuperscript{12} at the high end of oxidants tested were [NO][BF\textsubscript{4}] (0.87 V vs Fc),\textsuperscript{12} [Fe(bpy)	extsubscript{3}]\textsuperscript{3+} (0.70 V vs Fc) and [Fe(3,4,7,8-Me\textsubscript{4}phen)]\textsuperscript{3+} (0.46 V vs Fc) (Table 3.8).

**Table 3.8: Oxidant screen**

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Oxidation Potential (vs Fc)</th>
<th>Oxidize</th>
<th>Reduced by</th>
</tr>
</thead>
<tbody>
<tr>
<td>[NO][BF\textsubscript{4}]</td>
<td>0.87 V</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>[Fe(bpy)	extsubscript{3}]\textsuperscript{3+}</td>
<td>0.70 V</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>[Fe(3,4,7,8-Me\textsubscript{4}phen)]\textsuperscript{3+}</td>
<td>0.46 V</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Cu(OTf)	extsubscript{2}</td>
<td>0.40 V</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>[N(tol)	extsubscript{3}][PF\textsubscript{6}]</td>
<td>0.38 V</td>
<td>slow</td>
<td>slow</td>
</tr>
</tbody>
</table>

All of these oxidants were capable of rapidly oxidizing the Pt-alkyl, however, control reactions with only oxidant and substrate resulted in reduction of the oxidant (noted by color change in the Fe complexes). At the low end of the oxidants was [N(tol)	extsubscript{3}][PF\textsubscript{6}], this oxidant
was capable of oxidizing the Pt-alkyl in acetonitrile, however, in contrast to reactions with Cu(OTf)$_2$, this reaction was very slow. Control reactions with substrate and [N(tol)$_3$][PF$_6$], resulted in slow reduction of the oxidant (noted by a loss color in solution). That is, oxidants capable of oxidizing (triphos)Pt-R$^+$ seem prone to reduction by substrate. These results suggested that the redox incompatibility could not be overcome in the current catalytic manifold.

**Experimental Section**

All air and moisture sensitive procedures were performed using an MBraun glovebox or standard Schlenk line techniques. Commercially available reagents were used without further purification. The piperidinomethyl polystyrene resin (4.1 mmol/g) was purchased from NovaBiochem and used without further purification. Acetonitrile was distilled from CaH$_2$. NMR spectra were collected on a Bruker 600 MHz Avance spectrometer and referenced to residual solvent peaks. Reactions performed under elevated pressure were conducted in a Fisher Porter bottle. Compounds 3.1$^{13}$ 3.6$^{13}$ 3.7$^{14}$ and 3.10$^{15}$ were prepared as previously reported. HRMS was performed by Dr. Mee-Kyung Chung at the University of North Carolina at Chapel Hill except for compounds 3.5, 3.8 and 3.9 which were performed by the University of Illinois.

**General Procedure for Oxidation Reactions**

The oxidant of choice was added to a stirring solution of 3.1 (40 mg, 0.04 mmol) in CH$_3$CN (3.0 mL). Consumption of starting material was monitored by $^{31}$P NMR. Compounds were isolated using preparative TLC or column chromatography (4:1 hexanes:EtOAc for oxygenated products; hexanes for halogenated products).
**General Procedure for Catalytic Reactions**

To (PPP)PtI$_2$ (40 mg, 0.04 mmol) was added AgBF$_4$ (20 mg, 0.1 mmol) followed by 1.0 mL CD$_3$NO$_2$ in a 20 mL vial under N$_2$ in the dark. Simultaneously, Cu(OTf)$_2$ (80 mg, 0.22 mmol), piperidine resin base (95 mg, 0.4 mmol) and 1.0 mL CD$_3$NO$_2$ were added to a Fisher Porter bottle and pressurized to 2 atm O$_2$. Reactions were stirred for 1 hour at which time the solution of [(PPP)Pt][BF]$_2$ previously prepared as above was syringe filtered through a 0.2 µm PTFE syringe filter into the Fisher Porter containing Cu(OTf)$_2$ and the piperidine resin base. Substrate (0.2 mmol) was then added and the bottle re-pressurized to 2 atm O$_2$. Following completion the crude material was loaded onto a large silica gel plug and eluted with diethyl ether. Products were then isolated by column chromatography (4:1 hexanes:EtoAc).

**Characterization of Compounds**

Compounds 3.2, 3.5ax and 3.5eq were formed in the same reaction, separated by prep TLC and characterized individually.

**Compound 3.2:**

![Chemical Structure](image)

$^1$H NMR (600 MHz, CDCl$_3$): δ 7.13 (m, 1H), 7.05 (m, 1H), 6.87 (m, 1H), 6.83 (m, 1H), 2.7 (m, 1H), 2.60-2.45 (m, 4H), 2.25 (m, 2H), 2.05 (m, 2H), 1.38 (s, 3H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): δ 208.8, 153.3, 129.5, 127.9, 120.5, 120.4, 117.5, 75.0, 44.5, 38.8, 38.7, 38.0, 29.6, 16.1 ppm. HRMS (ESI) C$_{14}$H$_{16}$O$_2$ [M+H]$^+$/z calc. 217.1223, found 217.1217.
Compound 3.5:

\[
\begin{array}{c}
\text{[Pt]} + \text{BF}_4^- \\
\text{CH}_3\text{CN, 2 atm O}_2 <5 \text{ min} \\
\end{array}
\]

3.5eq: \( ^1\text{H NMR (600 MHz, CDCl}_3\): \( \delta \) 7.09 (m, 1H), 7.03 (m, 1H), 6.83 (m, 1H), 6.78 (m, 1H), 3.80 (m, 1H), 2.60 (m, 1H), 2.51 (m, 1H), 2.03 (br, 2H), 1.97 (m, 1H), 1.88 (m, 1H), 1.71 (m, 1H), 1.53 (m, 1H), 1.25 (m, 1H), 1.19 (s, 3H) ppm. \(^{13}\text{C NMR (152 MHz, CDCl}_3\):} \( \delta \) 153.7, 129.6, 127.6, 121.6, 120.0, 117.4, 76.4, 70.2, 38.6, 37.6, 37.3, 32.6, 29.2, 16.7 ppm. HRMS \( \text{C}_{14}\text{H}_{18}\text{O}_2\ [\text{M}] \) calc. 218.1307, found 218.1299. HRMS performed on mixture of 3.5eq and 3.5ax.

3.5ax: \( ^1\text{H NMR (600 MHz, CD}_2\text{Cl}_2\):} \( \delta \) 7.04 (m, 2H), 6.80 (m, 1H), 6.72 (m, 1H), 4.09 (br, 1H), 2.51 (m, 1H), 2.44 (m, 1H), 2.25 (m, 1H), 2.00 (m, 1H), 1.83 (d, 2H), 1.71 (m, 2H), 1.38 (m, 1H), 1.12 (s, 3H) ppm. \(^{13}\text{C NMR (152 MHz, CD}_2\text{Cl}_2\):} 154.1, 129.9, 127.6, 122.7, 120.0, 117.4, 77.3, 65.9, 37.2, 33.5, 33.4, 30.8, 29.1, 15.9 ppm. HRMS \( \text{C}_{14}\text{H}_{18}\text{O}_2\ [\text{M}] \) calc. 218.1307, found 218.1299. HRMS performed on mixture of 3.5eq and 3.5ax.

Compound 3.3:

\[
\begin{array}{c}
\text{[Pt]} + \text{BF}_4^- \\
\text{CH}_3\text{CN, 2 eq CuCl}_2 <5 \text{ min} \\
\end{array}
\]

3.3: Diagnostic \( ^1\text{H NMR signals (600 MHz, CDCl}_3\):} \( \delta \) 4.52 (br, 1H), 3.97 (m, 1H) ppm. HRMS (ESI) \( \text{C}_{14}\text{H}_{17}\text{ClO} [\text{M+H}]^+/z \) calc. 237.1041, found 237.1043.
3.4: Diagnostic $^1$H NMR signals (600 MHz, CDCl$_3$): δ 4.73 (br, 1H), 4.11 (m, 1H) ppm.

HRMS (ESI) C$_{14}$H$_{17}$BrO [M+H]$^+$/z calc. 281.0536, found 281.0536.

Compounds 3.8, 3.9ax and 3.9eq were formed in the same reaction, separated by prep TLC and characterized individually.

Compound 3.8:

3.8: $^1$H NMR (600 MHz, CDCl$_3$): δ 7.40 (m, 2H), 7.34 (m, 2H), 7.27 (m, 1H), 6.07 (m, 1H), 2.55 (m, 1H), 2.40-2.20 (m, 5H), 2.00-1.90 (m, 3H), 1.63-1.72 (m, 2H), 1.11 (s, 3H) ppm.

$^{13}$C NMR (152 MHz, CDCl$_3$): δ 211.4, 142.2, 135.6, 128.4, 127.0, 125.2, 122.4, 44.4, 43.0, 40.7, 40.3, 38.4, 32.0, 31.2, 15.7 ppm. HRMS (ESI) C$_{17}$H$_{20}$O [M] calc. 240.1514, found 240.1506.

Compound 3.9:
**3.9eq:** $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.38 (m, 2H), 7.32 (m, 2H), 7.24 (m, 1H), 6.05 (m, 1H), 2.3-2.1 (m, 3H), 1.80-1.95 (m, 3H), 1.50-1.70 (m, 4H), 1.25-1.35 (m, 2H), 0.90 (s, 3H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): $\delta$ 142.7, 135.7, 128.3, 126.8, 125.2, 123.3, 71.3, 43.8, 39.4, 38.1, 37.9, 31.9, 31.7, 30.8, 16.4 ppm. HRMS C$_{17}$H$_{22}$O [M] calc. 242.1671, found 242.1665. HRMS performed on mixture of 3.9eq and 3.9ax.

**3.9ax:** $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.38 (m, 2H), 7.30 (m, 2H), 7.23 (m, 1H), 6.06 (br, 1H), 4.05 (br, 1H), 2.29 (m, 1H), 2.05-2.17 (m ,2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.69 (m, 2H), 1.44 (m, 2H), 1.36 (m, 1H), 0.87 (s, 3H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): 142.9, 135.6, 128.3, 126.7, 125.2, 123.6, 67.0, 44.2, 35.5, 34.6, 32.9, 32.5, 30.6, 29.0, 15.5 ppm. HRMS C$_{17}$H$_{22}$O [M] calc. 242.1671, found 242.1665. HRMS performed on mixture of 3.9eq and 3.9ax.
References


CHAPTER 4: POLYENE CYCLOISOMERIZATION REACTIONS

Introduction

We have previously disclosed the cyclization of a variety of polyenes, including those terminating with nucleophilic heteroatoms as well as poorly nucleophilic alkenes. These methods have required highly electrophilic initiators to activate the substrate. Successful systems have thus far been based on multidentate phosphine ligands, which are sufficiently electrophilic to initiate reactivity. While stoichiometric reactions have been fruitful, the design of catalytic variants has proved challenging. The remarkable stability of phosphine ligated platinum alkyl compounds toward both acid and oxidants has complicated the pursuit of catalysis. Thus far, oxidation of intermediate Pt-alkyl compounds with XeF$_2$ or Cu(OTf)$_2$ has successfully turned over the catalyst, albeit with limited substrate scope. Bidentate phosphine ligands have enabled turnover through β-hydride elimination, however, these reactions require a complex mixture of reagents and produce multiple isomers of product in many cases.

Having been limited thus far by unfavorable redox properties of Pt phosphine complexes, alternative ligand frameworks were explored in an attempt to access new methods of turnover. A catalyst with very specific properties was desired: highly electrophilic to initiate cyclization, yet sufficiently electron rich to allow for turnover through milder means. We hypothesized that these two seemingly paradoxical properties could be

---

* Portions of this chapter were adapted with permission from Geier, M.J.; Gagné, M.R. J. Am. Chem. Soc., 2014, 136, 3032
realized by contrasting donor properties of the cis and trans positions. In the cis position, highly donating ligands would provide the electron density required to ease oxidation while a poorly donating ligand in the trans position would maintain the electrophilic nature of the catalyst (Figure 4.1).

A series of catalysts possessing these properties has been reported by Limbach for the hydrovinylation\(^6\) and hydroamination\(^7\) of simple olefins. Several variants of the ligands were reported, however, all possess a poorly donating pyridine ligand in the trans position and two strongly donating NHC ligands in the cis positions. These catalysts proved competent for the intermolecular hydrovinylation\(^6\) (Figure 4.2) and satisfied both our requirements and were thus explored in polyene cascade cyclization reactions.

![Figure 4.1: Desired ligand framework](image)

![Figure 4.2: Limbach’s Pt-catalyzed hydrovinylation](image)
Initial Results

Synthesis of (CNC)Pt catalyst 4.1 was first explored due to its high reactivity in both hydrovinylation and hydroamination reaction. Previous difficulties in the protodemetallation of Pt-alkyls led to the expectation that this trend would hold for (CNC) ligands, as well as the previously reported phosphines. Thus, initial reactions with two equivalents of 4.2 were run in presence of the piperidinomethyl polystyrene resin base used in previous experiments. These reactions failed to produce any cyclized products. Interestingly, omission of the base led to full consumption of the substrate and yielded the fully cyclized product 4.3, resulting from protodemetallation of the Pt-alkyl. Surprisingly, the intermediate Pt-alkyl complex proved sufficiently electron rich for the Pt-alkyl complex to be oxidized by the acid liberated by the cyclization (Figure 4.3).

![Chemical structures](image)

**Figure 4.3: Reaction of 4.1 with 4.2**

Any further attempts to trap the intermediate Pt-alkyl complex with base failed to cyclize, while attempts to trap the putative Pt-alkyl with any of the previously reported oxidants failed to produce the functionalized product. Despite the inability to trap the organometallic, the catalyst proved very effective for the cycloisomerization reaction of 4.2.
At a catalyst loading of 10%, a 93% yield of product was obtained, while lowering the loading to 5% produced an 88% yield with reaction times of 2 and 3 hours respectively. Remarkably, the fully cyclized product was formed without formation of the Brønsted acid catalyzed product, previously observed with Pt-phosphine initiated reactions. The absence of this product revealed a surprisingly low steady state concentration of acid despite the absence of base.

![Figure 4.4: Polyene cycloisomerization mechanism](image)

The proposed catalytic cycle begins with selective coordination of the dicationic platinum catalyst to the least substituted alkene, subsequent cyclization forms the intermediate Pt-alkyl complex which undergoes rapid protodemetallation to form 4.3 and regenerate the Pt catalyst (Figure 4.4). This reactivity observed with the nucleophilic phenol terminating group led to exploration of the cycloisomerization of alkene terminating substrates.
Alkene Terminating Substrates

We began by investigating some simple bicyclization reactions involving previously reported substrates.\textsuperscript{1b,5b} In the presence of 10 mol \% catalyst, these reactions were expectedly slower than the phenol terminating substrate. Under these conditions, reaction with substrate 4.4 and 4.6 failed to consume starting material. Despite the lack of reactivity noted with bases, the addition of diphenylamine as a proton shuttle led to shorter reaction times without poisoning the catalyst. Optimization of the diphenylamine loading was done using substrate 4.4 and monitoring consumption of starting material by gc/ms (Table 4.1). This screen led to use of 20 mol \% of diphenylamine which, not surprisingly, provided similar conversion to reactions employing stoichiometric amounts of diphenylamine.

Table 4.1: Optimization of proton shuttle loading

<table>
<thead>
<tr>
<th>X</th>
<th>3 hours</th>
<th>8 hours</th>
<th>21 hours</th>
<th>48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6%</td>
<td>17%</td>
<td>42%</td>
<td>70%</td>
</tr>
<tr>
<td>2.5</td>
<td>12%</td>
<td>29%</td>
<td>73%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>5</td>
<td>19%</td>
<td>46%</td>
<td>89%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>10</td>
<td>21%</td>
<td>52%</td>
<td>93%</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>24%</td>
<td>66%</td>
<td>&gt;95%</td>
<td>-</td>
</tr>
<tr>
<td>100</td>
<td>28%</td>
<td>70%</td>
<td>&gt;95%</td>
<td>-</td>
</tr>
<tr>
<td>Entry</td>
<td>Substrate</td>
<td>Product</td>
<td>Solvent</td>
<td>Isolated Yield</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>---------</td>
<td>--------------</td>
<td>----------------</td>
</tr>
<tr>
<td>1</td>
<td><img src="4.2" alt="Image" /></td>
<td><img src="4.3" alt="Image" /></td>
<td>CD$_3$NO$_2$</td>
<td>93%</td>
</tr>
<tr>
<td>2</td>
<td>CD$_3$NO$_2$</td>
<td>88%(5 mol%)</td>
<td>CD$_3$NO$_2$</td>
<td>88%(5 mol%)</td>
</tr>
<tr>
<td>3</td>
<td><img src="4.4" alt="Image" /></td>
<td><img src="4.5" alt="Image" /></td>
<td>CD$_3$NO$_2$</td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td><img src="4.4" alt="Image" /></td>
<td><img src="4.5" alt="Image" /></td>
<td>CH$_2$Cl$_2$</td>
<td>77%</td>
</tr>
<tr>
<td>5</td>
<td><img src="4.6" alt="Image" /></td>
<td><img src="4.7" alt="Image" /></td>
<td>CD$_3$NO$_2$</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td><img src="4.8" alt="Image" /></td>
<td><img src="4.9" alt="Image" /></td>
<td>CD$_3$NO$_2$</td>
<td>70%</td>
</tr>
<tr>
<td>7</td>
<td><img src="4.10" alt="Image" /></td>
<td><img src="4.11" alt="Image" /></td>
<td>CD$_3$NO$_2$</td>
<td>52%</td>
</tr>
<tr>
<td>8</td>
<td><img src="4.10" alt="Image" /></td>
<td><img src="4.11" alt="Image" /></td>
<td>CH$_2$Cl$_2$</td>
<td>59%</td>
</tr>
<tr>
<td>9</td>
<td><img src="4.12" alt="Image" /></td>
<td><img src="4.13" alt="Image" /></td>
<td>CD$_3$NO$_2$</td>
<td>61%</td>
</tr>
<tr>
<td>10</td>
<td><img src="4.14" alt="Image" /></td>
<td><img src="4.15" alt="Image" /></td>
<td>CD$_3$NO$_2$</td>
<td>23%</td>
</tr>
<tr>
<td>11</td>
<td><img src="4.16" alt="Image" /></td>
<td><img src="4.17" alt="Image" /></td>
<td>CH$_2$Cl$_2$</td>
<td>59%</td>
</tr>
<tr>
<td>12</td>
<td><img src="4.18" alt="Image" /></td>
<td><img src="4.19" alt="Image" /></td>
<td>CH$_2$Cl$_2$</td>
<td>39%</td>
</tr>
<tr>
<td>13</td>
<td><img src="4.20" alt="Image" /></td>
<td><img src="4.21" alt="Image" /></td>
<td>CH$_2$Cl$_2$</td>
<td>44%</td>
</tr>
</tbody>
</table>
Several other bicyclization reactions proceeded in the absence of the diphenylamine proton shuttle. Cyclization of substrate 4.8 resulted in formation of trisubstituted alkene containing 4.9. Formation of the trisubstituted alkene as the kinetic product has been reported previously. The formation of this product was surprising as the absence of base in these reactions was expected to lead to isomerization to the tetrasubstituted alkene. Subsequent reaction of trisubstituted alkene 4.9 with methanesulfonic acid led to formation of the thermodynamically preferred tetrasubstituted alkene product 4.22 (Figure 4.6).

**Figure 4.5: Isomerization of trisubstituted alkene to tetrasubstituted alkene**

Cyclization of aryl ether substrate 4.10 proceeded to give the rearranged product 4.11. This abnormal Claisen rearrangement has previously been observed by Yamamoto during Brønsted Lewis Acid mediated cyclizations. While the mechanism for this rearrangement was not determined, two possibilities were considered. Abnormal Claisen rearrangement to form the phenol followed by cyclization was favored (path A), however, A ring formation followed by phenoxy migration was not ruled out despite the involvement of a primary carbocation (path B) (Figure 4.5).
Figure 4.6: Abnormal Claisen rearrangement of aryl ether

Tricyclization of several substrates with varying termination geometries was also explored. 6-endo terminating substrates 4.12 and 4.16 underwent cyclization to fully cyclized tetrasubstituted alkene containing 4.13 and 4.17. In the case of 6-exo terminating substrate 4.14, two products were observed. The major product was formed in 46% yield as a result of premature termination, forming a structure consistent with bicyclic compound 4.23. The minor product, formed in 23% yield was the fully cyclized compound 4.15, the result of tricyclization and elimination akin to 6-exo terminating substrate 4.6.

In contrast to 6-endo and exo terminating substrates, 5-exo terminating substrates provided Wagner Meerwein rearranged products. The major product came as a result of cyclization to the exocyclic cation followed by a hydride shift, a methyl shift and elimination to arrive at the tetrasubstituted alkene product 4.19 in a 39% isolated yield. Elimination following the hydride shift resulted in formation of trisubstituted alkene product 4.24 in a
10% yield (Figure 4.7). The two products could be separated from one another by Ag\(^+\) impregnated silica gel.\(^{11}\)

![Diagram showing rearrangement of substrate](image)

**Figure 4.7: Rearrangement of substrate 4.16**

The full cyclization of 5-exo terminating 4.16 led to exploration of the tetracyclization of compound 4.20, a substrate which, when fully cyclized would provide the 6-6-6-5 steroid framework. Cyclization of 4.20 proceeded slowly, taking several days to observe complete consumption. Isolation of the major product revealed a tetracyclized product containing a tetrasubstituted alkene. Initial cyclization of this substrate leads to an exocyclic cation, akin to the protosterol cation observed in the enzyme mediated formation of lanosterol. In contrast to the skeletal rearrangement observed in nature in which the protosterol cation undergoes two methyl and two hydride shifts, the exocyclic cation undergoes only a hydride shift and a methyl shift, followed by elimination to produce 4.21, with unsaturation at the C/D ring junction (Figure 4.8).
Interestingly, while tetracyclization with 5-exo termination provided only fully cyclized products (determined by gc/ms), 6-exo terminating substrate 4.14 provided a mixture of bi and tricyclized products, suggesting a more concerted, efficient process in the case of 5-exo termination.

Use of nitromethane as solvent proved suitable in most cases, however, the slower tri and tetracyclization reactions saw shorter reaction which led to complete consumption of substrate in dichloromethane. This increase in reactivity despite the tendency of the catalyst to abstract chloride from dichloromethane, is likely attributed to better substrate-solvent
miscibility in dichloromethane as well as previous studies which have revealed a shift in equilibrium toward cyclized product in more poorly solvating solvents.\textsuperscript{12}

This catalytic system proved tolerant of a number of different substrates including a tetracyclization reaction. While many of the more challenging tri and tetracyclization reactions proceeded to completion, lower yields were observed. We have yet to identify the remainder of the mass balance, however, we suspect that formation of oligomeric species in the slower reactions may be responsible for the loss of mass balance.

The remarkable differences observed between phosphine based pincer complexes and those with NHC ligands in the cis position have enabled a novel cycloisomerization reaction involving several new, more complex alkene terminating substrates. While uncertain of the cause for this change, the enhanced sigma donating ability of the NHC ligands may provide sufficient electron density at the Pt center to allow for protodemetallation. This discovery has led to further exploration of this class of ligand, including the design of new chiral variants.

**Experimental Section**

**General Considerations**

All air and moisture sensitive procedures were performed using an MBraun glovebox or standard Schlenk line techniques. Commercially available reagents were used without further purification. Deuterated nitromethane (CD\textsubscript{3}NO\textsubscript{2}) was degassed by freeze-pump-thaw. Dichloromethane, diethyl ether and toluene were passed through a column of alumina prior to use. Diisopropylamine and triethylamine were distilled from calcium hydride. NMR spectra were collected on a Bruker 600 or 400 MHz spectrometer and referenced to residual
solvent peaks. HRMS was performed by University of Illinois except for compounds 4.10 and 4.11, which were performed by Dr. Mee-Kyung Chung at the University of North Carolina at Chapel Hill. Compounds 4.2, 4.3, 4.4, 4.6, 4.8, 4.12 and 4.18 have been reported previously.

**Substrate Synthesis**

New substrates 4.14, 4.16 and 4.20 were synthesized following established protocols for previously reported substrates, intermediates were characterized by $^1$H NMR and carried on.

![Chemical structure of (E)-1,3-dimethoxy-5-((3-methylhepta-2,6-dien-1-yl)oxy)benzene (4.10).](attachment:image.png)

(E)-1,3-dimethoxy-5-((3-methylhepta-2,6-dien-1-yl)oxy)benzene (4.10): Diethyl azodicarboxylate (DEAD) was added to a solution of (E)-3-methylhepta-2,6-dien-1-ol\textsuperscript{13} (0.63 g, 5 mmol), 3,5-dimethoxyphenol (2.31 g, 15 mmol) and PPh\textsubscript{3} (1.70 g, 6.5 mmol) in 25 mL THF. The solution was brought to reflux for 2 hours. Upon cooling, the solution was concentrated and purified by column chromatography using hexanes/EtOAc (19:1, R\textsubscript{f} = 0.4) resulting in a yellow oil (0.72 g, 55% yield)

$^1$H NMR (600 MHz, CDCl\textsubscript{3}): δ 6.13 (m, 2H), 6.10 (m, 1H), 5.85-5.81 (m, 1H), 5.53-5.50 (m, 1H), 5.03-5.07 (dd, 1H), 4.97-5.00 (dd, 1 H), 4.52 (d, $J = 6.6$ Hz, 2H), 3.79 (s, 6H) 2.24-2.18 (m, 4H), 1.75 (s, 3H) ppm. $^{13}$C NMR (152 MHz, CDCl\textsubscript{3}): δ 161.7, 160.9, 140.9, 138.3,
119.8, 114.8, 93.7, 92.9, 64.9, 55.3, 38.9, 31.9, 16.6 ppm. HRMS (ESI) C₁₆H₂₂O₃ [M+H]⁺/z calc. 263.1642 found 263.1639.

\[ \text{(E)-2,6,12-trimethyltrideca-1,6,11-trien-3-ol: (E)-4,10-dimethylundeca-4,9-dienal}^{1b} \]

\[ \text{(E)-4,8,14-trimethylpentadeca-4,8,13-trienal: (E)-2,6,12-trimethyltrideca-1,6,11-trien-3-ol} \]

(4.03 g, 20.7 mmol) was dissolved in 80 mL THF and cooled to -78°C. Isopropenyl magnesium bromide (50 mL, 0.5 M) was added slowly and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with saturated NH₄Cl (aq) (60 mL) and separated. The aqueous layer was extracted three times with diethyl ether. The organics were combined and washed with water and brine before drying over Na₂SO₄. Removal of volatiles produced a colourless oil (4.4 g, 18.6 mmol, 89%).

\[ ^1H \text{NMR (300 MHz, CDCl}_3\text{): } \delta 5.21-5.09 \text{ (m, 2H), 4.96 (s, 1H), 4.87 (s, 1H), 4.08-4.04 (m, 1H), 2.07-1.97 (m, 5H), 1.74-1.56 (m, 16H), 1.40-1.32 (m, 2H) ppm.} \]

(4.49 g, 18.6 mmol) in ethyl vinyl ether (60 mL) was added to mercury trifluoroacetate (0.79 g, 1.86 mmol). The reaction was stirred for 2 days at room temperature. Ethyl vinyl ether was then removed under vacuum and the residue was passed through a silica gel plug in ethyl acetate. Upon removal of ethyl acetate, 10 mL toluene was added and the solution was
heated to 130°C in a pressure tube for 6 hours. Removal of solvent left a colourless oil (4.2 g, 16.0 mmol, 85%)

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 9.77 (s, 1H), 5.18-5.14 (m, 4H), 2.54-2.51 (m, 2H), 2.32-2.35 (m, 2H), 2.12-1.97 (m, 7H), 1.70 (s, 3H), 1.66-1.61 (m, 9H), 1.38-1.32 (m, 2H) ppm.

![Chemical structure](image)

$(5E,9E)$-5,9,15-trimethylhexadeca-1,5,9,14-tetraene (4.14): To methyltriphenylphosphonium bromide (0.53 g, 1.48 mmol) in 6 mL THF was added nBuLi (0.6 mL, 2.5 M in hexane) at -78°C. The reaction was stirred for 1 hour and a solution of $(4E,8E)$-4,8,14-trimethylpentadeca-4,8,13-trienal (0.39 g, 1.48 mmol) in 6 mL THF was added. The reaction was stirred and allowed to warm to room temperature overnight. The reaction was quenched with 1 M HCl (15 mL). The layers were separated and the aqueous extracted three times with diethyl ether. The combined organics were washed with brine and dried over Na$_2$SO$_4$.

Removal of volatiles and purification by silica gel (hexanes, $R_f = 0.5$) yielded the desired product as a colourless oil (0.18 g, 0.692 mmol, 47%)

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.85-5.80 (m, 1H), 5.16-5.13 (m, 3H), 5.04-5.01 (m, 1H), 4.97-4.95 (m, 1H), 2.17-1.98 (m, 12H), 1.70 (s, 3H), 1.62-1.61 (m, 9H), 1.40-1.37 (m, 2H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): $\delta$ 138.8, 135.0, 134.4, 131.4, 124.8, 124.7, 124.6, 114.2, 39.7, 39.1, 32.4, 30.1, 27.7, 27.6, 26.6, 25.8, 25.3, 17.8, 16.0 ppm. HRMS (EI) C$_{19}$H$_{32}$ [M]$^+$ calc. 260.2504 found 260.2508.
(5E,9E)-11-bromo-5,9-dimethylundeca-1,5,9-triene: A solution of (2E,6E)-3,7-dimethylundeca-2,6,10-trien-1-ol<sub>14</sub> (0.8 g, 4.1 mmol) in 15 mL THF was cooled to 0°C. Methanesulfonyl chloride (0.5 mL, 6.46 mmol) and triethylamine (1.2 mL, 8.6 mmol) were added slowly and the reaction was stirred for 45 minutes at 0°C. A solution of lithium bromide (1.5 g, 17.2 mmol) in 5 mL THF was then added at 0°C and the reaction stirred for 1 hour at 0°C. Addition of 50 mL water and 50 mL hexanes formed a biphasic solution which was separated and the aqueous extracted three times with hexanes (3 x 50 mL). The combined organics were washed with saturated NaHCO<sub>3</sub>(aq) and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and the removal of volatiles left a colourless oil (0.841 g, 3.3 mmol, 79%).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 5.84-5.79 (m, 1H), 5.56-5.53 (m, 1H), 5.12-5.10 (m, 1H), 5.04-5.00 (m, 1H), 4.96-4.94 (m, 1H), 4.04 (d, J = 8.4 Hz, 2H), 2.17-2.06 (m, 8 H) 1.74 (s, 3H), 1.62 (m, 3H) ppm.

2-((2E,6E)-3,7-dimethylundeca-2,6,10-trien-1-yl)cyclohexan-1-one: A solution of diisopropylamine (0.45 mL, 3.16 mmol) in 10 mL THF was cooled to -78°C and n-BuLi (1.2 mL, 2.5 M) was added slowly. The reaction was stirred for one hour, at which time cyclohexanone (0.26 g, 2.64 mmol) was added. The reaction was stirred for one hour and
(5E,9E)-11-bromo-5,9-dimethylundeca-1,5,9-triene (0.815 g, 3.16 mmol) was added at -78°C and the reaction was left to warm to room temperature overnight. The reaction was quenched with 1 M HCl (15 mL) and separated, the aqueous layer was extracted three times with diethyl ether and the combined organics were washed with brine and dried over Na₂SO₄. Removal of solvent under vacuum produced a colourless oil (0.63 g, 2.3 mmol, 87%).

¹H NMR (600 MHz, CDCl₃): δ 5.87-5.78 (m, 1H), 5.12-5.10 (m, 2H), 5.04-5.01 (m, 1H), 4.96-4.94 (m, 1H), 2.47-2.39 (m, 2H), 2.35-2.28 (m, 2H), 2.18-1.97 (m, 10H), 1.89-1.84 (m, 1H), 1.72-1.66 (m, 2H), 1.61 (m, 6H), 1.40-1.34 (m, 2H) ppm.

1-((2E,6E)-3,7-dimethylundeca-2,6,10-trien-1-yl)-2-methylene cyclohexane (4.16): To a solution of 2-((2E,6E)-3,7-dimethylundeca-2,6,10-trien-1-yl)cyclohexan-1-one (0.2 g, 0.73 mmol) in 25 mL diethyl ether was added (trimethylsilyl)methylmagnesium chloride (1.46 mL, 1.0 M). The solution was heated to reflux for 18 hours at which time the reaction was cooled to 0°C and thionyl chloride (0.22 mL, 3.03 mmol) was added. The reaction was stirred for an hour and quenched with saturated NH₄Cl(aq) (25 mL). The layers were separated and the aqueous extracted twice with diethyl ether. The combined organics were dried over Na₂SO₄. Removal of volatiles produced a colourless oil which was purified by silica gel chromatography (hexanes, R₇ = 0.6) to yield the product (0.107 g, 0.39 mmol, 54%).
H NMR (600 MHz, CDCl₃): δ 5.85-5.80 (m, 1H), 5.17-5.13 (m, 2H), 5.03 (dd, J = 1.2, 16.8 Hz, 1H), 4.95 (dd, J = 1.2, 10.2 Hz, 1H), 4.68 (m, 1H), 4.60 (m, 1H), 2.32-2.16 (m, 2H), 2.17-2.02 (m, 12H), 1.78-1.83 (m, 1H), 1.72-1.68 (m, 2H), 1.63-1.61 (m, 6H), 1.45-1.44 (m, 2H) ppm. ¹³C NMR (152 MHz, CDCl₃): δ 153.3, 138.8, 135.4, 134.4, 124.6, 123.6, 114.2, 105.2, 43.5, 39.8, 39.1, 35.6, 33.6, 32.4, 30.9, 28.9, 26.5, 25.0, 16.2, 16.0 ppm. HRMS (EI) C₂₀H₃₂ [M]+/z calc. 272.2504 found 272.2507.

(6E,10E)-2,6,10,15-tetramethylhexadeca-1,6,10,14-tetraen-3-ol: (4E,8E)-4,8,13-trimethyltetradeca-4,8,12-trienal⁽¹⁾b (2.20 g, 8.87 mmol) was dissolved in 25 mL THF and added slowly to the isopropenyl magnesium bromide (26.6 mL, 0.5 M) at -78°C. The reaction was stirred at room temperature for two hours. The reaction was quenched with NH₄Cl(aq) (60 mL) and separated. The aqueous layer was extracted three times with diethyl ether. The organics were combined and washed with water and brine before drying over Na₂SO₄. Removal of volatiles produced a colourless oil (2.0 g, 6.89 mmol, 78%).

¹H NMR (300 MHz, CDCl₃): δ 5.17-5.14 (m, 3H), 4.94 (s, 1H), 4.84 (s, 1H), 4.04 (m, 1H), 2.08-1.99 (m, 11H), 1.74-1.55 (m, 17H) ppm.
(4E,8E,12E)-4,8,12,17-tetramethyloctadeca-4,8,12,16-tetraenal: 6E,10E)-2,6,10,15-tetramethylhexadeca-1,6,10,14-tetraen-3-ol (2.0 g, 6.89 mmol) in ethyl vinyl ether (45 mL) was added to mercury trifluoroacetate (0.294 g, 0.69 mmol). The reaction was stirred for 2 days at room temperature. Ethyl vinyl ether was then removed under vacuum and the residue was passed through a silica gel plug in ethyl acetate. Upon removal of ethyl acetate, 40 mL toluene was added and the solution was heated to 130°C in a pressure tube for 6 hours. Removal of solvent left a colourless oil. Purification by column chromatography using hexanes/ethyl acetate (9:1) afforded the desired product (1.85 g, 5.85 mmol, 85%).

$^1$H NMR (600 MHz, CDCl$_3$): δ 9.77 (s, 1H), 5.13-5.19 (m, 4H), 2.54-2.51 (m, 2H), 2.35-2.33 (m, 2H), 2.12-1.98 (m, 12H), 1.71 (s, 3H), 1.65-1.62 (m, 12H) ppm.

(5E,9E,13E)-5,9,13,18-tetramethylnonadeca-1,5,9,13,17-pentaene (4.20): To methyltriphenylphosphonium bromide (1.22 g, 3.41 mmol) in 15 mL THF was added nBuLi (1.37 mL, 2.5 M in hexane) at -78°C. The reaction was stirred for 1 hour and a solution of (4E,8E,12E)-4,8,12,17-tetramethyloctadeca-4,8,12,16-tetraenal (0.900 g, 2.85 mmol) in 10 mL THF was added. The reaction was stirred and allowed to warm to room temperature overnight. The reaction was quenched with 1 M HCl (15 mL). The layers were separated and the aqueous extracted three times with diethyl ether. The combined organics were washed with brine and dried over Na$_2$SO$_4$. Removal of volatiles and purification by silica gel (hexanes, R$_f$ = 0.5) yielded the desired product as a colourless oil (0.6 g, 1.91 mmol, 67%).
\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta 5.85-5.81\) (m, 1H), \(5.18-5.15\) (m, 4H), \(5.17-5.01\) (dd, 1H), \(4.97-4.95\) (dd, 1H), \(2.19-2.03\) (m, 16H), \(1.72\) (s, 3H), \(1.63\) (m, 12H) ppm. \(^1^3\)C NMR (152 MHz, CDCl\(_3\)): \(\delta 138.8, 135.2, 134.9, 134.4, 131.5, 124.6, 124.5, 124.4, 124.3, 114.2, 39.8, 39.7, 39.1, 32.4, 28.4, 28.3, 26.64, 26.61, 25.8, 17.7, 16.04, 16.01, 15.97\) ppm. HRMS (EI) C\(_{23}\)H\(_{38}\) [M]+/z calc. 314.2974 found 314.2978.

**Standard Cyclization Procedure**

To (CNC)PtBr\(_2\) (0.015 mmol) was added solvent (1 mL) and AgBF\(_4\) (0.0375 mmol). The mixture was stirred for 1 hour under N\(_2\) in the dark at which time AgBr was removed by syringe filter (0.45 µM PTFE) and substrate (0.15 mmol) was added to the solution. Upon completion, the reaction was loaded directly onto a silica gel column and eluted with hexanes to yield the desired product. Isolation of 4.19, 4.21 and 4.24 was performed using Ag\(^+\) impregnated silica gel.\(^{11}\)

![Diagram](image)

4.5: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.41\) (d, 2H), \(7.33\) (t, 2H), \(7.26\) (t, 1H), \(6.07\) (m, 1H), \(2.24-2.18\) (m, 1H), \(2.14-2.11\) (m, 2H), \(1.89-1.77\) (m, 2H), \(1.62-1.22\) (m, 8H), \(0.90\) (s, 3H).

\(^1^3\)C NMR (101 MHz, CDCl\(_3\)): \(\delta 142.9, 135.5, 128.2, 126.5, 125.1, 123.7, 44.5, 41.5, 39.9, 32.6, 31.0, 28.7, 26.9, 22.3, 16.3\) ppm. HRMS (EI) C\(_{17}\)H\(_{22}\) [M]+/z calc. 226.1722, found 226.1725.
4.7: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.83 (m, 1H) 4.63 (m, 1H), 1.83-1.76 (m, 1H), 1.74 (s, 3H), 1.72-1.68 (m, 2H), 1.55-1.48 (m, 2H), 1.44-1.36 (m, 3H), 1.28-1.21 (m, 7H), 1.08-1.00 (m, 1H), 0.85 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 147.9, 112.1, 56.8, 47.1, 40.0, 37.5, 29.7, 29.1, 29.0, 28.1, 26.9, 24.5 22.1, 12.2 pm. HRMS (EI) C$_{14}$H$_{24}$ [M]$^+$/z calc. 192.1878, found 192.1877. Compound 8 is volatile under high vac.

4.9: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.71 (d, $J = 7.6$ Hz, 1H), 7.16-7.11 (m, 3H), 6.45 (m, 1H), 2.86-2.80 (m, 2H), 2.09-2.02 (m, 3H), 1.96-1.90 (m, 2H), 1.76 (m, 1H), 1.62 (m, 1H), 1.50-1.41 (m, 4H), 1.31-1.26 (m, 2H), 1.13-1.05 (m, 1H) 0.79 (s, 3H). $^{13}$C NMR (151 MHz, CD$_2$Cl$_2$): $\delta$ 136.8, 134.9, 133.7, 129.1, 126.1, 125.7, 123.0, 119.2, 49.6, 40.9, 38.4, 34.9, 30.99, 30.98, 28.7, 26.5, 22.7, 22.3, 11.5 ppm. HRMS (EI) C$_{19}$H$_{24}$ [M]$^+$/z calc. 252.1878, found 252.1883.
4.11: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.05 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.61-2.57 (dd, 1H), 2.08-2.03 (m, 1H), 1.95-1.93 (m, 1H), 1.82-1.76 (m, 3H), 1.73-1.68 (m, 1H), 1.63-1.58 (m, 1H), 1.52-1.45 (m, 1H), 1.39-1.32 (m, 1H), 1.21-1.13 (m, 1H), 1.17 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 159.4, 158.3, 154.6, 103.6, 93.6, 90.8, 77.5, 55.4, 55.3, 39.4, 39.3, 30.0, 26.0, 23.6, 23.5, 16.3 ppm. HRMS (ESI) $\text{C}_{16}\text{H}_{22}\text{O}_3 [\text{M+H}]^+$/z calc. 263.1642, found 263.1641.

4.13: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.37 (m, 1H), 2.05-1.98 (m, 2H), 1.91-1.86 (m, 2H), 1.71-1.61 (m, 3H), 1.58 (s, 3H), 1.56-1.10 (m, 11H), 0.89 (s, 3H), 0.81 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 132.0, 120.3, 51.5, 51.1, 48.4, 42.3, 39.3, 36.4, 33.5, 28.7, 26.8, 26.1, 23.8, 22.8, 21.6, 20.5, 12.6 ppm. HRMS (EI) $\text{C}_{17}\text{H}_{28} [\text{M}]^+$/z calc. 232.2191, found 232.2194.
4.15: $^1$H NMR (600 MHz, CDCl$_3$): δ 4.86 (m, 1H), 4.61 (m, 1H), 1.84-1.82 (m, 2H), 1.77 (s, 3H), 1.71-1.57 (m, 4H), 1.52-1.43 (m, 2H), 1.37-1.14 (m, 7H), 1.09 (d, 1H), 1.05-0.98 (m, 2H), 0.92-0.81 (m, 3H), 0.94 (s, 3H), 0.77 (s, 3H). $^{13}$C NMR (162 MHz, CDCl$_3$): δ 148.1, 112.5, 58.8, 58.2, 48.5, 41.3, 39.5, 38.8, 37.0, 28.7, 28.4, 27.5, 26.8, 26.2, 25.7, 21.7, 20.7, 14.7, 13.2 ppm. HRMS (EI) C$_{19}$H$_{32}$ [M]$^+$/z calc. 260.2504, found 260.2509.

4.17: $^1$H NMR (600 MHz, CDCl$_3$): δ 1.87-1.76 (m, 7H), 1.71-1.65 (m, 4H), 1.57-1.53 (m, 1H), 1.51-1.45 (m, 4H), 1.44-1.36 (m, 2H), 1.30-1.14 (m, 7H), 1.18-1.12 (m, 1H), 0.87 (s, 3H), 0.82 (s, 3H). $^{13}$C NMR (162 MHz, CDCl$_3$): δ 126.8, 125.9, 52.0, 51.6, 48.4, 42.2, 39.3, 36.4, 33.7, 30.4, 30.1, 28.8, 27.9, 26.8, 26.2, 23.30, 23.28, 21.6, 20.5, 12.5 ppm. HRMS (EI) C$_{20}$H$_{32}$ [M]$^+$/z calc. 272.2504, found 272.2501.
4.19: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.19-2.12 (m, 2H), 1.88-1.72 (m, 4H), 1.64-1.25 (m, 12H), 0.97 (s, 3H), 0.89 (s, 3H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.74 (d, $J = 6.6$ Hz, 3H) ppm. $^{13}$C NMR (162 MHz, CDCl$_3$): $\delta$ 143.0, 137.8, 52.5, 44.3, 37.0, 35.2, 33.4, 30.2, 28.2, 28.1, 27.1, 26.2, 25.3, 22.4, 21.9, 18.2, 17.6, 17.2 ppm. HRMS (El) C$_{18}$H$_{30}$ [M]$^+$/z calc. 246.2348, found 246.2344.

![Diagram 4.20](image)

4.20 $\xrightarrow{10\% \text{(CNC)Pt}^{2+} \text{CH}_2\text{Cl}_2}$ 4.21

4.21: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.21-2.17 (m, 1H), 2.12-2.08 (m, 1H), 1.98-1.93 (m, 1H), 1.80-1.63 (m, 5H), 1.60 (sept., 1H), 1.54-1.04 (m, 14H) 0.98 (s, 3H), 0.96 (s, 3H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.79 (s, 3H), 0.74 (d, $J = 6.6$ Hz, 3H) ppm. $^{13}$C NMR (162 MHz, CDCl$_3$): $\delta$ 144.0, 137.3, 55.1, 52.3, 48.6, 39.1, 38.2, 36.7, 36.5, 33.5, 30.2, 28.6, 27.7, 26.9, 26.3, 25.4, 23.5, 21.6, 20.5, 18.2, 17.9, 17.7, 13.2 ppm. HRMS (El) C$_{23}$H$_{38}$ [M]$^+$/z calc. 314.2974, found 314.2969.

![Diagram 4.21](image)

Structural assignment of 4.21 was based upon the following NMR experiments. The presence of only two sp$^2$ carbons indicated the loss of four unsaturation equivalents and
formation of a tetracyclic product. The absence of vinylic protons indicated the formation of a tetrasubstituted alkene. Protons on diastereotopic methyl groups of C23 and C22 were identified by $^1$H NMR as the two upfield doublets. From here, the isopropyl proton was identified based upon correlation to protons on C23 (blue arrow) and C22 (red arrow) in COSY and NOESY experiments. Protons on C20 were then identified based upon correlation to the protons on C23 (green arrow) in NOESY and 1D Gradient NOESY 1 experiments and correlation to the isopropyl proton (orange arrow) in 1D Gradient NOESY 1. The C13-C14 alkene was identified based upon HMBC correlation of C13 to the protons on C23 (purple arrow) and the isopropyl proton (grey arrow). The protons on C18 were identified based upon HMBC correlation to C14 (cyan arrow). The protons on C19 were identified based upon NOESY and 1D Gradient NOESY 2 correlation to the protons on C18 (pink arrow).
COSY
NOESY
1D GRADIENT NOESY 1

irradiate here
1D GRADIENT NOESY 2

Irradiate here

[Diagram of molecular structure]

[Graph with axes labeled and data points]
As discussed in the text, a bicyclic byproduct was also formed in low yield. Enough material was obtained to collect the following characterization data, which suggested that it might have the following structure (or others similar to it). The presence of four sp² carbons in the
$^{13}$C NMR was indicative of a bicyclic product. The presence of the methyl doublet at 0.98 ppm and the absence of a correlation between the two alkenes by HMBC suggested that the alkene isomerises away from the methyl group and away from the second alkene. One structure that is consistent with these data and the presence of two vinylic protons is the following; there are no doubt others that are similarly consistent.

$\text{H NMR (600 MHz, CDCl}_3\text{): } \delta 5.64 (m, 2H), 5.14 (m, 1H), 2.32-2.28 (m, 1H), 2.09-2.04 (m, 1H), 1.96-1.93 (m, 2H), 1.86-1.79 (m, 1H), 1.71 (s, 3H), 1.62 (s, 3H), 1.57-1.51 (m, 2H), 1.48-1.23 (m, 9H), 0.98 (d, $J = 7.2$ Hz, 3H), 0.90 (s, 3H), 0.86-0.77 (m, 1H). \text{C NMR (162 MHz, CDCl}_3\text{): } \delta 133.2, 131.3, 126.1, 125.0, 42.1, 40.9, 37.8, 35.0, 33.6, 29.0, 28.8, 27.8, 25.7, 24.5, 24.1, 22.0, 21.6, 17.8, 17.1 \text{ ppm. HRMS (EI) } C_{19}H_{32} [M]^+ /z \text{ calc. 260.2504, found 260.2507.}$
References


CHAPTER 5: SECONDARY CARBOCATION IN POLYCYCLIZATIONS

Introduction

The complex nature of polyene cyclizations has attracted attention from different areas. While there is a long history of biomimetic work attempting to match the complexity observed in nature, recent advances in computational chemistry have generated significant interest in the nature of the cyclization itself. Detailed analysis of these cyclization reactions has provided a complex and occasionally contradictory picture of the nature of the cyclizations. While several reports have favored step-wise processes, recent work has generally confirmed the concerted, asynchronous formation of rings A, B and C in the formation of both lanosterol and hopene (Figure 5.1). These concerted, asynchronous reactions have no intermediates but involve a series of events that do not occur in concert and are often encountered in formation of terpenoid natural products. Though computational methods have provided significant insight, experimental study of such processes can be challenging.

Figure 5.1: Concerted formation of rings A, B and C of hopene

Having executed the tetracyclization of substrate 5.1 (Figure 5.2), we turned our attention to experimental study of the nature of biomimetic polyene cyclization reactions. The synthesis of substrate 5.1 involved the step-wise construction of individual rings,
providing an opportunity for the design of a new family of substrates with selective modification, enabling experimental study of the nature of the cyclization.

![Figure 5.2: Tetracyclization of 5.1](image)

W.S. Johnson has reported a series of secondary alkene containing substrates\(^{1c}\) which proceed through secondary carbocations upon cyclization. While comparison of vinyl and isopropenyl terminating groups resulted in cyclizations which struggled to engage the vinyl terminating group, direct comparison of substrates with selective placement of secondary alkenes throughout the cascade was not undertaken.\(^{1c}\) In a similar vein, E.J. Corey has reported the effect of replacement of the C-6 methyl group of 2,3-oxidosqualene with either a hydrogen or chloride (Figure 5.3), reducing the nucleophilicity of the alkene. This study provided experimental evidence of the concerted nature of A ring formation in lanosterol through the effect of alkene nucleophilicity upon oxirane opening.\(^{5}\)

![Figure 5.3: 2,3-oxidosqualene and analogs](image)

We proposed the synthesis of a series of substrates in which selective replacement of trisubstituted alkenes with secondary alkenes and comparison of their rates of cyclization
could provide an indication of the nature of the cyclization. Through exploration of the effect of positioning of the secondary carbocation within the cascade, experimental insight into the concertedness and comparison of these biomimetic reactions to their biosynthetic counterparts could be gleaned.

**Substrates**

To design a series of substrates to probe the nature of the Pt-catalyzed polyene cyclization, we required the ability to systematically remove methyl groups in selected positions throughout the substrate. The previously reported fully methylated substrate 5.1 was synthesized through a sequence in which individual rings were formed through a three step sequence involving the addition of isopropenylmagnesium bromide to an aldehyde, a mercury trifluoroacetate catalyzed vinylation and a claisen rearrangement (Figure 5.4).\(^6\)

![Figure 5.4: Synthesis of 5.1](image)

We hypothesized that simple replacement of isopropenyl magnesium bromide with vinyl magnesium bromide would yield the desired secondary alkene. While addition of the vinylmagnesium bromide and vinylation proceeded, this simple approach was unsuccessful, as the attempted Claisen rearrangement returned the vinyl ether to the alcohol (Figure 5.5).
To overcome the less favorable Claisen rearrangement, a literature search was performed and a new approach was undertaken. Following a report by Wei,\textsuperscript{7} a one pot vinylation/Claisen rearrangement was explored using (1,10-phenanthroline)Pd(OAc)\textsubscript{2} and triethyleneglycol divinylether. This approach furnished a convenient route to the desired secondary alkenes (Figure 5.6). With the ability to synthesize the necessary secondary and tertiary alkenes, a series of new substrates was prepared.

The synthesis of three new selectively demethylated substrates was achieved by selective placement of secondary alkenes throughout the cascade. These three, in addition to our previously synthesized fully methylated substrate, formed the library of substrates for this study (Figure 5.7). Naming of substrates was based upon the carbon at which the methyl group has been removed (i.e., “5” for the substrate demethylated at C5).
Cyclization

Cyclization of these new, secondary alkene containing substrates with (CNC)Pt$^{2+}$ proved, as expected, more challenging than their fully methylated counterpart. Reaction times were significantly elongated and accompanied by the formation of multiple products in several cases. Cyclization of the 9-demethylated substrate was performed, yielding the B/C demethylated analogue from the cyclization of fully methylated substrate 5.1 (Figure 5.8). Particularly noteworthy in the context of natural products, is the demethylated B/C ring junction, a structural motif that is characteristic to numerous natural sterols.$^{1d}$ In contrast to cyclization with the fully methylated substrate which proceeded at 10% catalyst loading, in this case, catalyst loading was increased to 15% to compensate for catalyst deactivation over the extended reaction time (4 days). Isolation of the desired product was achieved using Ag$^+$ impregnated silica gel$^8$ in 54% yield. The structure of 5.6 was determined by comparison to compound 5.2, providing a nearly identical spectrum, consistent with demethylation at the B/C ring junction.
Cyclization of the 13-demethylated substrate provided a mixture of two fully cyclized compounds. In contrast to the fully methylated substrate which rearranged to provide a tetrasubstituted alkene at the C/D ring junction, removal of the methyl group at C13 allowed for formation of a different tetrasubstituted alkene resulting from a single hydride shift and subsequent elimination. With a catalyst loading of 15%, this tetrasubstituted alkene was preferred, forming in a 32% yield while the C/D unsaturated product formed as the minor product in 20% yield (Figure 5.9). The two products were separated by Ag⁺ impregnated silica gel⁸ with 5.8 eluting first. The structure of 5.8 was determined by comparison of ¹H NMR with that of 5.2, providing a similar spectrum but lacking a methyl group. Compound 5.7 was characterized separately by ¹H, ¹³C and selective 1D experiments (see supporting information).

**Figure 5.8: Cyclization of 5.4**

![Chemical structure of 5.4 and 5.6 with reaction conditions](image)

5.4 "g"  \[\text{CH}_2\text{Cl}_2, 15\% (\text{CNC})\text{Pt}^{2+}\]  5.6

54%
Cyclization of the 5-demethylated substrate proved significantly more challenging, forming several fully cyclized products as determined by fragmentation of the isopropyl group in the gc-ms spectra. Attempts to run the reaction at a 15% or 30% catalyst loading resulted in catalyst deactivation prior to full consumption of substrate. Increasing the catalyst loading to 50% resulted in a reaction time of approximately 4 days with full consumption of starting material. While the expected C/D unsaturated tetracycle was formed as the major product as observed by gc-ms, isolation proved challenging. Separation was achieved after multiple Ag⁺ impregnated silica gel columns, resulting in an 18% isolated yield (Figure 5.10). The structure of 5.9 was determined by comparison of the $^1$H NMR with that of 5.2. While several other fully cyclized minor products were observed by gc-ms, they proved inseparable despite multiple attempts at isolation.
Competition Experiments

While standard cyclization reactions provided an indication of relative rates of cyclization of the demethylated substrates, particularly the slow cyclization of 5.5, competition experiments were performed so that more accurate measures of the methyl deletion experiments could be achieved. Monitoring the product/s.m. evolution over time by gc-ms proved particularly useful. While enzyme mediated cyclizations often proceed through a concerted, asynchronous mechanism, considering the effect of both stepwise and concerted reactions upon the relative rates of cyclization of the demethylated substrates proved helpful.

Figure 5.11: Relative rates for concerted, synchronous cyclization

In the case of a concerted, synchronous pathway in which no intermediates exist and all bonds are formed and broken simultaneously, the rates of cyclization of the three demethylated substrates should be very similar, but slower than the rate of cyclization of the fully methylated substrate (Figure 5.11). In this case, the positioning of the secondary alkene
is irrelevant, as all bonds are formed and broken in a single transition state. A reaction coordinate diagram for the concerted cyclizations can be envisioned. As is the case for concerted reactions, there are no intermediates or minima on the reaction coordinate and a single transition structure in which all bonds are formed and broken. In the case of a fully concerted, synchronous reaction, cyclization of “5”, “9” and “13” proceed through transition states of equal energy (Figure 5.12), with the transition structure of “0” being lower in energy.

![Reaction coordinate diagram](image)

**Figure 5.12: Reaction coordinate for a concerted, synchronous reaction**

A step wise mechanism in which A-ring formation is rate limiting and occurs without interaction from the forming B and C rings was expected to provide a significantly different picture. In this case, cyclization of the 5-demethylated substrate was expected to be slowest
due to formation of the secondary carbocation generated upon formation of the A ring. The three remaining substrates were anticipated to provide similar rates, due to the identical nature of their A-ring formation (Figure 5.12).

Figure 5.13: Relative rates for step-wise cyclization

Substrates were paired for competition experiments, with 1 equivalent of each substrate and 1 equivalent of catalyst in dichloromethane. Reactions were checked hourly by gc-ms and relative rates determined by relative product formation. Pairing of the fully methylated substrate and the 9-demethylated substrate revealed a relative rate ($k_0/k_9$) of 4.5. Pairing of the 9-demethylated and 13-demethylated substrate provided a relative rate ($k_{13}/k_9$) of 2.2. Significant changes in rate were observed in pairings with the 5-demethylated substrate, with the 9-demethylated substrate a relative rate of ($k_9/k_5$) of 10 was observed, while pairing with 13-demethylated substrate produced a relative rate ($k_{13}/k_5$) of 14.
Discussion

Taken together, these competition experiments paint a picture of a complex cyclization procedure. While a strictly concerted or strictly stepwise process can be ruled out, a combination of the two appears to be operative. These results suggest a concerted, yet highly asynchronous reaction appears to fit the data.\(^4\)

Concerted processes have been invoked in several cases to avoid the intermediacy of high energy secondary carbocations. Hess first proposed a concerted C ring expansion and D ring formation in the formation of lanosterol, avoiding a secondary carbocation intermediate.\(^9\) More recently, Tantillo has proposed concerted mechanisms to avoid similar high energy intermediates.\(^10\) The relative rate data obtained, suggesting a concerted mechanism, indicating secondary carbocations may be avoided in similar fashion in these biomimetic reactions.

The involvement of concerted, asynchronous reactions have also been proposed by Hess in the formation of hopene and lanosterol. Computational study revealed concerted, yet highly asynchronous formation of the A, B and C rings (with initial formation of a 5-membered C-ring) of both hopene\(^3a\) and lanosterol.\(^3b\) These processes were characterized by nearly full closure of the A ring prior to significant involvement from the forming B and C rings.

The significantly slower cyclization of the 5-demethylated substrate is consistent with rate limiting A ring formation, where full A ring closure is likely to occur without significant assistance from the forming B and C rings. The differences observed between the demethylated substrates \(5.3, 5.4, 5.5\) and the fully methylated substrate \(5.1\) suggest a concerted process, in which participation of the forming B, C and D rings are involved.
Relative rates increase as the secondary carbocation is farther removed from the A ring, suggesting progressively less involvement from rings B, C and D.

A reaction coordinate diagram similar to that for the strictly concerted reaction (Figure 5.12) can be envisioned with several key differences. In the case of a concerted asynchronous reaction, the transition structure for the cyclization of all substrates is different. Cyclization of “0” being the lowest in energy, followed by “13”, then “9” then “5”. Given the significantly slower cyclization, a transition structure in which nearly full formation of the A ring is observed without significant stabilization from the forming B and C rings can be expected. This transition structure, resembling A ring formation in which the carbocation in the A ring bears the majority of the developing positive charge, results in a significant gap in the relative energy between the transition structure in the cyclization of “5” and the others (Figure 5.14) as a result of the secondary carbocation involved in A ring formation in the cyclization of “5”.
Figure 5.14: Reaction coordinate diagram from concerted, asynchronous reaction

Interestingly, the concerted but highly asynchronous reactivity of this biomimetic reaction draws significant parallels to the formation of the A, B and C rings in the enzyme mediated formation of hopene and lanosterol. While the exact role of the enzyme has been debated, with some suggesting a role in carbocation stabilization while others have proposed the enzyme functions as a protector, preventing carbocation quenching. The similarities between the biological and these biomimetic reactions suggest at least in part, a limited role for the enzyme in determination of the nature of the cyclization.
Experimental Section

General Considerations

All air and moisture sensitive procedures were performed using an MBraun glovebox or standard Schlenk line techniques. Commercially available reagents were used without further purification. Dichloromethane and toluene were passed through a column of alumina prior to use. NMR spectra were collected on a Bruker 600 or 400 MHz spectrometer and referenced to residual solvent peaks. HRMS was performed by Dr. Mee-Kyung Chung at the University of North Carolina at Chapel Hill. Compounds 5.1 and 5.2 have been reported previously.

Competition Experiments

(CNC)PtBr$_2$ (0.017 mmol), dichloromethane (0.4 mL) and AgBF$_4$ (0.00625 mmol) were added together and the mixture was stirred for 1 hour under N$_2$ in the dark. AgBr was then removed by syringe filter (0.45 µM PTFE) and substrates (0.017 mmol of each) were added to the solution. The reactions were monitored by taking aliquots and analyzed by gc-ms. Relative rates were obtained by measuring through integration the relative amount of product by gc/ms.

Substrate Synthesis

All substrates were prepared following established protocols for previously reported substrates.$^{6-7}$
(E)-6,11-dimethyldodeca-1,6,10-trien-3-ol: Vinylmagnesium bromide (8.3 mL, 1.0 M in THF) was cooled to -78°C and (E)-4,9-dimethyldeca-4,8-dienal\textsuperscript{11} (1.0 g, 5.55 mmol) was added in 5 mL of THF. The reaction was left to warm overnight with stirring. The reaction was then quenched with a saturated solution of ammonium chloride, the layers were separated and the aqueous layer was washed three times with diethyl ether. The combined organics were washed with brine and dried over magnesium sulfate. Removal of solvent produced the desired product (0.90 g, 4.33 mmol, 78% yield) which was carried on without further purification.

\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): δ 5.92-5.86 (m, 1H), 5.26-5.23 (d, 1H), 5.20 (m, 1H), 5.15-5.12 (m, 2H), 4.12 (m, 1H), 2.11-2.02 (m, 6H), 1.71 (s, 3H), 1.67-1.62 (m, 2H), 1.63 (s, 3H), 1.62(s, 3H) ppm. \textsuperscript{13}C NMR (152 MHz, CDCl\textsubscript{3}): δ 141.1, 134.8, 131.6, 124.9, 124.3, 114.6, 73.0, 35.5, 35.1, 28.3, 28.2, 25.7, 17.7, 16.0 ppm.

(4E,8E)-8,13-dimethyltetradeca-4,8,12-trienal: Procedure adapted from Wei et al.\textsuperscript{7} (E)-6,11-dimethyldodeca-1,6,10-trien-3-ol (0.90 g, 4.33 mmol), tri(ethylene glycol) divinyl ether (TGDV) (1.31 g, 6.48 mmol) and (1,10-phenanthroline)Pd(OAc)\textsubscript{2} (0.009 g, 0.02 mmol) were combined in a roundbottom flask equipped with a reflux condenser open to air. The reaction was heated at 70°C for two days followed by 110°C for four hours. The crude mixture was then purified by silica gel column chromatography (10:1 hexanes : ethyl acetate, R\textsubscript{f} = 0.5) to yield the desired product (0.83 g, 3.55 mmol, 82% yield).
1H NMR (600 MHz, CDCl₃): δ 9.77 (m, 1H), 5.48-5.43 (m, 2H), 5.14 (m, 2H), 2.51-2.49 (m, 2H), 2.36-2.33 (m, 2H), 2.10-2.07 (m, 2H), 2.02-2.00 (m, 6H), 1.70 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H) ppm. 13C NMR (152 MHz, CDCl₃): δ 202.4, 134.6, 131.7, 131.5, 127.7, 124.6, 124.4, 43.5, 39.5, 31.0, 28.3, 28.2, 25.7, 25.2, 17.7, 16.0 ppm.

(6E,10E)-2,10,15-trimethylhexadeca-1,6,10,14-tetraen-3-ol: Isopropenylmagnesium bromide (10.6 mL, 0.5 M in THF) was cooled to -78°C and (4E,8E)-8,13-dimethyltetradeca-4,8,12-trienal (0.83 g, 3.55 mmol) was added with 5 mL THF. The reaction was left to warm overnight with stirring. The reaction was quenched with a saturated solution of ammonium chloride and the aqueous layer was washed three times with diethyl ether. The combined organic layers were washed with brine and dried over sodium sulfate. Removal of solvent yielded the desired product (0.50 g, 1.81 mmol, 52% yield)

1H NMR (600 MHz, CDCl₃): δ 5.46-5.44 (m, 2H), 5.16-5.15 (m, 2H), 4.96 (m, 1H), 4.85 (m, 1H), 4.09 (m, 1H), 2.11-2.02 (m, 12H), 1.74 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.63 (s, 3H) ppm. 13C NMR (152 MHz, CDCl₃): δ 147.5, 134.8, 131.5, 130.8, 129.6, 124.5, 124.4, 111.0, 75.4, 39.7, 34.7, 31.2, 28.8, 28.4, 28.2, 25.7, 17.7, 17.6, 16.0 ppm.
(4E,8E,12E)-4,12,17-trimethyloctadeca-4,8,12,16-tetraenal: (6E,10E)-2,10,15-trimethylhexadeca-1,6,10,14-tetraen-3-ol (0.50 g, 1.81 mmol), ethyl vinyl ether (15 mL) and mercury trifluoroacetate (0.08 g, 0.18 mmol) were stirred for 24 hours at room temperature. The ethyl vinyl ether was removed under reduced pressure and the residue loaded onto a silica gel plug and eluted with ethyl acetate to remove the mercury trifluoroacetate. The solvent was removed and the oil was dissolved in 8 mL of toluene and heated to 120°C for six hours. The toluene was removed and the residue purified by silica gel column chromatography (9:1 hexanes : ethyl acetate, Rf = 0.5) to produce the desired product (0.27 g, 0.89 mmol, 49% yield).

1H NMR (400 MHz, CDCl3): δ 9.76 (m, 1H), 5.42-5.40 (m, 2H), 5.17-5.14 (m, 3H), 2.52-2.50 (m, 2H), 2.35-2.33 (m, 2H), 2.07-2.01 (m, 12H), 1.70 (s, 3H), 1.61-1.60, (m, 9H) ppm.

13C NMR (101 MHz, CDCl3): δ 202.6, 134.8, 133.1, 131.4, 130.4, 129.7, 125.2, 124.44, 124.40, 42.2, 39.8, 32.6, 31.9, 31.2, 28.4, 28.2, 28.1, 25.7, 17.7, 16.1, 16.0 ppm.

5.4: (5E,9E,13E)-5,13,18-trimethylnonadeca-1,5,9,13,17-pentaene: To a solution of triphenylphosphonium bromide (0.383 g, 1.07 mmol) in THF (5 mL) at -78°C, was added n-BuLi (0.65 mL, 1.6 M in THF), the solution was then stirred for 1 hour at -78°C. (4E,8E,12E)-4,12,17-trimethyloctadeca-4,8,12,16-tetraenal (0.27 g, 0.89 mmol) in THF (3 mL) was then added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with a saturated solution of ammonium chloride and the layers
were separated. The aqueous layer was washed three times with diethyl ether and the combined organics washed with brine and dried over sodium sulfate. Removal of solvent and purification by silica gel column chromatography (hexanes, Rf = 0.6) yielded the product (0.085 g, 0.28 mmol, 32% yield)

1H NMR (600 MHz, CDCl₃): δ 5.86-5.81 (m, 1H), 5.45-5.43 (m, 2H), 5.18-5.16 (m, 3H), 5.05-5.02 (m, 1H), 4.97-4.96 (m, 1H), 2.19-2.03 (m, 16H), 1.72 (s, 3H), 1.64-1.62 (m, 9H) ppm. 13C NMR (152 MHz, CDCl₃): δ 138.8, 134.9, 134.6, 131.4, 130.2, 130.0, 124.5, 124.4, 124.39, 114.2, 39.8, 39.1, 32.8, 32.4, 31.3, 28.4, 28.2, 28.1, 25.7, 17.7, 16.03, 16.01 ppm. HRMS (EI) C_{22}H_{36} [M]+/z calc. 301.2890 found 301.2893.
(E)-2,11-dimethyldodeca-1,6,10-trien-3-ol: Isopropenylmagnesium bromide (10.85 mL, 0.5M in THF) was cooled to -78°C, at which time, (E)-9-methyldeca-4,8-dienal (0.6 g, 3.6 mmol) was added via 15 mL THF. The -78°C bath was removed and the reaction was stirred for two hours. The reaction was quenched with a saturated ammonium chloride solution, the layers were separated and the aqueous layer was washed twice with diethyl ether. The combined organics were washed with brined and dried with sodium sulfate. The solvent was removed and the residue purified by flash column chromatography (5:1 hexanes:ethyl acetate, Rf = 0.5) to yield a colourless oil (0.610 g, 2.9 mmol, 82% yield).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.46-5.44 (m, 2H), 5.13-5.11 (m, 1H), 4.95 (s, 1H), 4.84 (s, 1H), 4.09-4.07 (m, 1H), 2.05-2.03 (m, 8H), 1.73 (s, 3H), 1.70 (s, 3H), 1.62 (s, 3H) ppm. $^{13}$C
NMR (152 MHz, CDCl₃): δ 147.5, 131.6, 130.7, 129.7, 124.1, 111.0, 75.4, 34.7, 32.8, 28.7, 28.1, 25.7, 17.7, 17.6 ppm.

(4E,8E)-4,13-dimethyltetradeca-4,8,12-trienal: (E)-2,11-dimethyldodeca-1,6,10-trien-3-ol (0.61 g, 2.9 mmol) was dissolved in 10 mL of ethyl vinyl ether. Mercury trifluoroacetate (0.125 g, 0.29 mmol) was then added and the reaction was stirred for 2 days. Ethyl vinyl ether was then removed under vacuum and the mercury trifluoroacetate was removed by passing the residue through a silica gel plug in ethyl acetate. The ethyl acetate was then removed and the oil was dissolved in 10 mL of toluene and heated to 120°C in a pressure tube for 6 hours. The toluene was removed and the compound was purified by column chromatography (9:1 hexanes:ethyl acetate, Rᵣ = 0.6) to yield a colourless oil (0.53 g, 0.23 mmol, 77% yield).

¹H NMR (600 MHz, CDCl₃): δ 9.76 (m, 1H), 5.43-5.0 (m, 2H), 5.18 (m, 1H), 5.12 (m, 1H), 2.53-2.50 (m, 2H), 2.34-2.32 (m 2H), 2.04-2.02 (m, 8H), 1.69 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H) ppm. ¹³C NMR (152 MHz, CDCl₃): δ 202.6, 133.1, 131.5, 130.4, 129.8, 125.2, 124.2, 42.2, 32.8, 32.6, 31.9, 28.1, 28.0, 25.7, 17.7, 16.1 ppm.
(6E,10E)-2,6,15-trimethylhexadeca-1,6,10,14-tetraen-3-ol: A solution of isopropenylmagnesium bromide (4.2 mL, 0.5 M in THF) was cooled to -78°C. (4E,8E)-4,13-dimethyltetradeca-4,8,12-trienal (0.33 g, 1.41 mmol) was then added with 3 mL THF. The dry ice/acetone bath was removed and the reaction was stirred for 2 hours while warming. The reaction was quenched with a saturated ammonium chloride solution and the layers were separated. The aqueous layer was extracted three times with diethyl ether. The combined organics were washed with brine and dried over sodium sulphate. Removal of solvent produced the desired compound (0.315 g, 1.15 mmol, 82% yield).

$^{1}$H NMR (600 MHz, CDCl$_3$): $\delta$ 5.43 (m, 2H), 5.18-5.17 (m, 1H), 5.13-5.12 (m, 1H), 4.95-4.94 (m, 1H), 4.84 (m, 1H) 4.06-4.02 (m, 1H), 2.03-1.96 (m, 12H), 1.73 (s, 3H), 1.70 (s, 3H), 1.68-1.65 (m, 6H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): $\delta$ 147.5, 134.9, 131.5, 130.3, 130.0, 124.5, 124.2, 111.0, 75.6, 35.7, 33.2, 32.84, 32.78, 28.2, 28.1, 25.7, 17.7, 17.6, 16.0 ppm.

(4E,8E,12E)-4,8,17-trimethyloctadeca-4,8,12,16-tetraenal: (6E,10E)-2,6,15-trimethylhexadeca-1,6,10,14-tetraen-3-ol (0.315 g, 1.15 mmol), mercury trifluoroacetate (0.049 g, 1.15 mmol) and ethyl vinyl ether (10 mL) were stirred for two days at room temperature. The ethyl vinyl ether was removed under reduced pressure and the mercury removed by loading the residue on a silica gel plug and eluting with ethyl acetate. The ethyl acetate was removed, the oil dissolved in toluene (10 mL) and heated at 120°C for six hours. The solvent was removed to produce the desired product (0.30 g, 0.99 mmol, 86% yield).
$^1$H NMR (600 MHz, CDCl$_3$): δ 9.76 (m, 1H), 5.44 (m, 2H), 5.16-5.14 (m, 3H), 2.53-2.50 (m, 2H), 2.35-2.32 (m, 2H), 2.11-2.00 (m, 12 H), 1.71 (s, 3H), 1.63-1.62 (m, 9H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): δ 202.7, 134.8, 132.9, 131.5, 130.2, 130.1, 125.4, 124.3, 124.2, 42.2, 39.5, 32.9, 32.8, 31.9, 28.2, 28.1, 26.5, 25.7, 17.7, 16.1, 16.0 ppm.

5.3: (5E,9E,13E)-5,9,18-trimethylnonadeca-1,5,9,13,17-pentaene: To triphenylphosphonium bromide (0.43 g, 1.19 mmol) in THF (5 mL) at -78°C, was added n-BuLi (0.47 mL, 1.6 M in THF). The mixture was stirred for 1 hour at -78°C and (4E,8E,12E)-4,8,17-trimethyloctadeca-4,8,12,16-tetraenal (0.3 g, 0.99 mmol) was added via 4 mL THF. The reaction was left to warm overnight while stirring. The reaction was quenched with a saturated solution of ammonium chloride. The layers were separated and the aqueous extracted three times with diethyl ether. The combined organics were washed with brine and dried over sodium sulphate. Removal of solvent and purification by silica gel column chromatography (hexanes, R$_f$ = 0.6) furnished the desired product (0.053 g, 0.18 mmol, 13% yield).

$^1$H NMR (600 MHz, CDCl$_3$): δ 5.86-5.81 (m, 1H), 5.46 (m, 2H), 5.18-5.14 (m, 3H), 5.05-5.02 (m, 1H), 4.97-4.95 (m, 1H), 2.18-2.01 (m, 16H), 1.72 (s, 3H), 1.64-1.63 (m, 9H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): δ 138.8, 135.1, 134.4, 131.5, 130.2 (X2), 124.6, 124.2, 124.1,
114.2, 39.7, 39.1, 32.9, 32.4, 28.3, 28.1, 26.7, 26.5, 25.7, 17.8, 16.1, 16.0. HRMS (EI)

C_{22}H_{36}\ [M]^+/z\ \text{calc.}\ 301.2895\ \text{found}\ 301.2893.
(6E,10E)-6,10,15-trimethylhexadeca-1,6,10,14-tetraen-3-ol: A solution of vinylmagnesium bromide (4.8 mL, 1.0M in THF) was cooled to -78°C. (4E,8E)-4,8,13-trimethyltetradeca-4,8,12-trienal\(^\text{11}\) (0.8 g, 3.23 mmol) was then added via 5 mL THF and the -78°C bath was removed. The reaction was stirred for 2 hours, at which time the reaction was quenched with a saturated solution of ammonium chloride. The layers were separated and the aqueous extracted three times with diethyl ether. The combined organics were extracted with brine and dried over sodium sulphate. Removal of solvent produced the desired product which was carried on without further purification (0.7 g, 2.5 mmol, 78% yield).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta 5.88 (m, 1H), 5.22 (dd, 1H), 5.17-5.13 (m, 3H), 5.09 (dd, 1H), 4.08 (m, 1H), 2.11-1.98 (m, 12H), 1.68 (s, 3H), 1.61 (s, 9H)\) ppm. \(^13\)C NMR (152 MHz, CDCl\(_3\)): \(\delta 141.2, 135.0, 134.6, 131.4, 124.8, 124.41, 124.4, 114.5, 72.8, 39.6, 35.5, 35.2, 28.3, 28.2, 26.6, 25.7, 17.7, 16.0, 15.9\) ppm.

(4E,8E,12E)-8,12,17-trimethyloctadeca-4,8,12,16-tetraenal: Procedure adapted from Wei et al.\(^\text{7}\) (6E,10E)-6,10,15-trimethylhexadeca-1,6,10,14-tetraen-3-ol (0.7 g, 2.5 mmol), tri(ethylene glycol) divinyl ether (TGDV) (0.76 g, 3.76 mmol) and (1,10-phenanthroline)Pd(OAc)\(_2\) (0.006 g, 0.015 mmol) were added to roundbottom flask equipped
with a condenser open to air. The reaction was heated to 75°C for two days followed by 4 hours at 110°C. The residue was purified by silica gel column chromatography (15:1 hexanes: ethyl acetate) to yield the desired product (0.4 g, 1.32 mmol, 53% yield).

1H NMR (600 MHz, CDCl3): δ 9.77 (m, 1H), 5.48-5.39 (m, 2H), 5.16-5.09 (m, 3H), 2.49-2.48 (m, 2H), 2.34-2.33 (m, 2H), 2.10-1.99 (m, 12H), 1.69 (s, 3H), 1.61 (s, 9H) ppm. 13C NMR (152 MHz, CDCl3): δ 202.3, 135.1, 134.4, 133.9, 131.7, 127.7, 124.6, 124.5, 124.3, 39.7, 39.5, 31.1, 28.4, 28.33, 28.25, 26.6, 25.7, 25.2, 17.7, 16.01, 15.96 ppm.

5.5: (5E,9E,13E)-9,13,18-trimethylnonadeca-1,5,9,13,17-pentaene: To a solution of triphenylphosphonium bromide (0.62 g, 1.74 mmol) in THF (6 mL) at -78°C, was added n-BuLi (1.05 mL, 1.6 M in THF), the solution was then stirred for 1 hour at -78°C. (4E,8E,12E)-8,12,17-trimethyloctadeca-4,8,12,16-tetraenal (0.4 g, 1.32 mmol) in THF (4 mL) was then added and the reaction was allowed to warm to room temperature overnight. The reaction was quenched with a saturated solution of ammonium chloride and the layers were separated. The aqueous layer was washed three times with diethyl ether and the combined organics washed with brine and dried over sodium sulfate. Removal of solvent and purification by silica gel column chromatography (hexanes, Rf = 0.6) yielded the product (0.06 g, 0.2 mmol, 15% yield)
$^1$H NMR (600 MHz, CDCl$_3$): δ 5.88-5.81 (m, 1H), 5.44 (m, 2H), 5.16-5.13 (m, 3H), 5.04 (dd, 1H), 4.97 (dd, 1H), 2.11-2.04 (m, 16H), 1.72 (s, 3H), 1.62 (s, 9H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): δ 138.5, 135.1, 134.6, 131.5, 130.5, 129.4, 124.5, 124.4, 124.3, 114.5, 39.75, 39.74, 33.9, 32.0, 31.2, 28.4, 28.3, 26.6, 25.7, 17.7, 16.01, 16.03 ppm. HRMS (EI) C$_{22}$H$_{36}$ [M]$^+$/z calc. 301.2890 found 301.2892.
Cyclization Procedure

(CNC)PtBr₂ (0.005 mmol), dichloromethane (0.6 mL) and AgBF₄ (0.0125 mmol) were added together and the mixture was stirred for 1 hour under N₂ in the dark. AgBr was then removed by syringe filter (0.45 µM PTFE) and substrate (0.033 mmol) was added to the solution. Upon completion, the reaction was loaded directly onto a Ag⁺ impregnated silica gel⁸ column and eluted with hexanes to yield the desired product(s). Fractions were analyzed by gc/ms.

Cyclized products 5.6, 5.8 and 5.9 were characterized based upon the previously reported⁶ structure shown below. We have previously assigned the ¹H NMR shift of individual methyl groups of this fully methylated tetracycle. Removal of specific methyl groups from the substrate yielded cyclised products lacking the previously assigned methyl signal in the ¹H NMR (ie the 5-demethylated substrate produced a tetracyclic product which lacked the methyl signal at 0.79 ppm).
5.9: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.17-2.13 (m, 2H), 1.95-1.87 (m, 2H), 1.83-1.58 (m, 9H), 1.46-1.42 (m, 1H), 1.33-1.12 (m, 8H), 1.06-0.99 (m, 2H), 0.97 (s, 3H), 0.09 (s, 3H), 0.85 (d, $J = 7.2$ Hz, 3H), 0.74 (d, $J = 7.2$ Hz, 3H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): $\delta$ 143.2, 137.8, 52.6, 49.0, 44.6, 40.9, 37.0, 35.9, 34.5, 33.6, 30.6, 30.4, 29.9, 28.4, 27.0, 26.7, 25.4, 22.8, 20.5, 18.5, 18.4, 17.8 ppm. HRMS (EI) C$_{22}$H$_{36}$ [M]$^+$/z calc. 301.2890 found 301.2890.
5.6: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.23-2.17 (m, 1H), 2.09-2.01 (m, 2H), 1.98-1.94 (m, 1H), 1.92-1.88 (m, 1H), 1.87-1.68 (m, 6H), 1.62-1.41 (m, 4H), 1.34-1.22 (m, 7H), 1.13-1.06 (m, 2H), 0.98 (s, 3H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.78 (s, 3H), 0.75 (d, $J = 7.2$ Hz, 3H) ppm.

$^{13}$C NMR (152 MHz, CDCl$_3$): $\delta$ 139.4, 137.2, 52.53, 52.47, 47.1, 38.3, 36.9, 36.2, 33.8, 21.7, 30.8, 29.5, 28.8, 26.9, 25.1, 23.2, 22.5, 22.1, 18.3, 17.6, 11.7 ppm. HRMS (EI) C$_{22}$H$_{36}$ [M]$^+$/z calc. 301.2890 found 301.2892.
5.8: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.46-2.44 (m, 1H), 2.18-2.14 (m, 2H), 1.93-1.89 (m, 2H), 1.87-1.81 (m, 1H), 1.76-1.65 (m, 6H), 1.55-1.38 (m, 4H), 1.27-1.21 (m, 6H), 1.15-1.03 (m, 2H), 1.00 (s, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.79 (s, 3H), 0.69 (d, $J = 7.2$ Hz, 3H) ppm.

$^{13}$C NMR (152 MHz, CDCl$_3$): $\delta$ 146.0, 133.4, 55.3, 54.0, 48.6, 39.1, 38.1, 36.7 (x2), 29.0, 28.7, 28.6, 26.9, 26.6, 26.2, 22.6, 21.6, 21.3, 20.5, 17.9, 16.0, 13.2 ppm. HRMS (EI) C$_{22}$H$_{36}$ [M]$^+$/z calc. 301.2890 found 301.2893.
5.7: $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.73 (m, 1H), 2.57 (m, 1H), 2.22 (m, 2H), 1.77-1.60 (m, 5H), 1.52-1.47 (m, 2H), 1.40-1.02 (m, 12H), 0.99 (d, $J = 7.2$ Hz, 3H), 0.97 (d, $J = 7.2$ Hz, 3H), 0.87 (m, 1H), 0.76 (s, 3H), 0.68 (s, 3H) ppm. $^{13}$C NMR (152 MHz, CDCl$_3$): $\delta$ 138.1, 133.3, 62.8, 57.1, 48.5, 40.4, 39.7, 39.5, 36.9, 30.3, 28.8, 26.9, 26.5, 26.14, 26.06, 21.9, 21.7, 21.3, 21.2, 20.9, 14.1, 13.1. HRMS (EI) C$_{22}$H$_{36}$ [M]$^+$/z calc. 301.2890 found 301.2894.

 Structural assignment of 5.7 was based upon the following NMR experiments. The presence of only two sp$^2$ carbons indicated the loss of four unsaturation equivalents and formation of a tetracyclic product. The absence of vinylic protons indicated the formation of a
tetrasubstituted alkene. Protons on methyl groups of C21 and C22 were identified by $^1$H NMR as the two doublets at 0.97 and 0.99 ppm. From here, the isopropyl proton on C20 was identified as the downfield multiplet and confirmed by a selective 1D TOCSY experiment in which irradiation of this proton revealed a correlation to the protons on C21 and C22 (blue arrow). The absence of any other correlation in the 1D TOCSY experiment and the downfield shift of the proton on C20 indicated the positioning of the unsaturation. The location of the remaining methyl groups C18 and C19 was confirmed by a 1D NOESY experiment which showed correlation between the two (red arrow).
1D Gradient TOCSY
1D NOESY
References


APPENDIX A: NEW CYCLIZATION INITIATORS

Throughout this work, several new cyclization initiators were developed, producing new Pt-alkyl complexes. Several different approaches to this task were explored. The hard/soft acid-base theory has provided guidance in the search for complexes which may be easier to oxidize. As discussed by Puddephatt,\(^1\) soft ligands, such as phosphines, prefer to bind to soft metals, such as Pt(II), whereas complexes with hard ligands, such as nitrogen donors, will better accommodate hard metals, such as Pt(IV). With this in mind, Pt(terpy) was explored as a possible solution to the redox problems. Cyclization of 1 equivalent of 6-endophenol in the presence of 1 equivalent of piperidinomethyl polystyrene resin base resulted in formation of a new Pt-alkyl complex (Figure A.1). While the complex proved sensitive to acid, isolation was possible, albeit in low yield.

\[
\begin{align*}
\text{HO} & \quad + \quad \text{(terpy)Pt}^{2+} \\
& \xrightarrow{\text{CD}_3\text{NO}_2, \text{base}} \quad \text{(terpy)Pt}^{2+} \\
& \quad \text{Me} \quad \text{O} \\
\end{align*}
\]

**Figure A.1: Cyclization by (terpy)Pt\(^{2+}\)**

Reaction of the (terpy)Pt-R\(^{+}\) with several previously tested oxidants provided similar results to the (triphos)Pt-R\(^{+}\). Reaction with CuCl\(_2\) provided a mixture of halogenated diastereomers and XeF\(_2\) provided the stereoretentive fluoride. Attempts to enter a catalytic oxygenation scheme resulted in reactions that failed to consume starting material. Reaction of the (terpy)Pt\(^{2+}\) with substrate in the presence of base provided the Pt-alkyl complex, however, in the absence of base, some cycloisomerization of substrate was observed, although the complex was limited to several turnovers.
The use of $\text{P}_3\text{P}t^{2+}$ was briefly explored in the hope that the addition of a pendant phosphine may promote formation of a higher valent Pt-alkyl, making oxidation more facile. Reaction of $\text{P}_3\text{P}t^{2+}$ with substrate in the presence of the resin base resulted in clean formation of a Pt-alkyl species similar to the (triphos)Pt-$R^+$. However, upon activation of $\text{P}_3\text{P}t\text{I}_2$ with $\text{AgBF}_4$, one equivalent of Ag was trapped by the pendant phosphine and carried through the cyclization, resulting in $\text{P(Ag)}\text{P}_3\text{Pt}^-$ as identified by $^{31}\text{P}$ NMR (Figure A.2). Attempts to oxidize this complex resulted in complex mixtures of product, likely due in part to the presence of Ag in solution.

![Chemical structure](image)

**Figure A.2: Cyclization by $\text{P}_3\text{P}t^{2+}$**

Finally, the combination of a diphosphine and an NHC, previously reported by Marinetti$^2$ in cycloisomerization reactions was used in the cyclization. The combination of chiraphos and a simple NHC ligand formed a Pt-organometallic complex which proved stable to column chromatography (Figure A.3). Although limited to a dr of 1.2.1, the chiral disphosphine ligand allowed for some diastereoselectivity in the reaction. Despite the addition of the more electron donating NHC ligand, these complexes proved equally stable as the (triphos)Pt-$R^+$ complexes toward oxidation. This observation could potentially be explained by the removal of torsional strain in the complex relative to the triphos derivative. Additional torsional strain has been shown to help promote oxidation of Pt(II) complexes to Pt(IV) in previous protodemetallation chemistry.$^3$
Figure A.3: Cyclization by P$_2$CPr$^{2+}$
References


APPENDIX B: ADDITIONAL SUBSTRATES

Several new substrates with varying methylation patterns were also synthesized. Initial tests on the viability of secondary carbocations in the cycloisomerization chemistry were performed with a tricyclization reaction. The synthesis of this substrate was shorter and provided a simpler means to perform a test reaction. Cyclization of this complex with the (CNC)Pt$^{2+}$ catalyst formed two different products with initial reactions suggesting a solvent effect on product distribution. In DCM, a single product was observed and characterized as the product resulting from a hydride shift and elimination, a structure confirmed by a 1D TOCSY experiment. In nitromethane, a second product was formed roughly a 1:1 ratio, while this product was not fully characterized, crude NMR analysis suggested it was the product resulting from two hydride shift and elimination to form the B/C unsaturated product (Figure B.1).

Figure B.1: Tricyclization of secondary alkene containing substrate

A substrate with an additional methyl group, in the form of a tetrasubstituted alke was also synthesized as a 1:1 mixture of E and Z isomers. Cyclization of this substrate resulted in isolation of single product, while NMR suggested a structure consistent with that shown below, full characterization was not undertaken (Figure B.2). Stereochemical assignment of this compound was not made due to the mixture of isomers of starting material.
which could potentially lead to cis or trans ring junctions as predicted by the Stork
Eschenmoser postulate.

![Cyclization of tetrasubstituted alkene containing substrate](image)

**Figure B.2: Cyclization of tetrasubstituted alkene containing substrate**

**Experimental Section**

(5E,9E)-5,14-dimethylpentadeca-1,5,9,13-tetraene: Triphenylphosphonium bromide (0.366 g, 1.02 mmol) was dissolved in 6 mL of THF and cooled to -78°C, n-BuLi (0.39 mL, 2.5 M in THF) was the added and the reaction was stirred for 1 hour. (4E,8E)-4,13-
dimethyltetradeca-4,8,12-trienal was then dissolved in 4 mL THF and slowly added. The reaction was allowed to warm overnight and quenched with saturated ammonium chloride solution. The layers were separated and the aqueous was extracted three times with diethyl ether. The combined organics were washed with brine and dried over sodium sulfate. Removal of solvent and purification by column chromatography (hexanes, R<sub>t</sub> = 0.5) yield a colourless oil (0.11 g, 0.47 mmol, 56% yield).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): \( \delta \) 5.84-5.81 (m, 1H), 5.45 (m, 2H), 5.17-5.14 (m, 2H), 5.05-5.01 (m, 1H), 4.97-4.95 (m, 1H), 2.18-2.03 (m, 12H), 1.71 (s, 3H), 1.63 (s, 6H) ppm. <sup>13</sup>C NMR (152 MHz, CDCl<sub>3</sub>): \( \delta \) 138.8, 134.6, 131.5, 130.2, 130.2, 124.4, 124.2, 114.2, 39.1, 32.9, 32.8, 32.4, 28.2, 28.1, 25.7, 17.8, 16.0 ppm.
$^1$H, $^{13}$C and 1D TOCSY were recorded in CDCl$_3$. The structure was determined to be tricyclic by the presence of only two sp$^2$ carbon centres in the $^{13}$C NMR while the absence of vinyl peaks indicated a tetrasubstituted alkene. The location of the tetrasubstituted alkene was confirmed by 1D TOCSY experiment in which the isopropyl methyl groups were irradiated and correlated only to a single proton.
1D TOCSY

irradiate here