DICATIONIC PLATINUM-INITIATED CATION-OLEFIN REACTIONS OF SIMPLE ALKENES

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A dissertation submitted to the faculty of the University of 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
2013

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ABSTRACT

JOSEPH GREGORY SOKOL: Dicationic Platinum-Initiated Cation-Olefin Reactions of Simple Alkenes
(Under the direction of Michel R. Gagné, PhD)

The enzymatic transformation of polyolefin chains to their multi-cyclic counterparts is an efficient and elegant means for the generation of multiple rings with contiguous stereocenters. Many researchers have attempted to develop biomimetic systems capable of catalytically performing similar transformations with the same stereo-selectivity but current methods fall short due to premature termination processes and limited scope.

To improve upon these limitations, a dicationic platinum-initiated polyolefin cyclization was developed. Adaptation of this system to substrates with bio-like simple alkene terminating groups, a major advancement in the cyclization of poly-olefin hydrocarbon chains was achieved. Through the use of chiral phosphine based ligands, a cyclization was able to be performed enantioselectively. Investigations into the scope of reagents showed that the nucleophilicity and cation stability of the terminating alkene determined the reactivity of each compound. A wide range of substrates proved amenable to these conditions and a variety of carbon skeletons could be obtained.

Alteration of the ligand set on the dicationic platinum complex from tridentate to bidentate opened up the possibility for catalyzed cyclizations. Cyclization of substrates with an alkene terminus required significantly more optimization as compared to their protic terminated counterparts. The extended reaction times led to decreases in conversion and product purity as side reactivity became an issue. Improvement of the hydride abstraction

step, which regenerates the active catalyst, was critical for developing this methodology further.

Investigations have begun into a simplified catalytic pathway. Direct oxidation of the platinum-alkyl by copper(II) oxidants allows for catalyst regeneration and release of the organic fragment. While this work is still in the preliminary stages, the use of $Cu(OTf)_2$ has already shown itself to be promising in the catalytic cyclization of poly-ene chains with simple alkene termini. Through further reaction optimization it is very possible that an even more productive system can be produced.

ACKOWLEDGEMNTS

While properly acknowledging all the people who have had a positive impact on my graduate career would be impossible, there are a few who stand out.

I would like to thank Mike for the many opportunities he has provided me throughout my time at UNC. He provided me with the time and freedom to explore new ideas, problem solve when reactions did not go as expected, and he was supportive of my taking full advantage of graduate experiences that interested me - even if they were not always directly related to my research.

I would also like to thank Professor Jeff Johnson. His outgoing personality over my visitation weekend played a pivotal role in my selection of UNC for my graduate studies.

Thanks are in order for the Chemistry Department at Bucknell University which did a great job preparing me for the PhD experience…and sparking my love for intramural softball.

Special thanks to all Gagné group members, past and present. While I am only personally acknowledging a few, each of them has played an important role in making our lab into one of the best work environments I've ever been a part of.

Of my former co-workers I would like to thank Colleen Munro-Leighton. She was truly the optimal group member and I learned so much from working alongside her. I try to be as good to our new members as she was to me.

I begrudgingly thank Steve Andrews for all the times he begrudgingly helped me over the years. When Steve was in lab, everyone knew it, and it hasn't been the same since he left.

A debt of gratitude goes to Laura Adduci, who more than anyone helps carry the burden of day-to-day lab tasks that hamper productivity. She has turned into the motor that keeps our lab running.

A special thanks to Mike Geier who is always willing to listen to my ideas or whenever I needed to vent. Thanks for not quitting.

Thanks to all the guys I've played intramural sports with, the book club gang, the trivia squad, and my buddy Chris.

Thank you to my amazing family for all their love and support and for providing me with the opportunities and the drive that started me on this path. They are a constant source of optimism and motivation in my life.

Most of all, I must thank the most important person in my life, my loving and adoring wife, Brooke. Thank you for putting up with me all the times I over-prioritized work or missed my last bus home and you had to come pick me up. I can honestly say I wouldn't have made it without you.

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LIST OF ABBREVIATIONS

°C	degrees Celsius
Å	angstrom
α	alpha
aq	aqueous
β	beta
BF_4	tetrafluoroborate
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BIPHEP	2,2’-bis(diphenylphosphino)-1,1’-biphenyl
*n*BuLi	*n*-butyllithium
*t*Bu	*tert*-butyl
*t*BuLi	*tert*-butyllithium
COD	1,5-cyclooctadiene
δ	delta – change from standard value (NMR)
d	doublet (NMR)
DFT	density functional theory (calculations)
DMAP	4-(dimethylamino)pyridine
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1’-bis(diphenylphsohpino)ferrocene
dppm	1,2-bis(diphenylphosphino)methane
dppp	1,2-bis(diphenylphosphino)propane
dr	diastereomeric ratio
Ea	activation energy

ee	enantiomeric excess
endo	endocyclic
eq	equivalent
ESI	electrospray ionization
Et	ethyl
EtOH	ethanol
g	gram
mg	milligram
µg	microgram
GCMS	gas chromatography – mass spectroscopy
h	hour
hν	energy (from light)
HRMS	high resolution mass spectrum
Hz	hertz (NMR coupling constants)
L	liter
L	any unspecified ligand
J	three-bond H-H coupling constant
$J_{Pt\text{-}P}$	one-bond Pt-P coupling constant
Kcal	kilocalorie
mL	milliliter (10^{-3} liter)
µL	microliter (10^{-6} liter)
LDA	lithium diisopropylamide
m	multiplet (NMR)

m-	meta – 1,3 relationship on aromatic
M	molarity (concentration)
Me	methyl
MeOH	methanol
mg	milligram
$MgSO_4$	magnesium sulfate
min	minutes
mM	millimolar – 10^{-3} mol / liter (concentration)
mmol	millimole
µmol	micromole
mol %	mole percent (catalyst loading)
MS	molecular sieves
m/z	mass-to-charge ratio (mass spectrometry)
ND	not determined
NMR	nuclear magnetic resonance
Nuc	any unspecified nucleophile
o-	ortho, 1,2-relationship on aromatic
ORTEP	Oak Ridge thermal ellipsoid plot
p-	para, 1,4-relationship on aromatic
Ph	phenyl
π	pi – electrons involved in C-C multiple bonds
PF_6	hexafluorophosphate
Ph_2NH	*N*, *N*-diphneylamine

Ph_2NMe	*N*, *N*-diphneylmethylamine
PPh_3	triphenylphosphine
ppm	parts per million (NMR relative difference)
*i*Pr	*iso*-propyl
*i*PrOH	isopropyl alcohol
pyr	pyridine
q	quartet (NMR)
R-	any unspecified carbon-containing group
rt	room temperature
σ	sigma – electrons involved in C-C single bonds
σ*	antibonding orbital in C-C single bonds
s	seconds
s	singlet (NMR)
STP	standard temperature and pressure
t	triplet (NMR)
THF	tetrahydrofuran
Ts	*p*-toluenesulfonate
PhMe	toluene
xylyl	3,5-dimethylphenyl

Chapter 1 : Development of Biomimetic Polyolefin Cyclizations

Nature's Synthetic Strategies

Polyolefin cyclizations are an integral part of the biosynthesis of many natural products. Terpenoid compounds are made of mostly carbocyclic substances, consisting of multiple rings with contiguous stereocenters.[1] These compounds are excellent synthetic targets because they require the further development of available cyclization methodologies. In addition to providing the means to synthesize compounds of limited availability in nature, the development of synthetic methodologies with broad scopes would allow for the creation of compounds not found in nature. Making slight modifications to known compounds could boost their biological activity in addition to giving compounds with unique carbon scaffolding.[2]

Initial attempts to elucidate the enzymatic mechanism for the formation of hopanoids and steroids focused on exposing the enzymes to substrate analogues and analyzing the products.[3] A better understanding of these transformations was not available until advances in molecular and structural biology as well as computational chemistry were achieved more recently.[4] Of great interest to synthetic chemists was determining how the same poly-olefin chain was transformed into different products by slight variation within the enzyme (Figure 1.1) and whether those modifications could be made within a laboratory setting.

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[1] Biellman, J. F. *Chem. Rev.* **2003**, *103*, 2019-2033.
[2] Kotora, M.; Hessler, F.; Eignerova, B. *Eur. J. Org. Chem.* **2012**, 29-42.
[3] Abe, I.; Rohmer, M.; Prestwich, G. D., *Chem. Rev.* **1993**, *93*, 2189-2206.
[4] Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R., *Angew. Chem. Int. Ed.* **2000,** *39* (16), 2812-2833.

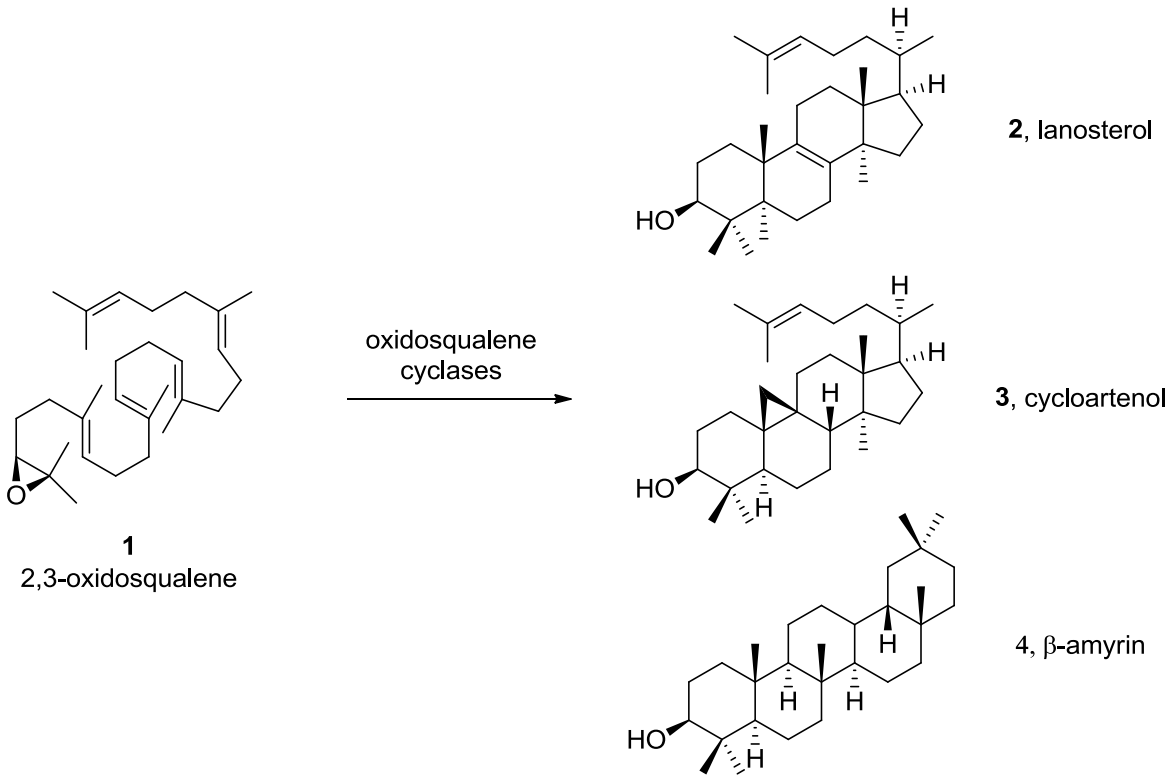


Figure 1.1 Various terpenoids formed by different oxidosqualene cyclases

The intramolecular addition of a carbocation to a carbon-carbon double bond to form a six-membered ring is highly exothermic (by approximately 20 kcal mol^{-1}) and requires little activation.[5] This allows multiple reaction modes of low activation energy to compete effectively. Using a conformationally mobile substrate (such as a linear polyolefin chain) leads to a variety of products unless external constraints are administered in the reaction environment. Looking at the structural and mechanistic work that has examined the transformation of squalene to hopene (Figure 1.2) gives insight that could be used to make strides in the synthetic development of this type of poly-olefin reactions.[6]

[5] Jenson, C.; Jorgensen, W. L., *J. Am. Chem. Soc.*, **1997,** *119*, 10846-10854.
[6] Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105,* 4730-4756.

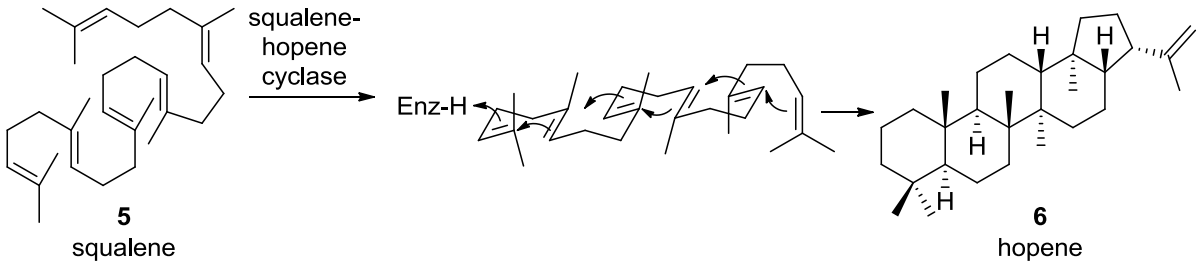


Figure 1.2: Enzymatic transformation of squalene to hopene

The transformation of squalene to hopene by squalene-hopene cyclase is used as a model template instead of any of the oxidosqualene cyclases because it is mechanistically simpler and instead of forcing boat-like intermediates, allows the substrate to adopt an all chair-like geometry.[7] The cocrystallization of squalene-hopene cyclase with the inhibitor 2-azasqualene has provided great insight into how the polyolefin fits into the enzyme pocket (Figure 1.3: Enzyme).[8] Through this crystal structure it was concluded that the cyclization is initiated by a carboxylic acid whose conjugate base would be greatly stabilized by the hydrogen bonding available in the surrounding environment. Furthermore, enzymatic aryl groups were positioned along the pocket in order for there to be cation-π stabilization of any intermediates. The existence of discrete cation intermediates has not yet been confirmed or denied but the large quantity of aromatic residues along the active site suggests that they stabilize positive charges that may develop during cyclization. Further investigation by Hoshino showed that when the phenylalanine at F365 was replaced with the non-aryl (and therefore non-cation stabilizing) alanine residue, only bicyclic compounds from partial cyclization were generated.[9] Also consistent, when the phenyl alanine residue was replaced with the more electron rich tyrosine a 41 fold increase in rate was observed.[10]

[7] Rajamani, R.; Gao, J. *J. Am. Chem. Soc.* **2003**, *125*, 12768-12781.
[8] Reinert, D. J.; Balliano, G.; Schulz, G. E. *Chem. Biol.* **2004**, *11*, 121-126.
[9] Hoshino, T.; Sato, T., *Chem. Commun.* **2002**, 291-301.
[10] Hoshino, T.; Sato, T. *Chem. Commun.* **1999**, 2005.

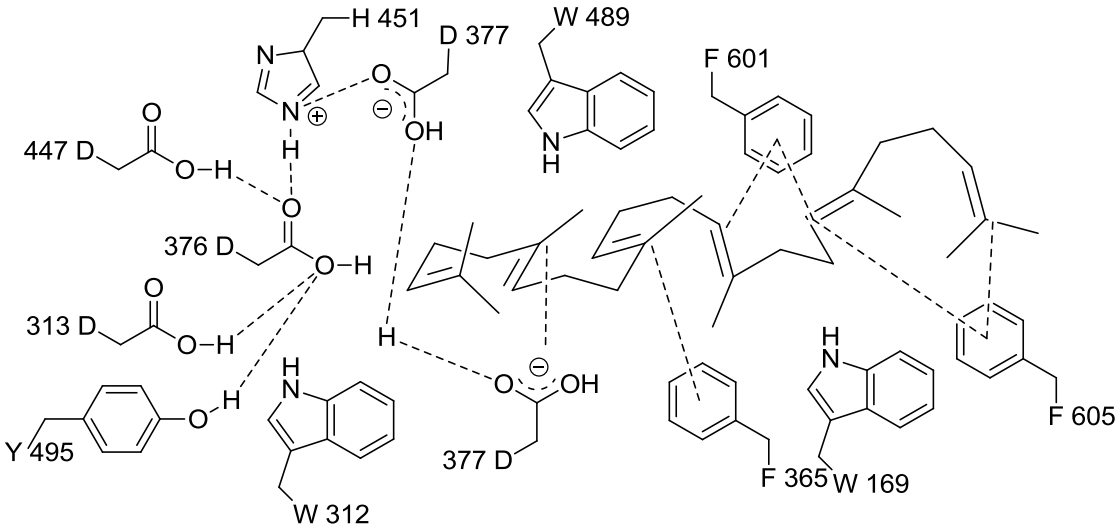


Figure 1.3: Enzyme pocket of squalene-hopene cyclase

This experimental data suggests that the cyclization of the C-ring undergoes first the formation of a 5-membered ring and the generation of the more stable Markovnikov cation followed by a subsequent ring expansion providing the observed product and setting the stage for the cyclization to continue (Figure 1.4, C to D). The cyclization is terminated when after E ring formation, the cation is finally quenched via deprotonation of an adjacent hydrogen providing the alkene product.

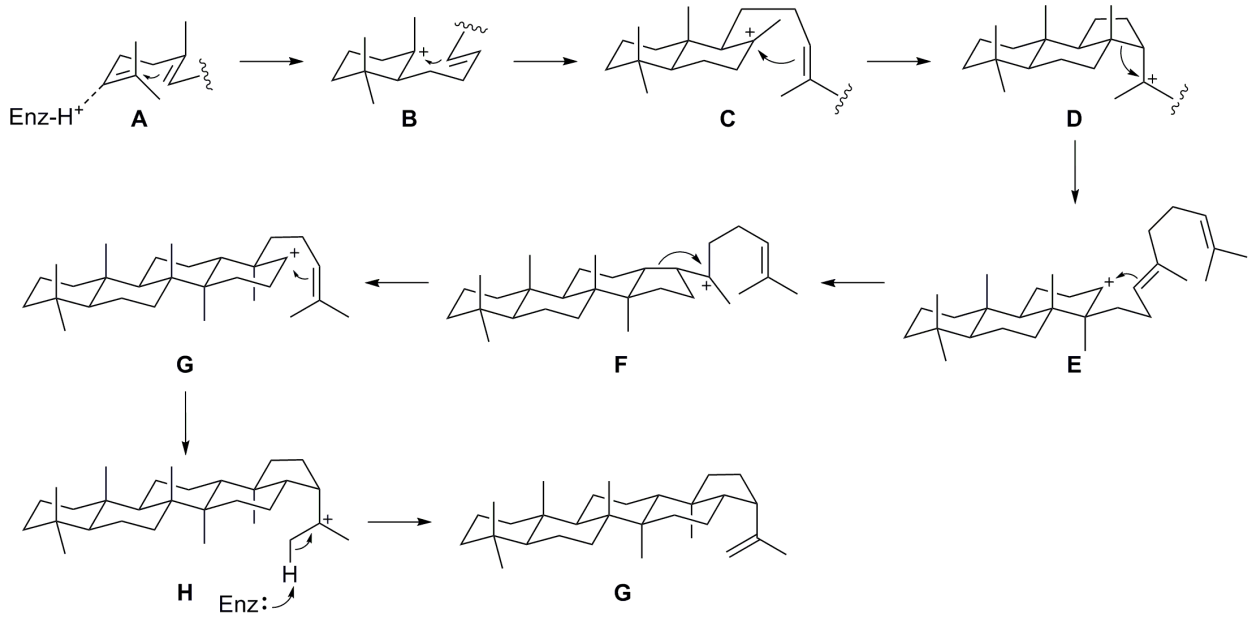


Figure 1.4: Step by step mechanism for the bio-transformation of squalene to hopene

Classic Approaches to the Biomimetic Synthesis of Terpenoids

Many biomimetic studies have been performed to explain how this process works and explore how it can be replicated in a laboratory setting. The Stork-Eschenmoser Hypothesis[11,12] (independently proposed by both Stork and Eschenmoser in 1955) greatly influenced the synthetic strategies taken by researchers synthesize this class of natural products. The Stork-Eschenmoser Hypothesis states that in a polyolefin cyclization, an E alkene leads to the kinetically favored trans ring juncture and a Z alkene leads to a cis ring juncture (Figure 1.5). This leads to the common trans-anti-trans relationship seen when at least three rings are formed. Being able to predict and install multiple stereo-centers in this manner shows just how powerful of a transformation this truly is.

[11] Stork, G.; Burgstahler, A. W., *J. Am. Chem. Soc*. **1955,** *77*, 5068-5077.
[12] Eschenmoser, A.; Arigoni, D., *Helv. Chim. Acta* **2005,** *88*, 3011-3050.

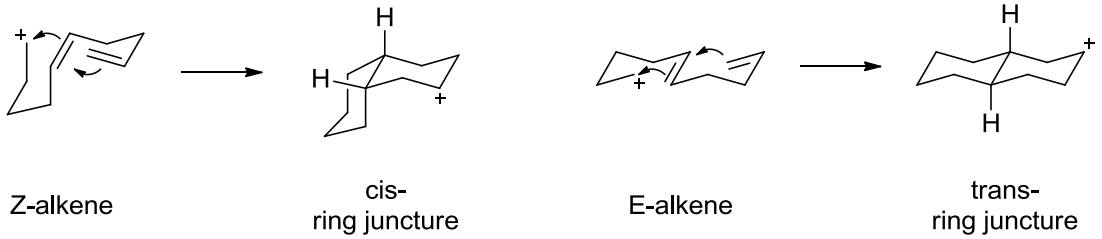


Figure 1.5: Proposed kinetic products predicted by the Stork-Eschenmoser hypothesis

The Stork-Eschenmoser postulate was not immediately verified due to the limited ability to initiate cyclizations. Trying to recreate the enzymatic conditions to start cycliztion by adding acid to polyolefin was not successful. Even using multiple equivalents of different strong acids only provided trace amounts of product (Figure 1.6) and various isomerizations.[13]

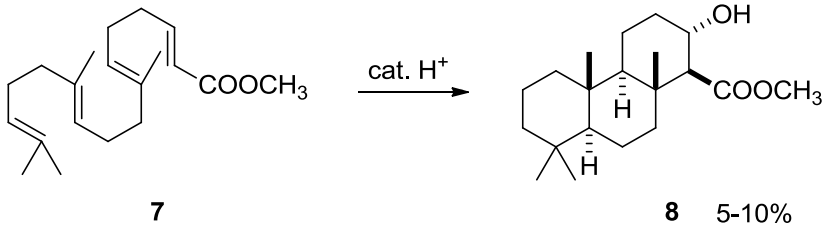


Figure 1.6: Acid catalyzed cyclization attempts

This led to W. S. Johnson investigating whether or not using cation-olefin cyclizations would prove to be a viable way to synthesize natural products. While his first experiments were also discouraging in terms of yield, he did provide the first demonstration that cationic polyolefin cascades would behave as Stork and Eschenmoser proposed (Figure 1.7). Using olefinic sulfonate ester solvolysis, Johnson was able to generate a cation capable of initiating a polyolefin cascade to form bicyclic products.[14]

[13] Eschenmoser, A.; Felix, D.; Gut, M.; Meier, J.;. Stadler, P. "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols," G. E. W. Wolstenholme and M. O'Conner, Ed., J. and A. Churchill, Ltd., London, 1959.
[14] a) Bartlett, P. A. *Asymmetric Synthesis, Vol. 3* (Ed.: J. D. Morrison), Academic Press, New York, **1984**, pp. 341-409. b) Bartlett, P. A. *Asymmetric Synthesis, Vol. 3* (Ed.: J. D. Morrison), Academic Press, New York, **1984**, pp. 411-454.

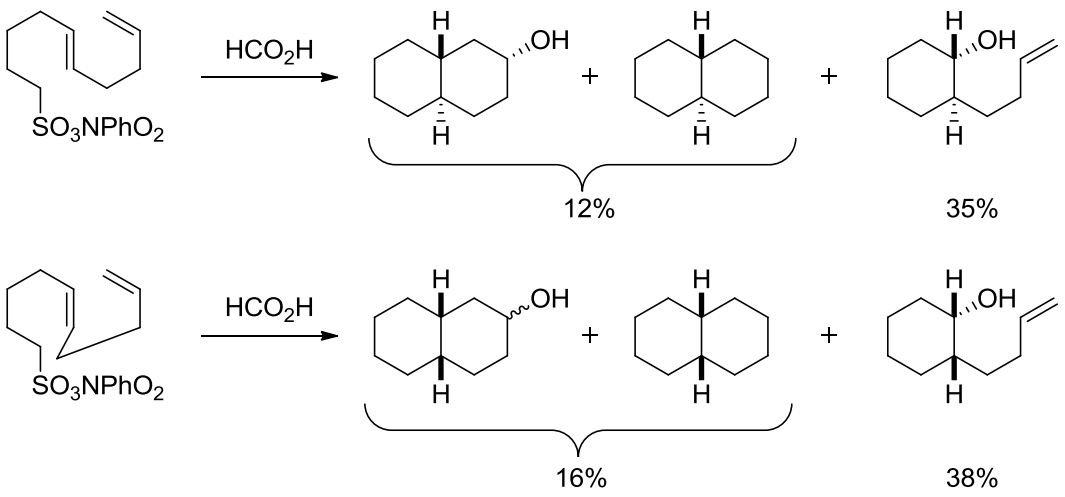


Figure 1.7: Evidence for the Stork-Eschenmoser hypothesis (W. S. Johnson)

Johnson soon discovered the acetal moiety to be a more favorable initiating functional group and began synthesizing natural products in earnest. Through his use of alkyne and allyl silane terminators, Johnson soon became the first author to report a pentacyclization (Figure 1.8) en route to the synthesis of (±)-Sophoradiol.[15] And although he was able to diastereoselectively generate many natural products, only through the creative use of pro-chiral functional groups and initiation by the opening of a chiral acetal was he able to generate enantioselective products (Figure 1.9).[16]

[15] Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324-2335.
[16] Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1-8.

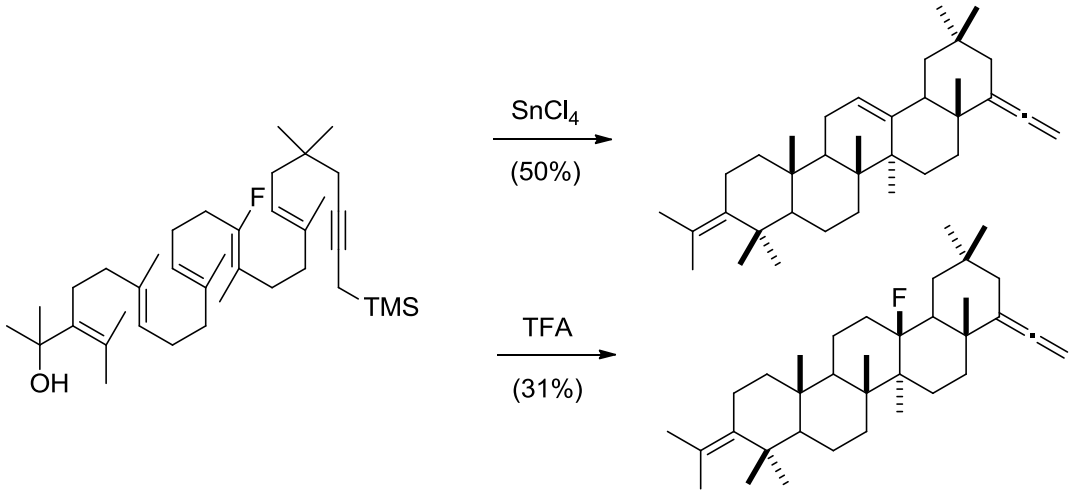


Figure 1.8: First reported pentacyclizations by Johnson

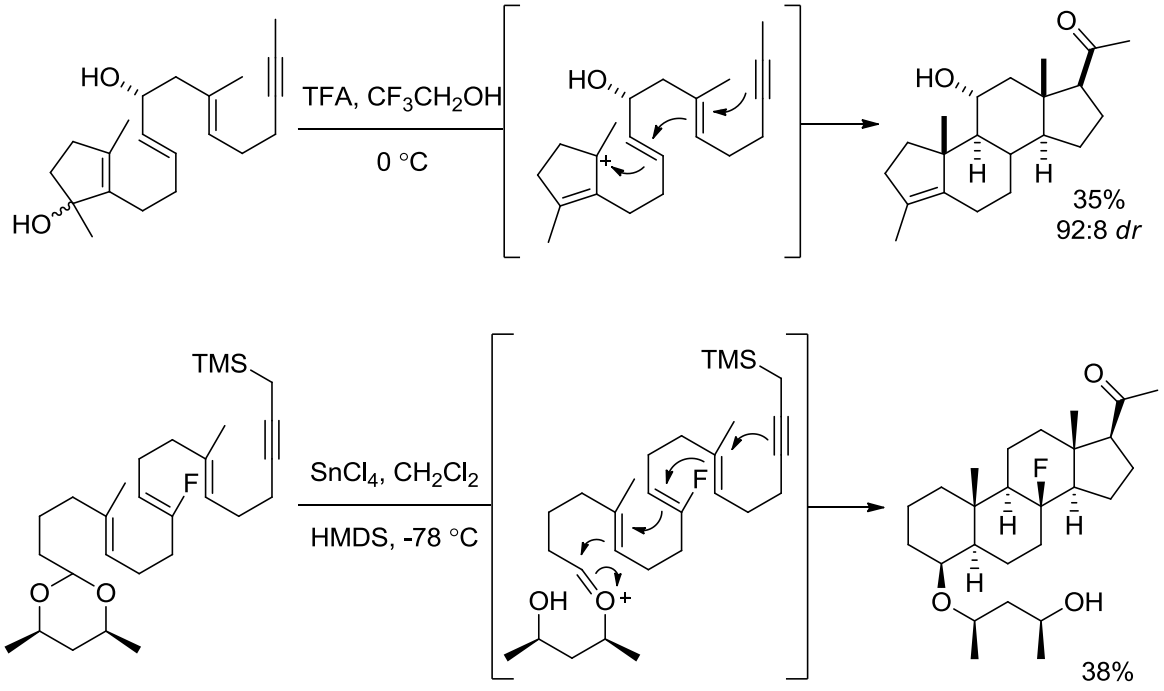


Figure 1.9: First enantioselective cyclizations using prochiral functional groups

Van Tamlen followed with using cation-olefin cascades to generate natural products.[17] He took advantage of his compounds being in solution versus being in an enzyme pocket and advanced the use of non-natural substrates.[6] By manipulating the

[17] van Tamelen, E. E.; Willet, J.; Schwartz, M; Nadeau, R. *J. Am. Chem. Soc.* **1966**, *88*, 5937-5938.

substrate, he was able to generate various multi-cyclic products with an arrangement of chair and boat rings.[18] This early work in substrate manipulation showed that methyl and hydride shifts were possible and likely to occur naturally with minimal enzyme assistance. (Figure 1.10)[19]

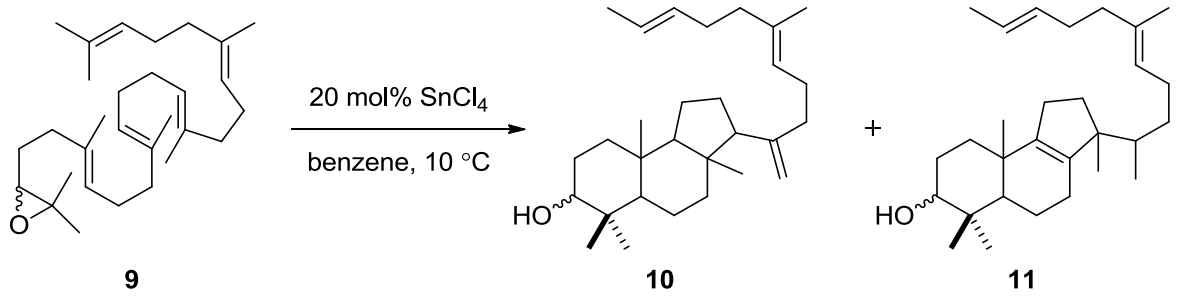


Figure 1.10: van Tamelen's work showed that certain rearrangements and shifts were still possible outside of an enzymatic environment

Modern Lewis Acid Approaches

Building on the work pioneered by Johnson and van Tamlen, Yamamoto performed the first enantioselective biomimetic cyclization of a polyprenoid using the Lewis acid-assisted chiral Brønsted acid **12**.[20] While this work showed that catalytic enantioselective cyclizations were possible, there were still several limitations. In addition to requiring a super-stoichiometric amount of catalyst, the substrates were limited to chains terminated with nucleophiles such as alcohols, and electron rich aryl rings. When using the more nucleophilic alcohol terminators, yields and diastereoselectivities were modest. The substrates with aryl terminators did procede diastereoselectively but resulted in mostly monocyclization (Figure 1.11).[21] They were able to convert most of the partially cyclized compound to the desired

[18] van Tamelen, E. E.; James, D. R. *J. Am. Chem. Soc.* **1977**, *99*, 950-552.
[19] van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152-158.
[20] a) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906-4907. b) Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *121*, 8131-8140.
[21] a) Ishihara, K; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505-1506. b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J Am. Chem. Soc.* **2002**, *124*, 3647-3655.

product by adding two more steps to the synthesis.[22] After several iterations of catalyst improvements and optimizations, the major drawbacks of this system, including partial cyclization, have still not been fully addressed.[23]

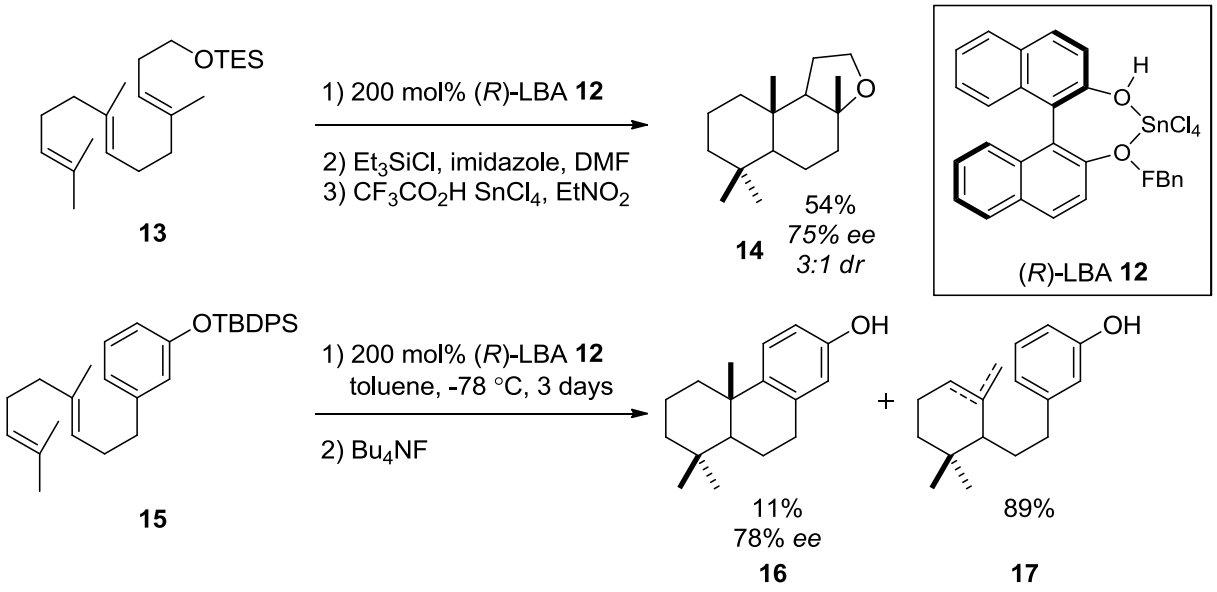


Figure 1.11: Yamamoto's Lewis acid assisted Brønsted acid catalysis

Similar to the Lewis acid promoted Brønsted acid catalysis was the development of a nuclophilie promoted activation of *N*-halosuccinimides.[24] Through the use of a chiral phosphoramidite and an electrophilic halide source, Ishihara was able to generate an ionic species capable of initiating cyclization. Similar to the previous Lewis acid promoted work, the main product of the cyclization was mono-cyclization, i.e. premature termination of the cation-olefin chain. After starting material was consumed, additional reagents were added to the reaction mixture in order to transform the monocyclic product to the desired one. While high *ee*'s (up to 99%) and high yields (up to 95%) were obtainable, they were mutually

[22] 1)Ac_2O, 2)BF_3Et_2O
[23] Kumazawa, K.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2004**, *6*, 2551-2554.
[24] Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900-903.

exclusive. The best compromise of the two resulted in 58% yield and 91% *ee* (Figure 1.12). Despite the monocyclization limitation, this system was able to functionalize the product in addition to initiating the cyclization. This additional functionality increases the value of the work despite the lack of complete cyclizations.

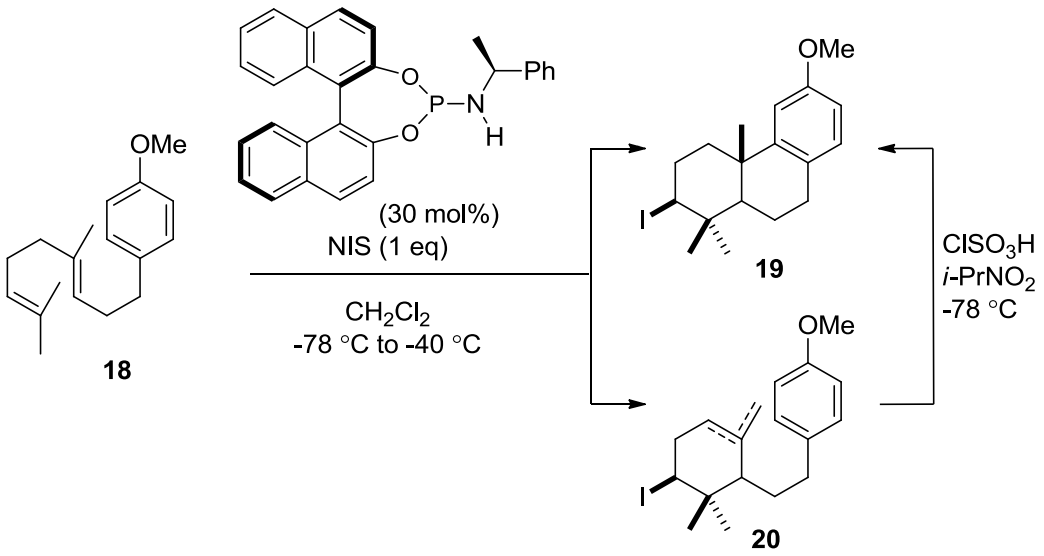


Figure 1.12: Cyclization by nuclophilie promoted activation of *N*-halosuccinimides

The state of the art in Lewis acid catalyzed polyolefin cyclizations has been developed by Corey and Surendra. They have made several updates to their system that has allowed them access to many natural products.[25] They began with using three equivalents of $MeAlCl_2$ in order to activate an epoxide and initiate a diastereoselective cyclization (Figure 1.13 A).[26] These tri- and tetracyclic forming cyclizations provided for the formal synthesis of germanicol and other pentacyclic triterpenes. Their subsequent work improved on these methods by using indium tribromide to initiate the cyclization of an alkyne polyolefin. By using a starting material with a chiral bulky functional group, they generated products that were mostly stereoretentive at the functional site and still diastereoselective (Figure 1.13

[25] Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 13928-13929.
[26] Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865-8869.

B).[27] Most recently, they improved upon the Lewis acid assisted Brønsted acid catalysis of Yamamoto by using (R)-BINOL-$SbCl_5$ to consistently generate over 70% yield with no mention of partial cyclization (Figure 1.13 C).[28] Even with these improvements, many of the limitations associated with Lewis acid assisted catalysis were still persistent. Substrates were limited to aryl terminating groups and high catalyst loading was required. Transforming these cyclized products to natural products often required the reduction of the aryl terminating ring to match the compounds found in nature.[26]

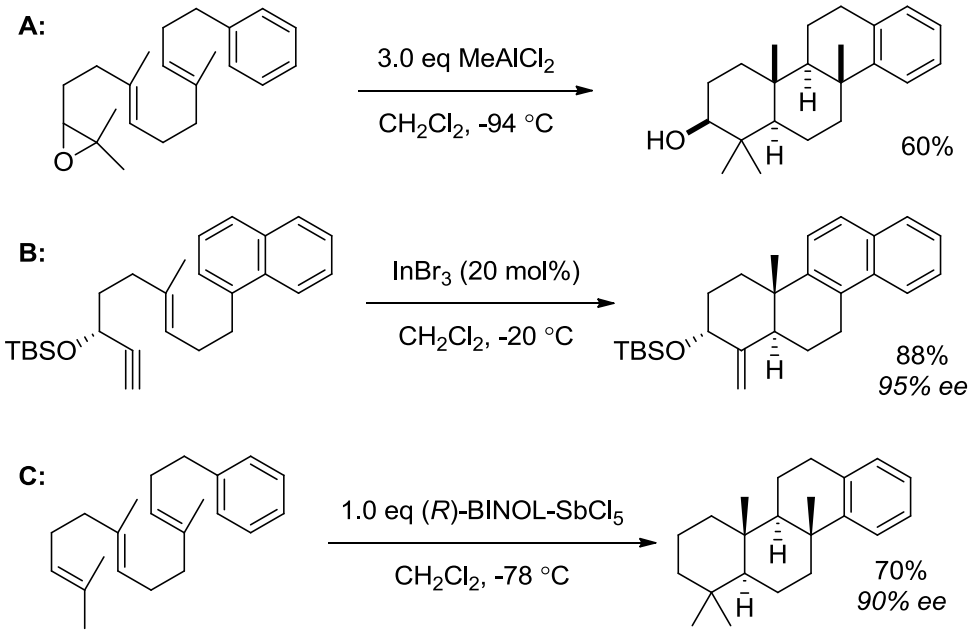


Figure 1.13: Several iterations of Lewis acid assisted catalysis by Corey and Surendra

Transition Metal Catalyzed Cyclizations

Attempts to create better initiators led researchers to investigate transition metals. Finding one that preferentially coordinates to the starting olefin would give it positive character and allow it to initiate cyclization. Using transition metals could allow for new catalytic pathways and also opens up the potential for further functionalization of the

[27] Surendra, K.; Qiu, W.; Corey, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 9724-9726.
[28] Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2012**, *134*, 11992-11994.

cyclization products. The traditional examples of thallium[29] and selenium[30] were used with only limited success. The first major advancement utilized mercuric salts as the initiator.[31] An electrophilic mercury salt could coordinate to the terminal alkene and thus start the cyclization. The resulting cation could then be quenched via the base assisted deprotonation at an adjacent carbon center resulting in a double bond. The mercury could then be replaced with a hydrogen, hydroxyl, or halogen allowing for more reactivity beyond cyclization. This system was characterized by its own set of limitations. The cyclization went through a step-wise mechanism and the early addition of a nucleophile would result in a mix of mono-, bi-, and tricyclic products. In addition, the mercury was not very selective for a terminal alkene over the internal options.[32] This created internal alkene isomerization as well as allowed for initiation at an internal alkene and cyclization to proceed from there.

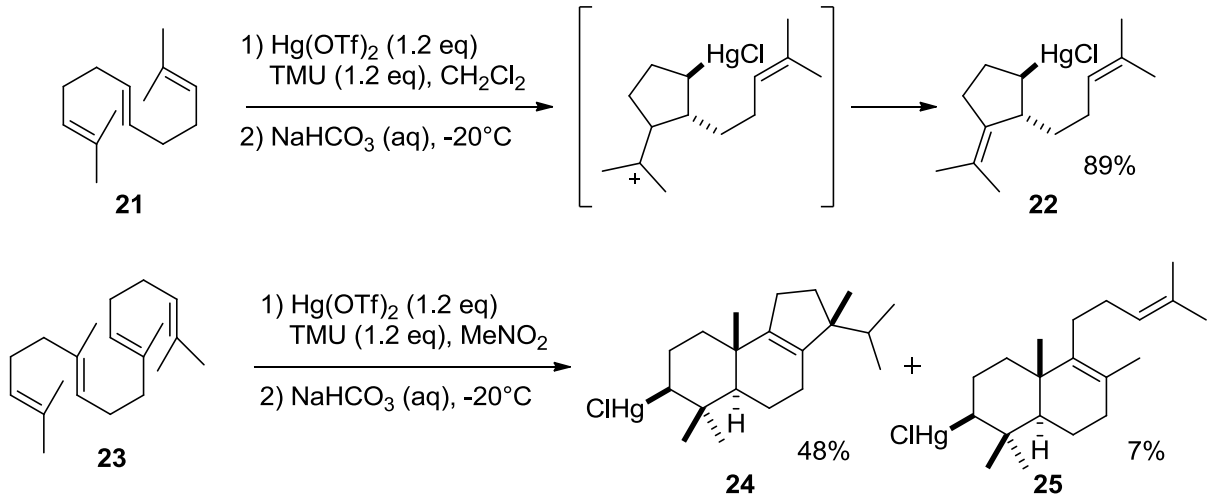


Figure 1.14: Nishizawa's mercuric salt iniated polyolefin cyclizations

Mercury salts have not yet been used successfully to catalyze the bio-like substrates shown previously but they have been shown to be very efficient at initiating cyclizations of

[29] Yamada, Y.; Nakamura, S.; Iguchi, K.; Hosaka, K., *Tett. Lett.* **1981,** 22, 1355-1356.
[30] Wirth, T., *Angew. Chem. Int. Ed.* **2000,** 39, 3740-3749.
[31] Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806-813.
[32] Takao, H.; Wakabayashi, A.; Takahashi, K.; Imagawa, H.; Sugihara, T.; Nishizawa, M. *Tett. Lett.* **2004**, *45*, 1079-1082.

similar compounds. By switching the desired coordinating alkene to an alkyne, the mercuric salt is significantly more proficient at initiating a cyclization when a nucleophilic terminating group was in place (Figure 1.15). The resulting vinyl-mercury could then be protodemetallated and the catalyst regenerated. Like the other catalytic work shown to date, strong nucleophiles (such as alcohols and electron rich aryl groups) were required to complete the cyclization.[33]

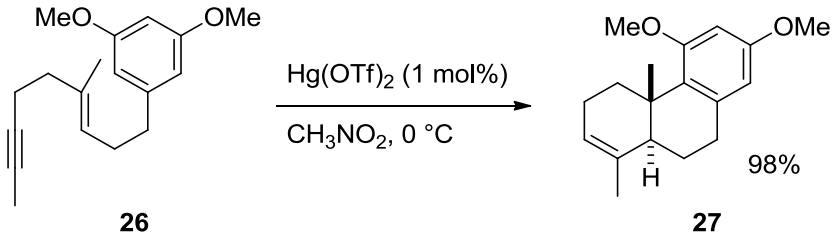


Figure 1.15: Mercury iniated catalytic cyclization terminated by electron rich aryl

Coordination of alkynes allows alternative electrophilies to initiate poly-ene cyclizations. Gold has been demonstrated to be an effective catalyst, albeit with the same limitations requiring nucleophilic terminating groups.[34] Many other systems have been developed[35] as well but each has resulted in similar limitations to the examples discussed previously.

Alkene Activation by Electrophilic Transition Metals

There are few transition metals with the combination of features that let them perform the electrophilic activation of alkenes that is required to initiate a polyolefin cyclization. Those that do are capable of forming a metal-carbon sigma bonded species, which has the

[33] a)Nishizawa, M.; Takao, H.; Yadav, V. K.; Imagawa, H.; Sugihara, T. *Org. Lett*. **2003**, *5*, 4563-4565. b) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451-453.
[34] a) Sethofer, S. G.; Mayer, T.; Toste, F. D., *J. Am. Chem. Soc.* **2010**, 132, 8276-8277. b) Pradal, A.; Chen, Q.; Faudot dit Bel, P.; Toullec, P. Y.; Michelet, V., *Synlett* **2012**, 74-79.
[35] a) Liskin, D. V.; Sibbald, P. A.; Rosewall, C. F.; Michael, F. E., *J. Org. Chem.* **2010**, *75*, 6294-6296. b) Cannon, J. S.; Olson, A. C.; Overman, L. E.; Solomon, N. S., *J. Org. Chem.* **2012**, *77*, 1961-1973. c) Li, B.;Lai, Y. C.; Zhao, Y.; Wong, Y. H.; Shen, Z. L.; Loh, T. P. *Angew. Chem. Int. Ed.* **2012**. *51*, 10619-10623.

potential to mediate subsequent reactivity under the control of the metal, substrate, and co-reagents. Palladium and platinum have both shown a propensity to catalyze the addition of amines and other nucleophiles to unactivated alkenes.[36] In addition, cationic platinum(II) alkene complexes have been shown to undergo nucleophilic addition more readily then neutral or anoionic complexes with their products tend to be more stable.[37]

Due to the relatively high electron density at the metal center, the double bond character of the coordinated alkene is considerably reduced. The coordinated alkene can be seen as a metal-stabilized carbocation by slipping from an η^2 to an η^1 coordination mode. This makes the alkene very susceptible to nucleophilic attack as shown by Vitagliano with the activation of ethylene using a tridentate PNP ligated palladium(II) or platinum(II) complex (Figure 1.16).[38]

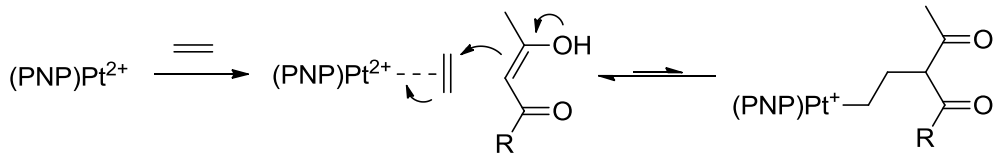


Figure 1.16: Alkene activation followed by nucleophilic attack

Using the properties expressed by palladium(II) and platinum(II) species, Widenhoefer has reported both intra- and intermolecular nucleophilic addition to alkenes coordinated onto platinum dichloride (Figure 1.17).[39] The monocyclization products that are produced from the intramolecular hydroarylation reactions show the potential for using platinum as the initiator of longer polyolefin cascade reactions.

[36] Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2007**, *46*, 4042.
[37] Hahn, C. *Chem. Eur. J.* **2004**, *10*, 5888-5899.
[38] Cucciolito, M. E.; D'Amora, A.; Vitagliano, A., *Organometallics* **2010,** 29, 5878-5884.
[39] Liu, C.; Bender, C. F.; Han, X.; Widenhoefer, R. A. *Chem. Commun.* **2007**, 3607-3618.

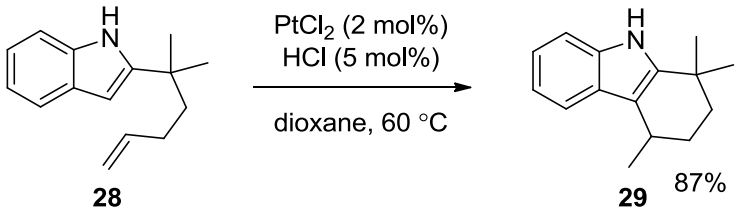


Figure 1.17: Dicationic platinum initiated nucleophilic attack on an alkene

Electrophilic Metal Catalysis in the Gagné Lab

Initial investigations into the ability of dicationic platinum species to mediate polyolefin cyclizations resulted in 1,6-diene cyclosiomerizations (Figure 1.18).[40] Using a tridentate ligand to inhibit beta-hydride elimination allowed for the rearrangement to proceed after the initial cyclization and cyclopropanation to proceed instead of a default beta elimination and monocycle formation. Further investigations into using a P_2P ligand variant allowed for enantioselective cyclizations.[41]

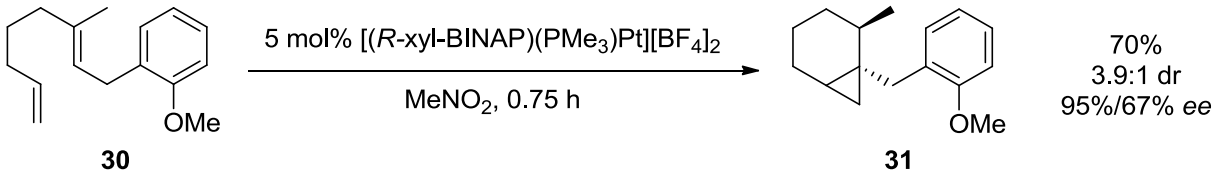


Figure 1.18: Platinum catalyzed 1,6-diene cycloisomerization

By slightly modifying the substrate and giving it a nucleophilic terminus, the originally desired reactivity was achieved. Thus, a dicationic platinum complex was able to quickly and efficiently coordinate to the terminal alkene and give the desired cyclized product (Figure 1.19). Under the investigated conditions, the $(PPP)Pt^{2+}$ catalyst was

[40] a) Kerber, W. D.; Koh, J. H.; Gagné, M. R., *Org. Lett.* **2004**, *6*, 3013-3015. b) Kerber, W. D.; Gagné, M. R., *Org. Lett.* **2005**, *7*, 3379-3381.
[41] Feducia, J. A.; Campbell, A. N.; Doherty, M. Q.; Gagné, M. R., *J. Ame. Chem. Soc.* **2006**, *128*, 13290.

diastereoselective and the platinum-alkyl species was obtained as a single diastereomer. The organic fragment could be removed by reduction with sodium borohydride.[42]

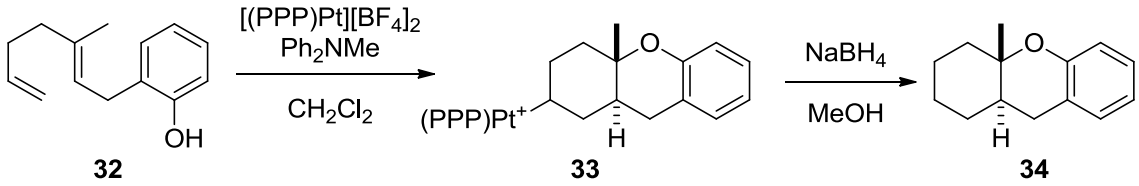


Figure 1.19: Dicationic platinum initiated polyolefin cyclization with protic trap

Transitioning these results to achieve catalytic turnover required several changes to the platinum framework. First, switching to a bidentate ligand created an open coordination site, thus enabling beta-hydride elimination as a viable turnover mechanism after forming the platinum-alkyl.[43] This resulted in the unsaturated alkyl product and a platinum-hydride. Because the metal lacked coordinating X^- ligands (Cl^-, ^-OAc, etc) standard oxidizing agents such as benzoquinone, O_2, and $CuCl_2$ proved ineffective at converting this hydride to a form that was effective at reinitiating catalysis. A solution was found in the hydride abstracting agent triphenylcarbeniumtetrafluoroborate ($TrBF_4$), which proved reactive enough to regenerate the active catalysis. Triphenylmethylether was a convenient source of Tr^+ and a stoichiometric base, due to only becoming active after being protonated by the hydrogen eliminated during the cyclization (Figure 1.20).[44] By changing the bidentate phosphine ligand to a chiral one, enantioselective results were obtainable.[45]

[42] Koh, J. H.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3459.
[43] Campbell, A. N.; Gagné, M. R. *Organometallics* **2007**, *26*, 2788-2790.
[44] Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880-11881.
[45] Mullen, C. A.; Campbell, A. N.; Gagné, M. R. *Angew. Chem. Int Ed.* **2008**, *47*, 6011-6014.

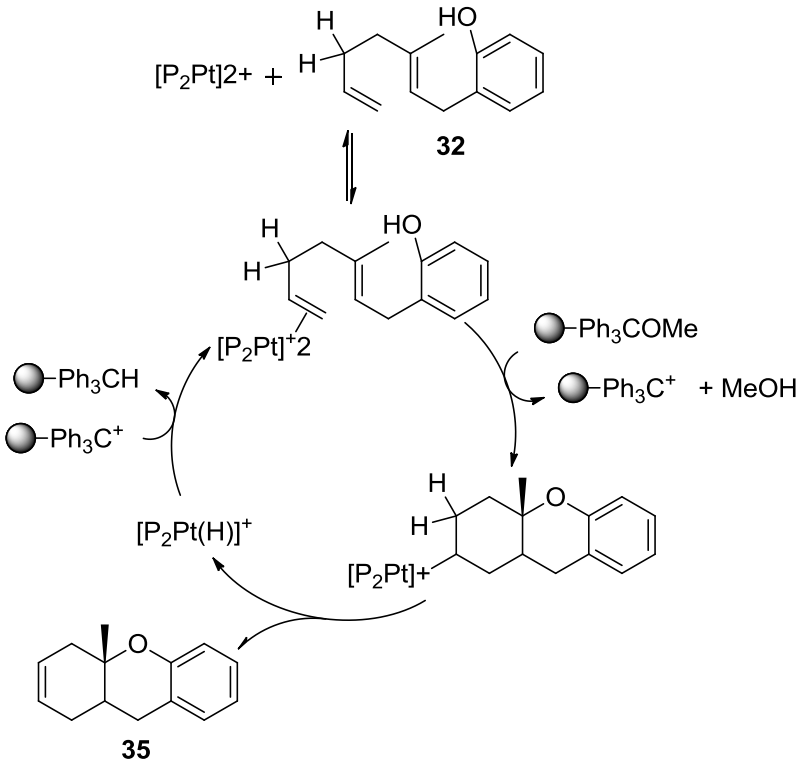


Figure 1.20: Proposed mechanism for the platinum catalyzed cyclization of polyolefins

Research Objectives

Lewis acid catalysts and Lewis acid assisted Brønsted catalyts have been shown to cyclize polyolefin chains, but with many limitations. The purpose of the reasearch reported herein was to show that bio-like simple alkene termini are feasible. To prove the feasibility of using electrophilic platinum complexes to cyclize poly-olefins terminated in biomimetic alkenes, complexes designed to not turnover by forming stable platinum-alkyl products were investigated (Chapter 2). Investigations into substrate scope and other mechanistic properties were additionally performed. The considerable challenge of rendering these reactions catalytic in platinum was also explored using modified reaction conditions (Chapter 3). Based on recent developments concerning the oxidation of platinum-alkyls, an alternative turnover mechanism was explored (Chapter 4).

Chapter 2 : Terminating Platinum-Initiated Cation-Olefin Reactions with Simple Alkenes

Investigations into Platinum Initiated Polyolefin Cyclizations

While there have been many cyclization techniques developed for polycyclic terpenoids, the few examples that successfully cyclize hydrocarbon chains are generally very limited in scope or give multiple products. With the exception of the mercury (II) reagents developed by Nishizawa, which are prone to rearrangement and partial cyclization, few electrophilic metal catalysts cyclize poly-enes with bio-like alkene terminators. The development of electrophilic metal catalysts which can initiate, cyclize, and terminate poly-enes under ligand control would mark a significant advancement in current polyolefin cyclization methodology.

Expanding upon the previously reported work using platinum to initiate a cation-olefin reaction[40-45] we developed an alkene terminated cation-olefin cascade reaction that is initiated by the dicationic platinum complex [(PPP)Pt][BF_4]$_2$), **36**.[46] Compound **36** selectively initiates cyclizations where the polyene carries a mono-substituted alkene terminus.[47] Studies were performed on the diastereoselective formation of polycyclic products with a broad variety of terminating alkenes which lack the premature termination processes and rearrangements observed when other transition metals were used.

[46] Furstner, A.; Davies, P. W. *Angew Chem. Int. Ed.* **2007**, *46*, 3410-3449.
[47] Hahn, C.; Cucciolito, M. E.; Vitagliano, A. *J. Am. Chem. Soc.* **2002**, *124*, 9038-9039.

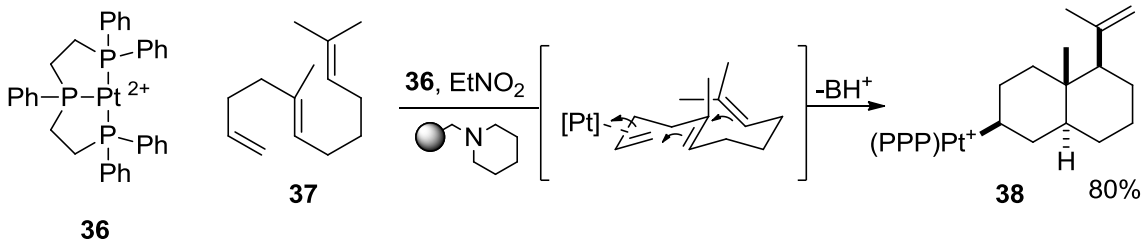


Figure 2.1: Dicationic platinum initiation of a polyolefin

The major challenge in transitioning from poly-enes with a protic trap to all hydrocarbon substrates is the lack of hydrogen bonding between the substrate and base in solution. Computational analysis showed that when a base was hydrogen bonded to the protic terminus and the alkene was in a suitable geometry, the cyclization was highly favorable and virtually barrierless.[48] In contrast, base-free calculations were characterized by high energy intermediates and significantly less favorable thermodynamics. This latter scenario most likely describes the early stages of a poly-ene cascade that terminates with a non-protic group, which in the case of an alkene is not even acidic until the cation is fully formed. The difficulty of productively engaging a Brønsted base at an alkene terminus thus likely explains why most reported alkene terminators consist of vinyl fluorides[49] and vinyl silanes.[6]

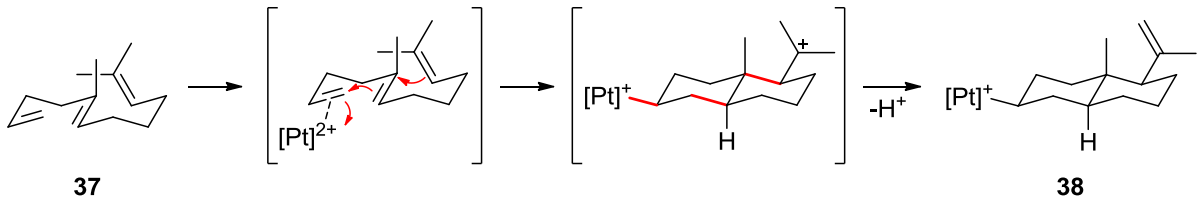


Figure 2.2: Arrow pushing mechanism for the transformation of 37 to 38

Reaction Optimization

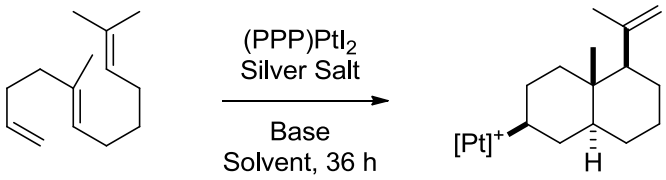
The combination of a polar solvent and base led to an efficient and highly diastereoselective cyclization of triene **37** to **38**. Due to the kinetic cost of generating a

[48] Nowroozi-Isfahani, T.; Musaev, D. G.; Morokuma, K.; Gagné, M. R. *Organometallics* **2007**, *26*, 2540-2549.
[49] Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.***1993**, *115*, 497-504.

discrete tertiary cation the reaction proceeds much more slowly (minutes for protic termini vs. 36 h for **37** to **38**). Further reaction optimization showed that changes in non-nucleophilic base, silver salt, and solvent had little effect on the outcome of the reaction (Table 2.1). As long as an excess of a non-coordinating base was used, there was little difference between reaction times. The resin bound piperidine proved to be most useful due to the ease of removal after the reaction was complete. When having a heterogeneous mixture was problematic (e.g. reactions run in an NMR tube) one of the soluble bases, Ph_2NH or Ph_2NCH_3, could be substituted with no change in reaction times or product purity.

Variations in silver salt also resulted in little change with the lone exception being when silver oxide was used. While there was no change in reaction time, the use of silver oxide resulted in a change in purity of the product with trace amounts of 4 isomers being visible by phosphorus NMR. A polar solvent was necessary due to the poor solubility of the platinum compounds. While methylene chloride provides a fast reaction time, it resulted in a small amount of the triphos-platinum-chloride adduct ([(PPP)Pt-Cl][BF_4]) being formed when the substrates with long reaction times were used. This could be combated by the addition of a labile ligand such as pentafluorobenzonitrile. Reaction times were slightly longer when nitromethane was used but the product was cleaner. Nitroethane brought the desired balance of accelerated reaction times and clean product.

Table 2.1: Reaction Optimization While Varying Solvent, Silver Salt, and Base



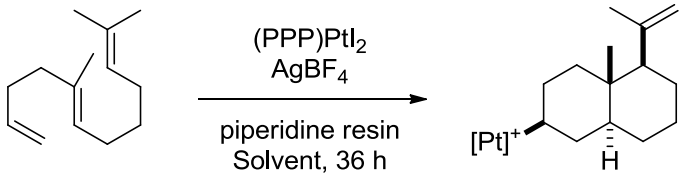
37 **38**

Entry	Silver Salt	Base	Solvent	Time to 100% Conversion[a]
1	$AgBF_4$	Ph_2NH	$EtNO_2$	36 h
2	$AgBF_4$	Ph_2NCH_3	$EtNO_2$	36 h
3	$AgBF_4$	piperdinomethyl resin	$EtNO_2$	36 h
4	$AgBF_4$	2,6-^{t}bu-pyridine resin	$EtNO_2$	36 h
5	Ag_2O	Ph_2NCH_3	$EtNO_2$	36 h
6	$AgPF_6$	Ph_2NCH_3	$EtNO_2$	36 h
7	$AgBF_4$	Ph_2NCH_3	CD_2Cl_2	36 h
8	$AgBF_4$	Ph_2NCH_3	CD_3NO_2	36 h

Reaction conditions: Substrate (10 µmols) and base (30 µmols) were added to a solution of $(PPP)PtI_2$ (10 µmols) and silver salt (25 µmols) in solvent (0.5 mL) that had been filtered to remove AgI. [a]Determined by GCMS analysis.

Substrate concentration was the last area where optimizations were necessary. Not surprisingly it was found that higher substrate concentration resulted in a faster reaction completion. When 1.2-1.5 equivalents of substrate was used, reaction times were moderately longer and small amounts of platinum byproducts were observed. Two equivalents of substrate relative to platinum was found to give the best combination of short reaction times and full consumption of $(PPP)Pt^{2+}$. Using three or more equivalents continued to decrease reaction time with diminishing returns and was not an efficient use of starting materials.

Table 2.2: Effects of Substrate Concentration on Reaction Time



37 38

Entry	Equivalents of Substrate	Time to 100% Conversion (h)[a]
1	1.2	44
2	1.5	42
3	2.0	36
4	3.0	34
5	5.0	33
6	10.0	32

Reaction conditions: Substrate and piperidinomethyl polystyrene resin (30 µmols) were added to a solution of $(PPP)PtI_2$ (10 µmols) and $AgBF_4$ (25 µmols) in $EtNO_2$ (0.5 mL) that had been filtered to remove AgI. [a]Determined by ^{31}P NMR.

Crystallographic characterization of **38** pointed to a predictable initiation at the least substituted alkene, a *chair-chair* cyclization conformer, and the intermediacy of an exocyclic tertiary cation that eliminates to give the isopropenyl group (Figure 2.33). Several features are notable in the solid state structure of **38**. The first is the Pt-CH orientation, which positions the C-H vector in the square plane to minimize steric congestion. This rotamer positions the angular CH_3 group near the face of one P-Ph group, which causes an upfield shifting of this CH_3 group in the ^1H NMR (to ~0.1 ppm). This resonance proved to be diagnostic and was observed in each of the described structures.

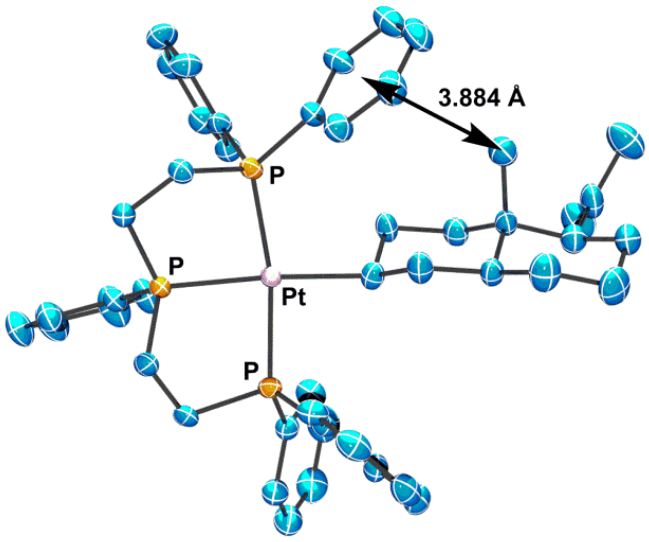


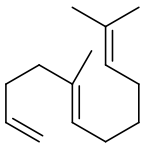
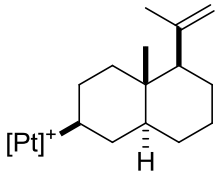
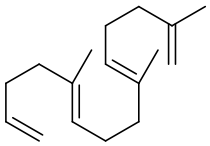
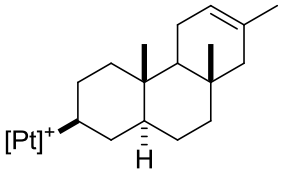
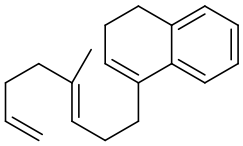
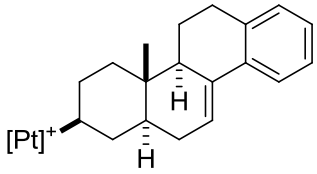
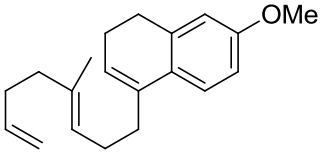
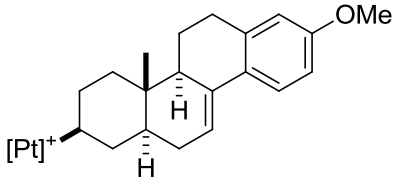
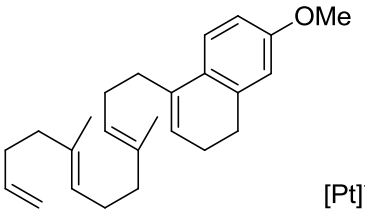
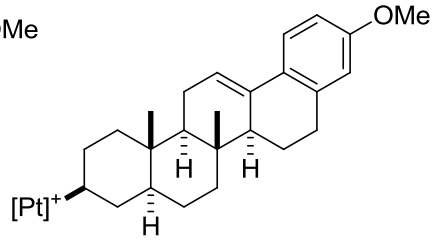
Figure 2.3: X-ray structure of 38 showing the diagnostic interaction between the axial-methyl group and the center of the P-Ph ring.

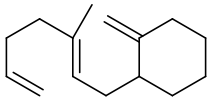
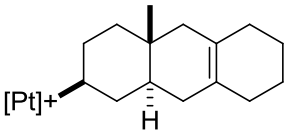
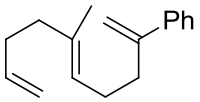
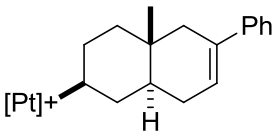
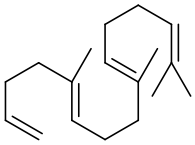
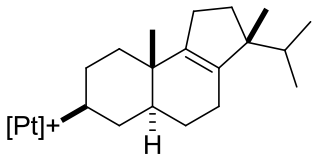
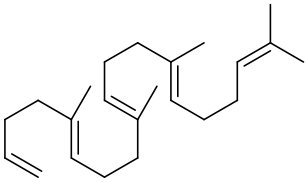
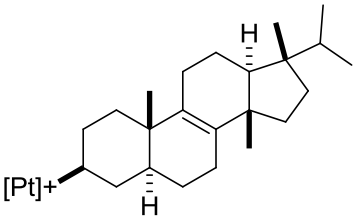
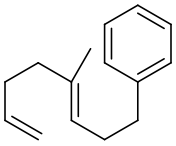
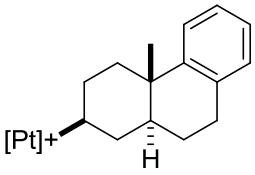
Scope and Observations

A number of poly-enes with terminating tertiary carbocations were examined that varied in the number of rings formed (two-three), the arrangement of the terminating alkene (*endo* versus *exo*-cyclic), and the ring size (Table 2.1). Even more facile than the 6-exo termini were reactions in which the terminating alkene was arranged to react with the 6-endo geometry. These reactions were 2-4 times faster than the 6-exo analog **38**, and provided a number of carbon skeletons. In the case of **40**, the putative tertiary cation, formed from a chair/chair/chair transition state, eliminates to give the more stable C12/13 alkene isomer (Figure 2.4.4). Products that would have arisen from premature quenching of a putative cation at C5 or C9 were not observed (<5%). In most cases, the structure of the resulting Pt-complex was confirmed by X-ray methods.[50]

[50] Crystallographic information is available in Appendix 2.

Table 2.3: Scope of Polyolefin Cyclizations Initiated by Dicationic Platinum Complex 36.

Entry	Substrate[a]	Product[b]	Time (h)	Isolated Yield (%)
1	 **37**	 **38** X-ray	36	80
2	 **39**	 **40**	16	74
3	 **41**	 **42**	16	89
4	 **43**	 **44** X-ray	2	97
5	 **45**	 **46** X-ray	2	95

Entry	Substrate	Product	Time (h)	Isolated Yield (%)
6	 **47**	 **48** X-ray	4	76
7	 **49**	 **50**	12	92
8	 **51**	 **52** X-ray	36	80
9	 **53**	 **54**	36	30
10	 **55**	 **56**	72	38

Reaction conditions: Substrate (200 µmols) and piperidinomethyl polystyrene resin (300 µmols) were added to a solution of (PPP)PtI_2 (100 µmols) and $AgBF_4$ (250 µmols) in $EtNO_2$ (1.0 mL) that had been filtered to remove AgI.

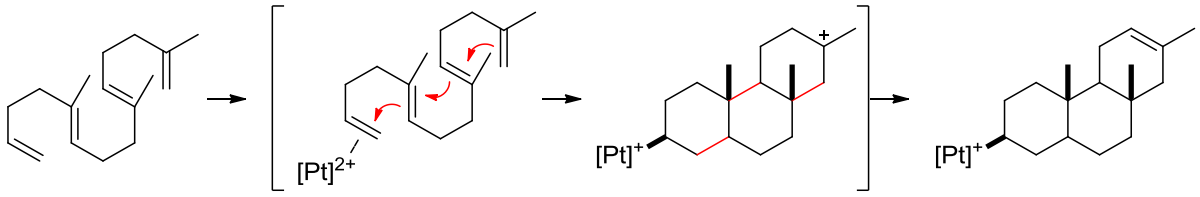


Figure 2.4: Arrow pushing mechanism for the generation of compound 40.

Proving to be even more reactive were the conformationally constrained dihydro-naphthalene terminating groups (**41**, **43**, and **45**), which efficiently converted to the tetra- and pentacyclic products (entries 3-5). The conversion of **43** to **44** was ~4 fold faster than the non-methoxy substituted example (entry 3), suggesting that the nucleophilicity[51] and/or cation stability of the terminus plays a significant role in the reaction kinetics. As judged by comparing the cyclization rates of **43** and **45**, an additional isoprene unit in the main chain does not significantly affect the reaction barrier.

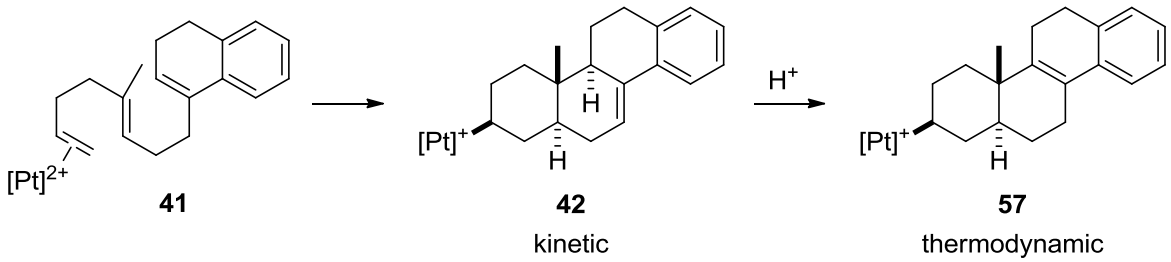


Figure 2.5: Kinetic and thermodynamic products of the cyclization of 41

In the case of **41**, extended reaction times led to partial conversion to the tetra substituted isomer at the B/C ring junction (Figure 2.6).[52] This isomerization could be accelerated by acids, though methane sulfonic acid also caused protodemetallation of the Pt.[53] The more bulky acid $[Ph_2NH_2][BF_4]$ did not produce nearly as much protodemetallation product suggesting that the ligand sterically hindered access to the platinum center. By

[51] Mayr, H.; Kempf, B.; Ofil, A. *Acc. Chem. Res.* **2003**, *36*, 66-77.
[52] The Lewis acid initiated cyclization of terminal epoxy analogue of **X** gave both the tri- and tetrasubstituted alkenes, see reference 26.
[53] Feducia, J. A.; Campbell, A. N.; Anthis, J. W.; Gagné, M. R. *Organometallics* **2006**, *25*, 3114-3117.

contrast, the tertiary cation formed upon cyclization of **47** preferentially eliminates to the more stable tetrasubstituted alkene product **48**.[54]

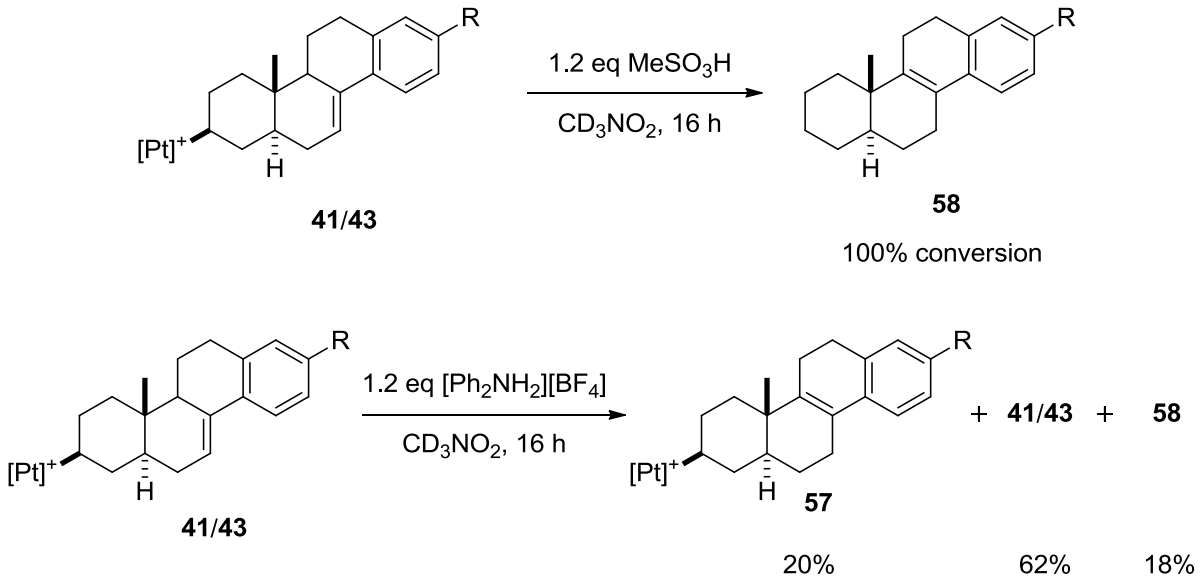


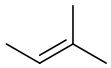
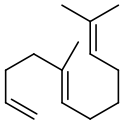
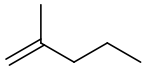
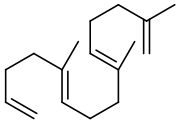
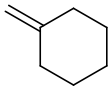
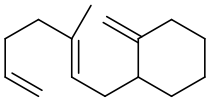
Figure 2.6: Acid initiated protodematallation and alkene rearrangement

Aryl terminating groups made up a significant portion of the termini in the previous reported literature. It was to our surprise that the benzyl terminated substrate **55** did not efficiently convert to the cyclized product. Also in contrast to previous reports using aryl terminated substrates, only one platinum alkyl was generated and characterization proved that the major product was indeed the fully cyclized **56**.

When the reaction times of the substrates in Table 2.3 were compared to the reported nuleophilicity values of analogs of their terminal alkenes, there was a clear correlation.[51] The substrates whose terminal alkene analog had the highest nucleophilicity values also had the shortest reaction times (Table 2.4). Although no analog was available for the phenyl stabilized substrates **41**, **43**, **45**, and **49**, their fast reaction times agree with the principle that high nucleophilicity and cation stabilization are the key to rapid cyclizations.

[54] Feducia, J. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 592-599.

Table 2.4: Comparison of Mayr Nucleophilicity Values[51] to Reaction Time

Analog	N	Substrate	Reaction Time (h)
 **59**	0.71	 **37**	36
 **60**	1.02	 **39**	16
 **61**	1.7	 **47**	4

Thermodynamic Rearrangments and Calculations

An entirely different path was followed when terminating the cascade to a tertiary carbenium ion required a 5-exo geometry. In these cases a clean Wagner-Meerwein rearrangement converted the tertiary cation to the rearranged carbon skeleton of **52** (Figure 2.7), which was confirmed by X-ray analysis.

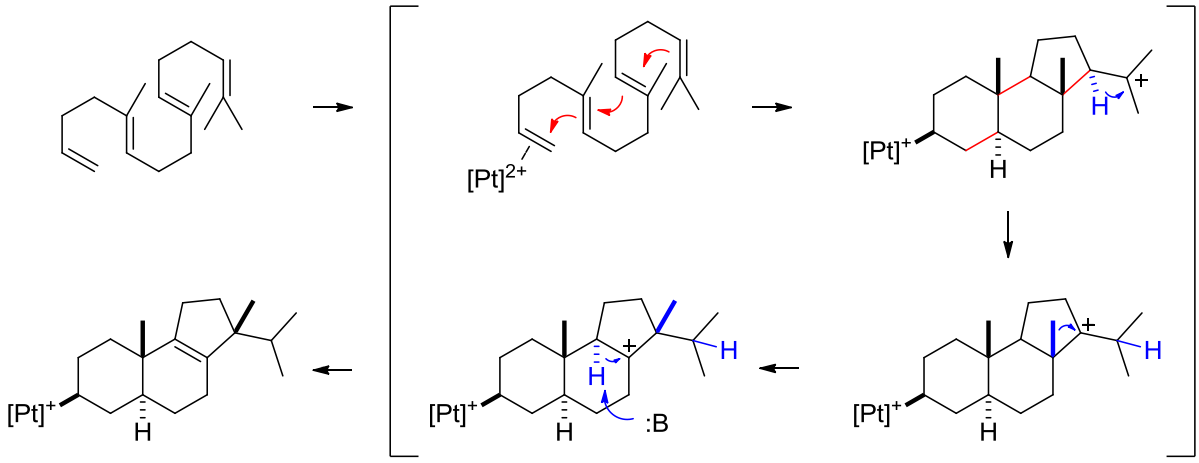


Figure 2.7: Arrow pushing mechanism of the observed Wagner-Meerwein rearrangement

To gain insight into the diverging behaviour of 6-exo and 5-exo terminated reactions, a computational analysis (DFT B3LYP/6-31G*)[55] of the key 1,2-shifts were carried out on simplified model systems (Figure 2.8). Revealing was the differential activation energy for the initiating 1,2-hydride shift, which was 7.3 kcal/mol more favourable for the 5-exo terminated ring systems than for the 6-exo. The subsequent steps were lower in energy suggesting that it is a slower initiating 6-6 1,2-H-transfer that diverts the reaction towards a base induced elimination.

[55] MacSpartan 2008 calculations; energies were uncorrected.

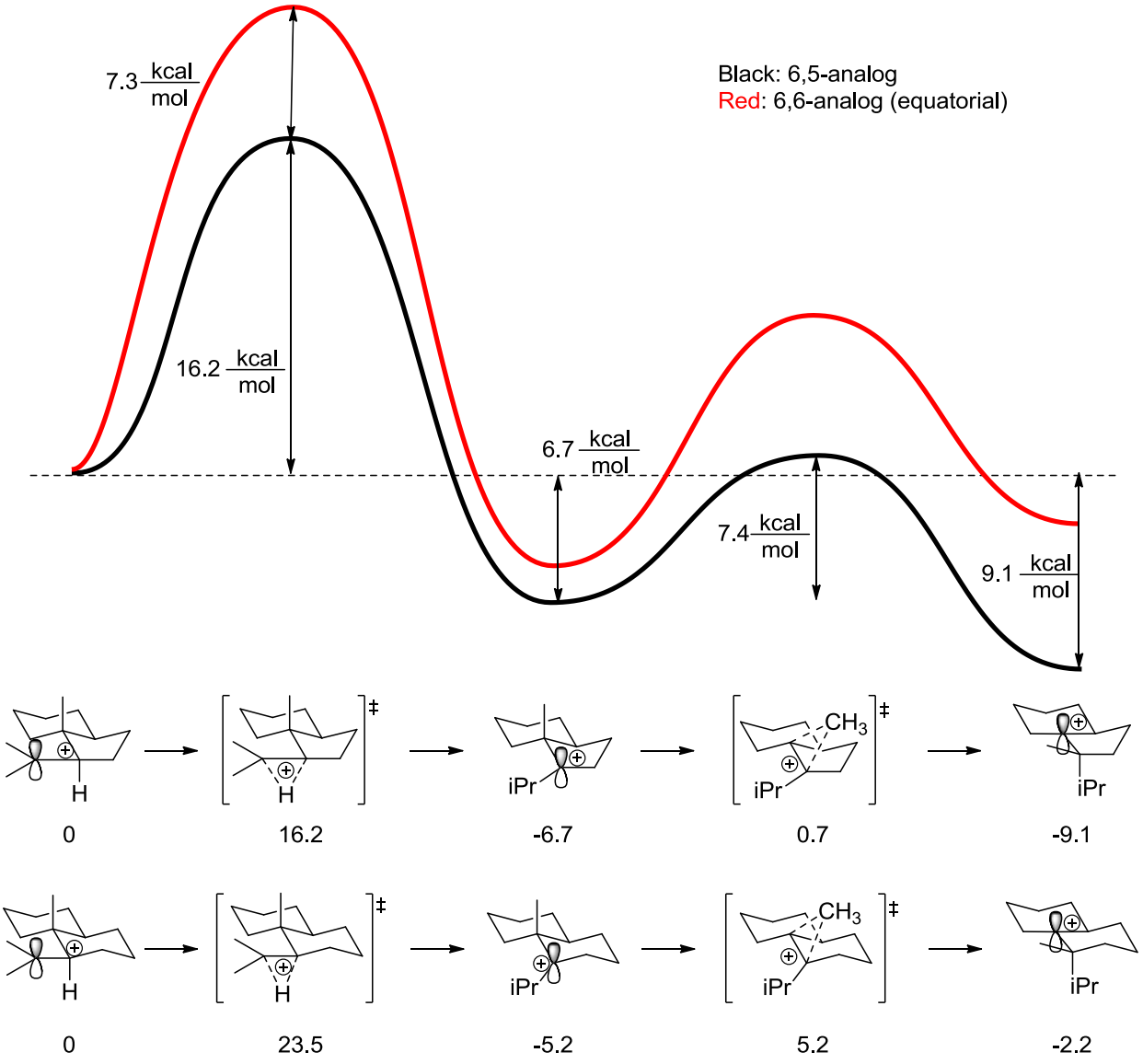
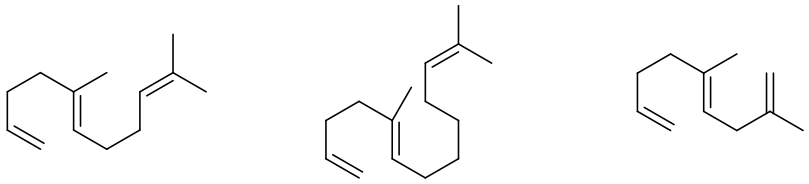


Figure 2.8: A comparison of the 6,5 and 6,6 energies (kcal/mol) along the Wagner-Meerwein reaction coordinate

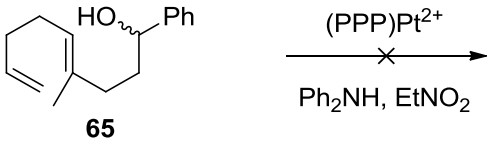
While most of the substrates that were tried reacted successfully, there were a few that never went to completion (Figure 2.9.9). Formation of a 6,5 bicyclic product lacked the requisite drop in relative energy to make up for the lack of a strong enough nucleophile terminator. This was observed for 5-exo and 5-endo compounds. Formation of a 7-exo or 7-endo cyclizations were incomplete no matter how many rings were formed.



62 **63** **64**

Figure 2.9: Unreactive substrates

While this study has only focused on using simple alkene termini, the occasional protic trap terminus was used in order to elucidate whether a pathway was worth pursuing. Compound **65** was synthesized to determine the viability of substrates that could cyclize without going through a tertiary carbo-cation (Figure 2.10). Johnson showed that the methyl on internal alkenes could be in the position shown if a vinyl fluorine was used to stabilize the cation. It was observed that even with the electrophilic platinum driving force, we could not overcome the lack of charge stabilization.



65

Figure 2.10: Unreactive alcohol terminated substrate

Compound **36**, ((PPP)PtI_2) was additionally investigated for its ability to cyclize a squalene analog (**66**) that lacks the terminal methyl groups (Figure 2.11). Although the spectral complexity was significant and more than one isomer was formed, similarities to **52** suggested that the cyclization followed a 6-6-5-exo pathway to a C14 cation, which non-selectively rearranged akin to **51**. Unlike cyclase enzymes, the environment of the terminating cation is not conducive to ring expansion/D-ring annulation.[56] van Tamelen made similar observations in Brønsted-mediated reactions on squalene oxide.[19]

[56] a) Tantillo, D. J.; *Chem. Soc. Rev.* **2010**, *39*, 2847-2854. b) Hess Jr., B. A.; Smentek, L. *Org. Lett*. **2004**, *6*, 1717-1720.

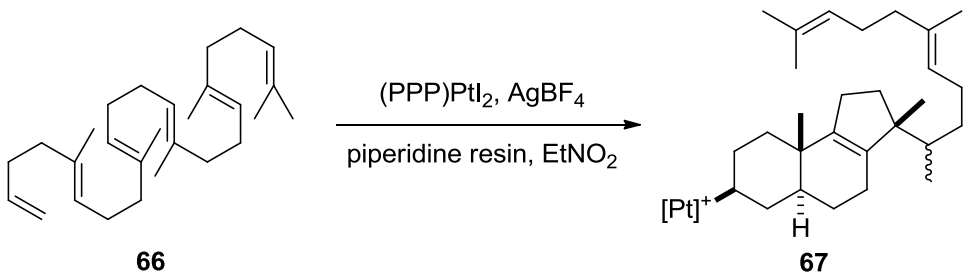


Figure 2.11: Partial cyclization of squalene analog

Enantioselectve Investigation

The viability of performing an asymmetric cascade cyclization was investigated using the chiral P_2PPt^{2+} complex (P_2 = DTBM-SEGPHOS, P = PMe_3) **68**. The combination of a chiral P_2 ligand and an achiral monodentate phosphine has been previously shown to catalyze cyclorearrangment reactions with high ee's.[41] When **68** was reacted with **43** under the standard conditions (Figure 2.12), NMR spectroscopy indicated that a single stereoisomer was obtained (^1H, ^{31}P), ie. the chiral initiator efficiently and diastereoselectively activates a single olefin face. This was in contrast to (R)-BINAP and some other catalysts that did not give high diastereoselectivities in this stoichiometric process. The bulky P_2 ligand did provide one diastereomer but also significantly increased reaction times. When slower substrates were used, the platinum complex would begin to decompose before conversion was complete.

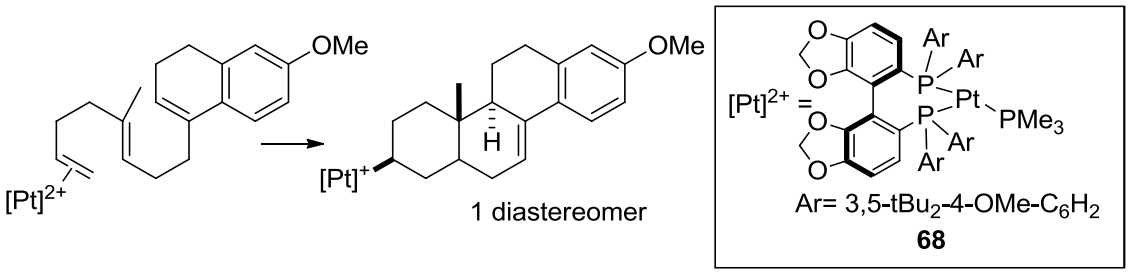


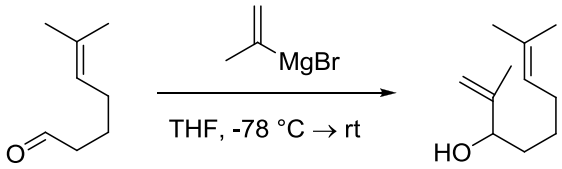
Figure 2.12: Enantioselective cyclization of poly-olefin substrate

Conclusion

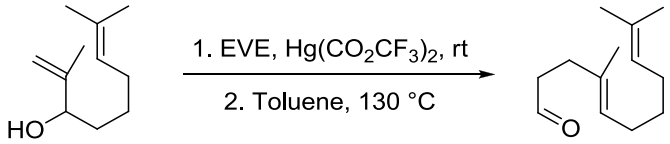
Pt(II) mediated cyclizations have been shown to be succesffuly extended to bio-like simple alkene substrates. The scope of this work reinforces the notion that the nucleophilicity/cation stability of the terminating alkene is crucial. Through the use of different substrate configurations a variety of structures with different carbon skeletons could be obtained. Electrophilic platinum dications are also shown to be unique when compared to their literature counterparts in their ability to activate and mediate the cascade reactivity of poly-ene reactants.

Experimental Section

All reagents were reagent grade quality and used as received from Aldrich unless otherwise indicated. The piperidinomethyl polystyrene resin was purchased from NovaBiochem and used without further purification. All reactions were conducted under inert conditions (Ar or N_2) or in a nitrogen filled glove box unless otherwise indicated. All glassware was oven dried unless otherwise indicated. Anhydrous THF was distilled from sodium/benzophenone prior to use. Anhydrous CH_2Cl_2, ether, and toluene were passed through a column of alumina. Anhydrous diisopropylamine (iPr$_2$NH) and triethylamine (Et_3N) were distilled from CaH_2 prior to use. Anhydrous nitroethane ($EtNO_2$) was distilled from P_2O_5 and degassed by freeze-pump-thaw prior to use. Column chromatography was performed using SilaFlash P60 40-63 μm (230-400 mesh). All NMR spectra were recorded on Bruker Avance 600 MHz, 500 MHz, or 400 MHz spectrometer at STP. All deuterated solvents were used as received from Cambridge Isotope Laboratories, Inc. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR chemical shifts are reported in δ units, parts per million (ppm) relative to the chemical shift of residual solvent or an external standard. ^{31}P reference peak was set at 0 ppm for phosphoric acid (H_3PO_4, 85%) as an external standard. High-resolution mass spectra (HRMS) were obtained using a Micromass Q-Tof Ultima for the organic substrates and a Varian 820-MS for the inorganic cationic complexes.



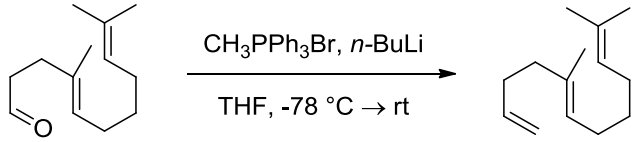
2,8-dimethylnona-1,7-dien-3-ol: A solution of 6-methylhept-5-enal[57] (6.0 g, 48 mmol) in 150 mL THF was added to a solution of isopropenyl magnesium bromide (200 mL, 0.5 M in THF) at -78 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was lowered into an ice bath (0 °C) and quenched with saturated $NH_4Cl_{(aq)}$ (100 mL). The product was extracted using ether (50 mL) three times. The combined organics were then washed with water (50 mL) and brine (50 mL). The organics were then dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil. (4.7 g, 28 mmol, 60 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.13 (t, *J* = 6.8 Hz, 1 H), 4.95 (t, *J* = 1.0 Hz, 1 H), 4.848 (t, *J* = 1.4 Hz, 1 H), 4.08 (t, *J* = 5.0 Hz, 1 H), 2.02 (dt, *J* = 1.2, 7.2 Hz, 2 H), 1.74 (s, 3 H), 1.70 (s, 3 H), 1.62 (s, 3 H), 1.50-1.39 (m, 2 H), 1.36-1.25 (m, 2 H).



(**E)-4,10-dimethylundeca-4,9-dienal**: A solution of 2,8-dimethylnona-1,7-dien-3-ol (2.2 g, 13 mmol) in 60 mL ethyl vinyl ether (EVE) was added to a solution of mercury (II) trifluoroacetate (0.6 g, 1.5 mmol) in 10 mL of ethyl vinyl ether. The reaction was then stirred for 48 hours at room temperature. The reaction mixture was then passed through a silica gel plug, rinsing with ethyl acetate. The volatiles were then removed under vacuum.

[57] K. A. Korthals, W. D. Wulff, *J. Am. Chem. Soc.* **2008**, *130*, 2898-2899.

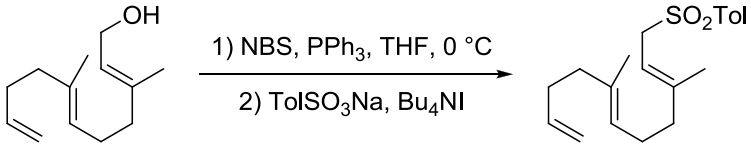
The resulting crude material was dissolved in 80 mL of toluene and placed in a pressure tube where it was brought to reflux at 130 °C for 6 hours. The volatiles were removed under vacuum and silica gel flash column chromatography was performed using 10% ethyl acetate in hexanes resulting in a yellow oil (1.9 g, 9.8 mmol, 75 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1 H), 5.18 (t, *J* = 6.2 Hz, 1 H), 5.12 (t, *J* = 6.2 Hz, 1 H), 2.51 (dt, *J* = 1.6, 9.2 Hz,2 H), 2.34 (t, *J* = 8.0 Hz, 2 H), 2.04-1.95 (m, 4 H), 1.70 (s, 3 H), 1.61 (s, 3 H), 1.61 (s, 3 H), 1.37 (quintuplet, *J* = 7.2 Hz, 2 H).



37

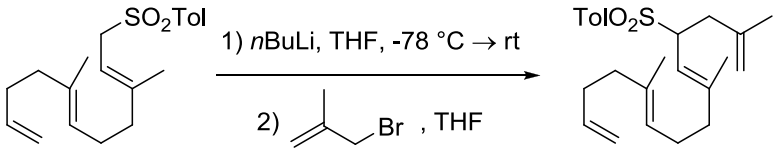
(E)-5,11-dimethyldodeca-1,5,10-triene, 2: A solution of *n*-butyllithium (7.5 mL, 12 mmol, 1.6 M in hexanes) was added to a solution of methyltriphenylphosphoniumbromide (3.9 g, 10.9 mmol) in 60 mL of THF at -78 °C. The reaction was stirred for one hour at -78 °C. A solution of (E)-4,10-dimethylundeca-4,9-dienal (1.92 g, 9.9 mmol) in 25 mL THF was added to the reaction mixture at -78 °C. The reaction mixture was warmed slowly to room temperature and left to stir overnight. The reaction mixture was quenched using 10 mL of 0.1 M $HCl_{(aq)}$. The aqueous layer was then separated and extracted with ether (25 mL) three times. The combined organics were then washed with water (25 mL) and brine (25 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum. The crude product was removed from the resulting mixture using pentane (15 mL) three times. Silica gel flash column chromatography was performed using hexanes (R_f = 0.5) resulting in a colorless oil (0.75 g, 3.9 mmol, 40 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.85-5.75 (m, 1 H), 5.15-5.09 (m,

2 H), 5.01 (dd, *J* = 1.6, 15.6 Hz, 1 H), 4.93 (dd, *J* = 1.6, 10 Hz, 1 H), 2.16-2.10 (m, 2 H), 2.07-2.04 (m, 2 H), 2.01-1.94 (m, 4 H), 1.68 (s, 3 H), 1.59 (s, 6 H), 1.38-1.34 (m, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.8, 134.6, 131.4, 124.9, 124.8, 114.2, 39.1, 32.4, 30.0, 27.7, 27.5, 25.7, 17.6, 15.9. HRMS: [M] = 192.1877 measured, 192.1878 calculated.

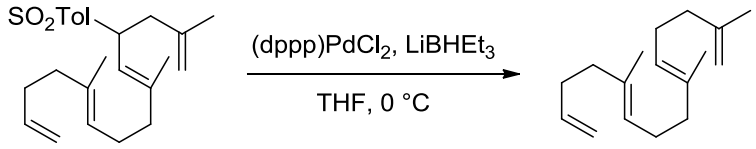


1-((2E,6E)-3,7-dimethylundeca-2,6,10-trienylsulfonyl)-4-methylbenzene: A solution of *N*-bromosuccinimide (0.53 g, 2.9 mmol) in 12 mL THF was added over 20 minutes to a solution of (2E,6E)-3,7-dimethylundeca-2,6,10-trien-1-ol[58] (0.48 g, 2.5 mmol) and triphenylphosphine (0.84 g, 3.2 mmol) in 20 mL THF at 0 °C. The reaction was stirred for 15 minutes. Tetrabutylammonium iodide (0.09 g, 0.25 mmol) and sodium *p*-toluenesulfonate (0.66 g, 3.7 mmol) were added and the reaction was stirred overnight. The reaction was then quenched using saturated $NH_4Cl_{(aq)}$ (15 mL). The aqueous layer was removed and extracted with ethyl acetate (10 mL) three times. The combined organics were dried with $MgSO_4$ and the volatiles were removed under vacuum. Silica gel flash column chromatography was performed using 20% ethyl acetate in hexanes resulting in a yellow oil (0.64 g, 1.9 mmol, 80 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 2 H), 7.29 (d, *J* = 7.6 Hz, 2 H), 5.88-5.68 (m, 1 H), 5.18 (t, *J* = 6.4, 1 H), 5.08 (t, *J* = 6.2, 1 H), 4.99 (d, *J* = 14.2 Hz, 1 H), 4.89 (d, *J* = 8.6 Hz, 1 H), 3.78 (d, *J* = 6.2 Hz, 2 H), 2.45 (s, 3 H), 2.19-1.86 (m, 8 H), 1.58 (s, 6 H).

[58] Yildzhan, S.; van Loon, J.; Sramkova, A.; Ayasse, M.; Arsene, C.; ten Broeke, C.; Schulz, S. *Chem. Bio. Chem.* **2009**, *10*, 1667-1677.



1-methyl-4-((5E,9E)-2,6,10-trimethyltetradeca-1,5,9,13-tetraen-4-ylsulfonyl)benzene: A solution of *n*-butyllithium (0.32 mL, 2.5 M in hexanes) was added to a solution of 1-((2E,6E)-3,7-dimethylundeca-2,6,10-trienylsulfonyl)-4-methylbenzene (240 mg, 0.72 mmol) in 2.5 mL THF at -78 °C. The reaction was left to stir for one hour. The 3-bromo-2-methylpropene (0.11 mL, 1.1 mmol) was then added and the reaction temperature was allwed to warm to room temperature. The reaction was then left to stir overnight. The reaction was quenched using saturated $NH_4Cl_{(aq)}$. The aqueous layer was separated and extracted with ether three times, dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil (210 mg, 0.53 mmol, 74 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 5.79-5.75 (m, 1 H), 5.06-5.01 (m, 2 H), 4.96 (d, *J* = 12.4 Hz, 1 H), 4.89 (d, *J* = 10.0 Hz, 1 H), 4.75 (s, 1 H), 4.66 (s, 1 H), 3.89 (dt *J* = 8.4, 10.4 Hz, 1 H), 2.88 (d, *J* = 14.4 Hz, 2 H), 2.44 (s, 3 H), 2.32 (t, *J* = 12.8 Hz, 2 H), 2.14-1.94 (m, 6 H), 1.64 (s, 3 H), 1.58 (s, 3 H), 1.56 (s, 3 H).



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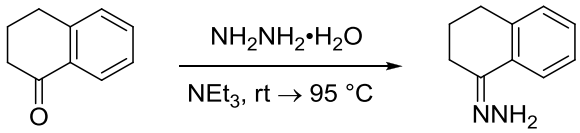
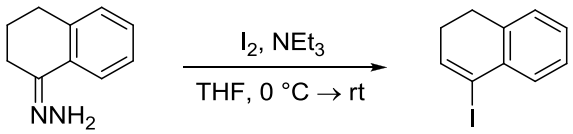
(5E,9E)-2,6,10-trimethyltetradeca-1,5,9,13-tetraene: A solution of lithium triethylborohydride (0.4 mL, 1 M in THF) was added to a mixture of 1-methyl-4-((5E,9E)-2,6,10-trimethyltetradeca-1,5,9,13-tetraen-4-ylsulfonyl)benzene (65 mg, 0.16 mmol) and $(dppp)PdCl_2$ (10 mg, 0.016 mmol) in 2 mL THF at 0 °C. The reaction mixture was stirred

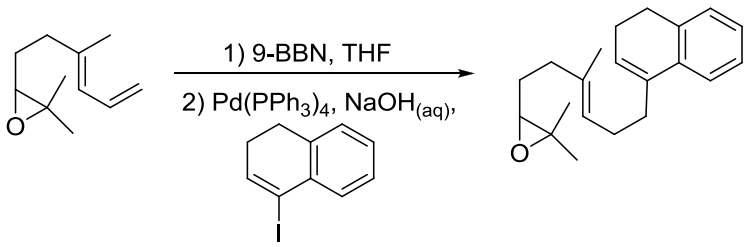
for 45 minutes at 0 °C. The reaction was quenched using saturated $NH_4Cl_{(aq)}$ (2 mL). The product was extracted with ether (2 mL) three times, dried with $MgSO_4$, and the volatiles were removed under vacuum. Silica gel flash column chromatography was performed using 20% ethyl acetate in hexanes (R_f = 0.8) resulting in a colorless oil (32 mg, 0.14 mmol, 82 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.88-5.78 (m, 1 H), 5.17 (t, *J* = 6.1 Hz, 2 H), 5.03 (dd, *J* = 1.5, 17.2 Hz, 1 H), 4.96 (dd, *J* = 1.5, 9.9 Hz, 1 H), 4.742 (s, 1 H), 4.721 (s, 1 H), 2.21-2.02 (m, 12 H), 1.80 (s, 3 H), 1.65 (s, 3 H), 1.64 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.6, 138.6, 134.9, 134.3, 124.6, 124.2, 114.2, 109.9, 39.7, 39.1, 37.9, 32.4, 26.6, 26.3, 22.4, 15.9 (2 C). [M] = HRMS: 231.2191 calculated, 231.2109 measured.



(3,4-dihydronaphthalen-1(*2H*)-ylidene)hydrazine : A heterogeneous mixture of hydrazine monohydrate (8.2 mL, 170 mmol) and triethylamine (5.0 mL, 36 mmol) was added in 1 mL increments to a vigorously stirred solution of α-tetralone (4.7 mL, 35 mmol) at room temperature over 3 h. The reaction mixture was stirred at 95 °C for 1 h. The reaction mixture was cooled to room temperature and extracted with chloroform (3 x 50 mL). The combined organics were dried with K_2CO_3 and the solvent was evaporated to yield a colorless oil (4.9 g, 31 mmol, 89 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 4.4, 4.8 Hz, 1 H), 7.21-7.19 (m, 2 H), 7.11 (d, *J* = 5.6 Hz, 1 H), 5.35 (s, 2 H), 2.72 (t, *J* = 6.0 Hz, 2 H), 2.46 (t, *J* = 6.4 Hz, 2 H), 1.94 (dt, *J* = 6.0, 6.4 Hz, 2 H).



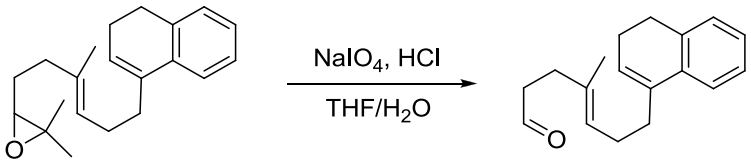
4-iodo-1,2-dihydronapthalene : A saturated solution of iodine (15 g, 59 mmol) in 20 mL THF was added rapidly to a sirring solution of (3,4-dihydronaphthalen-1(*2H*)-ylidene)hydrazine (4.9 g, 31 mmol) in 25 mL of triethylamine at 0 °C. The reaction mixture was allwed to warm to room temperature and stirred for an additional hour. After diluting the reaction mixture with 150 mL of distilled water, it was extracted with hexane until the extractant appeared colorless. The combined organic layers were washed with 0.1 M HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine solution (100 mL). The organic solution was dried with $MgSO_4$ and the volatiles were removed under vacuum resulting in a dark red crude oil. Silica gel flash column chromatography was performed using hexanes (R_f = 0.6) resulting in a dark yellow oil (4.1 g, 16 mmol, 52 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.6 Hz, 2 H), 7.20 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.05 (d, *J* = 7.2 Hz, 1 H), 6.86 (t, *J* = 4.8 Hz, 1 H), 2.87 (t, *J* = 8.0 Hz, 2 H), 2.38 (dt, *J* = 3.2, 4.8 Hz, 2 H).



(E)-3-(6-(3,4-dihydronaphthalen-1-yl)-3-methylhex-3-enyl)-2,2-dimethyloxirane: A solution of 9-BBN (25mL, 0.5 M in THF) was added to a solution of (E)-2,2-dimethyl-3-(3-methylhexa-3,5-dienyl)oxirane[59] (1.87 g, 11 mmol) in 20 mL THF at 0 °C. The reaction was allwed to warm to room temperature and then stirred overnight. A solution of 4-iodo-1,2-

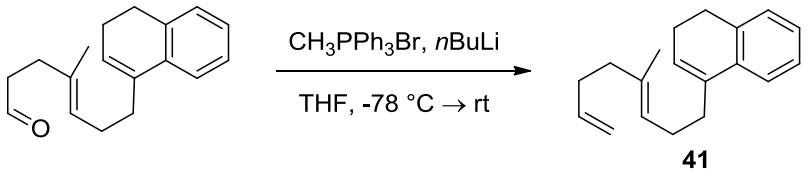
[59] K. Surendra, E. J. Corey, *J. Am. Chem. Soc.*, **2008**, *130*, 8865-8869.

dihydronaphthalene (1.5 g, 6 mmol) in 20 mL THF was added followed by $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.25 g, 0.3 mmol) and sodium hydroxide (9 mL, 36 mmol, 4N in H_2O). The reaction was then stirred overnight. The aqueous layer was separated and extracted with ether (25 mL) three times. The combined organics were washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum. Silica gel flash column chromatography was performed using 10% ether in hexanes (R_f = 0.4) resulting in a yellow oil (1.1 g, 3.7 mmol, 72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 5.2 Hz, 1 H), 7.21-7.15 (m, 2H), 7.13 (dd, *J* =1.2, 3.2 Hz, 1 H), 5.88 (t, *J* = 4.4 Hz, 1 H), 5.28 (dt, *J* = 1.2, 6.8 Hz, 1 H), 2.77-2.73 (m, 2 H), 2.49 (t, *J* = 8.0 Hz, 1 H), 2.27-2.09 (m, 8 H), 1.689-1.62 (m, 2 H), 1.60 (s, 3 H), 1.33 (s, 3 H), 1.29 (s, 3 H).



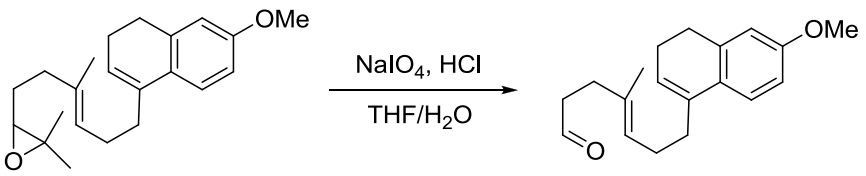
(E)-7-(3,4-dihydronaphthalen-1-yl)-4-methylhept-4-enal: (E)-3-(6-(3,4-dihydronaphthalen-1-yl)-3-methylhex-3-enyl)-2,2-dimethyloxirane (1.1 g, 3.8 mmol) and sodium *m*-periodate (1.1 g, 5.0 mmol) were added to a mixture of 10 mL THF and 2 mL H_2O. Concentrated hydrochloric acid (5 drops) was added and the reaction was stirred for 2 hours at room temperature. 20 mL of saturated $Na_2S_2O_{3\,(aq)}$ was added and the precipitate was filtered off. The aqueous layer was removed and extracted with ether (10 mL) three times. The combined organics were washed with saturated $NaHCO_{3(aq)}$ (20 mL) and brine (20 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil (0.74g, 2.9 mmol, 77%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 2.0 Hz, 1 H), 7.25 (d, *J* = 8.4 Hz, 1 H), 7.22-7.17 (m, 2 H), 7.12 (d, *J* = 3.6 Hz, 1 H), 5.86 (t, *J* = 4.4, 1 H), 5.25 (t, *J* = 6.4, 1 H),

2.73 (t, *J* = 8.0 Hz, 2 H), 2.51 (dt, *J* = 1.2, 6.8 Hz, 2 H), 2.46 (t, *J* = 7.2 Hz, 2 H), 2.33 (t, *J* = 7.6, 2 H), 2.45-2.20 (m, 4 H), 1.60 (s, 3 H).

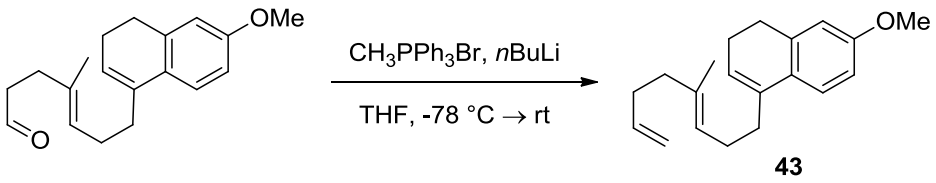


41

(E)-4-(4-methylocta-3,7-dienyl)-1,2-dihydronaphthalene, 41: A solution of *n*-butyllithium (3 mL, 1.6 M in hexanes) was added to a solution of methyltriphenylphosphoniumbromide (1.8 g, 5.0 mmol) in 20 mL of THF at -78 °C. The reaction was stirred for one hour at -78 °C. A solution of (E)-7-(3,4-dihydronaphthalen-1-yl)-4-methylhept-4-enal (0.7 g, 2.9 mmol) in 5 mL THF was added to the phosphonium ylide at -78 °C. The reaction mixture was allowed to warm to room temperature and left to stir overnight. The reaction mixture was quenched using 0.1 M $HCl_{(aq)}$ (10 mL). The aqueous layer was then removed and extracted with ether (10 mL) three times. The combined organics were then washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum. The resulting oil was then extracted using pentane (10 mL) three times. Silica gel flash column chromatography was performed using hexanes (R_f = 0.5) resulting in a clear oil (0.49 g, 1.9 mmol, 65 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 4 H), 5.88 (t, *J* = 4.4 Hz, 1 H), 5.85-5.81 (m, 1 H), 5.24 (t, *J* = 7.2 Hz, 1 H), 5.04 (d, *J* = 17.2 Hz, 1 H), 4.97 (d, *J* = 10.4 Hz, 1 H), 2.75 (dt, *J* = 8.0, 11.2 Hz, 2 H), 2.48 (t, *J* = 7.6 Hz, 2 H), 2.25 (dt, *J* = 6.4, 7.2 Hz, 4 H), 2.17 (t, *J* = 7.2 Hz, 2 H), 2.09 (t, *J* = 7.4 Hz, 2 H), 1.59 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.8, 136.8, 136.2, 135.1, 134.9, 127.6, 126.5, 126.3, 124.9, 124.4, 122.6, 114.3, 39.1, 32.8, 32.4, 28.5, 27.0, 23.2, 16.1. [M] = HRMS: 252.18878 measured, 252.18878 calculated.



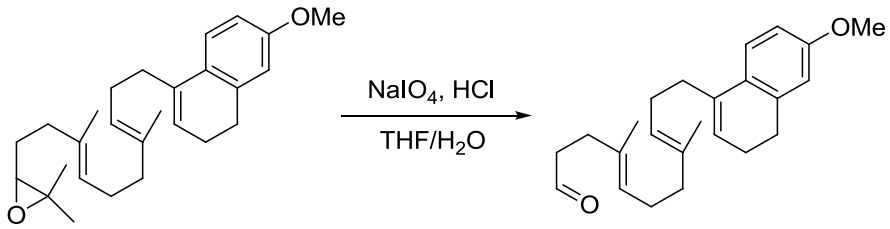
(E)-7-(6-methoxy-3,4-dihydronaphthalen-1-yl)-4-methylhept-4-enal: The (E)-3-(6-(6-methoxy-3,4-dihydronaphthalen-1-yl)-3-methylhex-3-enyl)-2,2-dimethyloxirane[3] (2.5 g, 7.7 mmol) and sodium *m*-periodate (2.5 g, 11.6 mmol) were added to a mixture of 28 mL THF and 10 mL H_2O. Concentrated hydrochloric acid (15 drops) was added, and the reaction was stirred for 2 hours at room temperature. Saturated $Na_2S_2O_{3\,(aq)}$ (50 mL) was added, and the precipitate was filtered off. The aqueous layer was separated and extracted with ether (25 mL) three times. The combined organics were washed with saturated $NaHCO_{3(aq)}$ (50 mL) and brine (50 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil (2.0 g, 7.1 mmol, 92 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1 H), 7.16 (d, *J* = 9.0 Hz, 2 H), 6.72 (d, *J* = 9.1 Hz, 2 H), 5.70 (t, *J* = 4.4 Hz, 1 H), 5.21 (t, *J* = 6.2 Hz, 1 H), 3.80 (s, 3 H), 3.79-3.75 (m, 2 H), 2.73-2.32 (m, 10 H), 2.21 (s, 3 H).



43

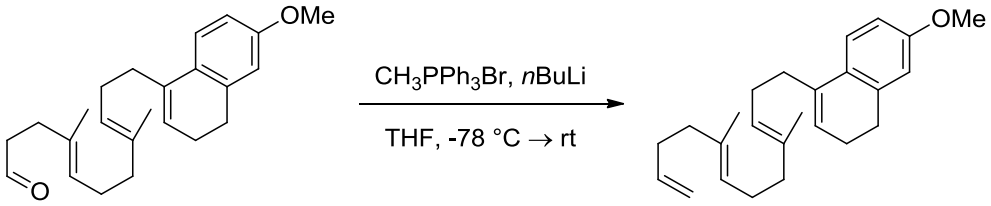
(E)-7-methoxy-4-(4-methylocta-3,7-dienyl)-1,2-dihydronaphthalene: A solution of *n*-butyllithium (5.3 mL, 8.5 mmol, 1.6 M in hexanes) was added to a solution of methyltriphenylphosphoniumbromide (3.0 g, 8.4 mmol) in 30 mL of THF at -78 °C. The reaction was stirred for one hour at -78 °C. A solution of (E)-7-(6-methoxy-3,4-dihydronaphthalen-1-yl)-4-methylhept-4-enal (2.0 g, 2.9 mmol) in 10 mL THF was added to the reaction mixture at -78 °C. The reaction mixture was allowed to warm to room

temperature and left to stir overnight. The reaction mixture was quenched with 10 mL 0.1 M $HCl_{(aq)}$. The aqueous layer was then seperated and extracted with ether (5 mL) three times. The combined organics were washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum. The resulting oil was then extracted using pentane three times. Silica gel flash column chromatography was performed using hexanes (R_f = 0.5) resulting in a yellow oil (1.5 g, 5.3 mmol, 75 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.227 (d, *J* = 16.8 Hz, 1 H), 6.80-6.78 (m, 2 H), 5.94-5.83 (m, 1 H), 5.80 (t, *J* = 4.4 Hz, 1 H), 5.30 (t, *J* = 7 Hz, 1 H), 5.10 (dd, *J* = 1.8, 17.1 Hz, 1 H), 5.03 (dd, *J* = 1.8, 11.3 Hz, 1 H), 3.83 (s, 3 H), 2.79-2.73 (m, 2 H), 2.51 (t, *J* = 7.3 Hz, 2 H), 2.34-2.27 (m, 4 H), 2.23 (t, *J* = 7.6 Hz, 2 H), 2.17-2.14 (m, 2 H), 1.65 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.2, 138.6, 138.4, 135.8, 134.6, 128.1, 124.4, 123.6, 122.1, 114.1, 113.7, 110.7, 54.9, 39.0, 32.8, 32.3, 28.9, 27.0, 23.0, 15.9. HRMS: [M] = 282.19837 calculated, 282.19782 measured.



(4E,8E)-11-(6-methoxy-3,4-dihydronaphthalen-1-yl)-4,8-dimethylundeca-4,8-dienal: 3-((3E,7E)-10-(6-methoxy-3,4-dihydronaphthalen-1-yl)-3,7-dimethyldeca-3,7-dienyl)-2,2-dimethyloxirane[3] (0.51 g, 1.3 mmol) and sodium *m*-periodate (0.43 g, 2.0 mmol) were added to a mixture of 5 mL THF and 2 mL H_2O. Concentrated hydrochloric acid (3 drops) was added, and the reaction was stirred for 2 hours at room temperature. Saturated $Na_2S_2O_{3(aq)}$ (20 mL) was added, and the precipitate was filtered off. The aqueous layer was removed and extracted with ether (10 mL) three times. The combined organics were washed with

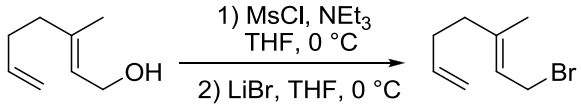
saturated $NaHCO_{3(aq)}$ (20 mL) and brine (20 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil (0.39 g, 1.1 mmol, 88 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1 H), 7.19 (d, *J* = 11.5 Hz, 2 H), 6.72 (d, *J* = 9.6 Hz, 2 H), 5.72 (t, *J* = 4.4 Hz, 1 H), 5.20-5.15 (m, 2 H), 3.80 (s, 3 H), 2.71 (t, *J* = 10.0 Hz, 2 H), 2.43-2.00 (m, 8 H), 1.57 (t, *J* = 14.6 Hz, 4 H), 1.30 (s, 3 H), 1.26 (s, 3 H).



45

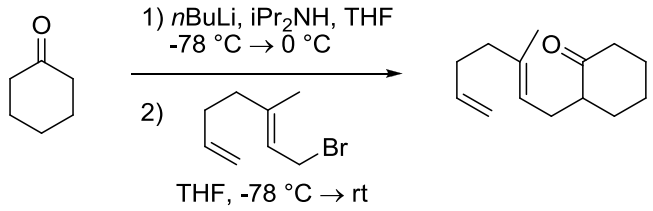
4-**((3E,7E)-4,8-dimethyldodeca-3,7,11-trienyl)-7-methoxy-1,2-dihydronaphthalene**: A solution of *n*-butyllithium (0.9 mL, 1.4 mmol, 1.6 M in hexanes) was added to a solution of methyltriphenylphosphoniumbromide (0.52 g, 1.5 mmol) in 10 mL of THF at -78 °C. The reaction was stirred for one hour at -78 °C. A solution of (4E,8E)-11-(6-methoxy-3,4-dihydronaphthalen-1-yl)-4,8-dimethylundeca-4,8-dienal (0.39 g, 1.1 mmol) in 5 mL THF was added to the reaction mixture at -78 °C. The reaction mixture was slowly brought to room temperature and left to stir overnight. The reaction mixture was quenched using 0.1 M $HCl_{(aq)}$ (5 mL). The aqueous layer was separated and extracted with ether (5 mL) three times. The combined organics were then washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum. The crude product was removed from the resulting mixture using pentane (10 mL) three times. Silica gel flash column chromatography was performed using hexanes (R_f = 0.5) resulting in a colorless oil (0.38 g, 1.1 mmol, 74 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 9.0 Hz, 1 H), 6.80-6.78 (m, 2 H), 5.92-5.84 (m, 1 H), 5.80 (t, *J* = 4.4 Hz, 1 H), 5.29 (t, *J* = 6.8 Hz, 1 H), 5.22 (t, *J* = 6.4 Hz,

1 H), 5.09 (dd, *J* = 1.5, 17.2 Hz, 1 H), 5.02 (dd *J* = 1.5, 9.3 Hz, 1 H), 3.86 (s, 3 H), 2.78 (t, *J* = 7.9 Hz, 2 H), 2.51 (t, *J* = 7.6 Hz, 2 H), 2.31 (t, *J* = 7.3 Hz, 2 H), 2.27-2.07 (m, 10 H), 1.69 (s, 3 H), 1.65 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.2, 138.7, 138.5, 135.9, 135.1, 134.3, 128.1, 124.6, 124.2, 123.7, 122.2, 114.2, 113.7, 110.7, 55.1, 39.7, 39.0, 32.9, 32.4, 29.0, 27.0, 26.6, 23.1, 16.0, 15.9. HRMS: [M] = 350.26097 calculated, 350.25908 measured.

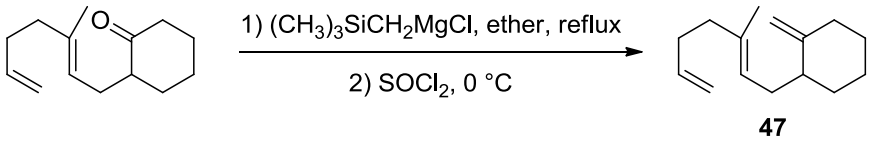


(E)-7-bromo-5-methylhepta-1,5-diene: A solution of methanesulfonyl chloride (7.5 mL, 97 mmol) in triethylamine (19.5 mL, 140 mmol) was added to a solution of (E)-3-methylhepta-2,6-dien-1-ol[60] (8.7 g, 68 mmol) in 200 mL THF at 0 °C. The reaction was stirred at 0 °C for 45 minutes. A solution of lithium bromide (30 g, 350 mmol) in 150 mL of THF was then added. The reaction was stirred at 0 °C for one hour. The reaction mixture was diluted with 300 mL hexanes and 200 mL H_2O. The aqueous layer was separated and extracted with hexanes (50 mL) three times. The combined organics were washed with saturated $NaHCO_{3(aq)}$ (100 mL) and brine (100 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil (8.8 g, 47 mmol, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.80-5.76 (m, 1 H), 5.55 (t, *J* = 8.4 Hz, 1 H), 5.03 (d, *J* = 17.2 Hz, 1 H), 4.97 (d, *J* = 10.4 Hz, 1 H), 4.03 (d, 8.4 Hz, 2 H), 2.21-2.10 (m, 4 H), 1.74 (s, 3 H).

[60] Foote, K. M.; Hayes, C. J.; John, M. P.; Pattenden, G. *Org. Biomol. Chem.* **2003**, *1*, 3917-3948.



(E)-2-(3-methylhepta-2,6-dienyl)cyclohexanone: A solution of *n*-butyllithium (25 mL, 1.6 M in hexanes) was added to a solution of diisopropylamine (6 mL, 42.5 mmol) in 30 mL THF at -78 °C. The reaction was stirred for one hour. Cyclohexanone (4 mL, 39 mmol) was then added, and the solution was stirred for one hour. The (E)-7-bromo-5-methylhepta-1,5-diene (8.8 g, 46 mmol) was then added and the temperature of the reaction mixture was brought to room temperature. The reaction was left to stir overnight. The reaction was quenched using 0.5 M HCl (5 mL), and the product was extracted using ether (5 mL) three times. The organics were washed with brine (50 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil (6.6 g, 32 mmol, 83%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.89-5.76 (m, 1 H), 5.12 (t, *J* = 7.2 Hz, 1 H), 5.01 (dd, *J* = 1.6, 10.8 Hz, 1 H), 4.95 (d, *J* = 10.0 Hz, 1 H), 2.46-1.79 (m, 15 H), 1.61 (s, 3 H).

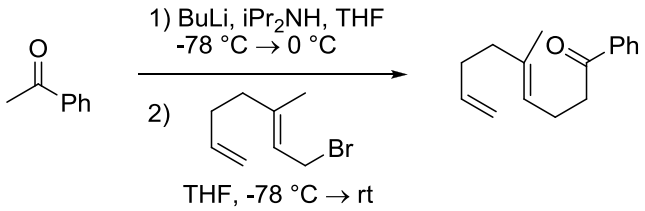


47

(E)-1-methylene-2-(3-methylhepta-2,6-dienyl)cyclohexane:

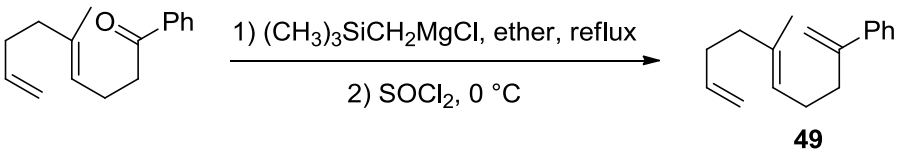
(Trimethylsilyl)methylmagnesium chloride (20 mL, 1.0 M in diethyl ether) was added to a solution of E)-2-(3-methylhepta-2,6-dienyl)cyclohexanone (2 g, 9.7 mmol) in 100 mL diethyl ether. The reaction mixture was heated to reflux for 24 hours. The mixture was cooled to 0 °C, and thionyl chloride (3 mL, 40 mmol) was added. The reaction was stirred for one hour at 0 °C. The reaction was quenched using saturated $NH_4Cl_{(aq)}$ (50 mL). The reaction mixture

was vacuum filtered through a fritted funnel, and the aqueous layer was removed and extracted with ether (25 mL) three times. The combined organics were then dried with $MgSO_4$ and the volatiles were removed under vacuum. Silica gel flash column chromatography was performed using hexanes (R_f = 0.6) resulting in a colorless oil (1.7 g, 8.3 mmol, 86 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.86-5.80 (m, 1 H), 5.19 (t, *J* = 5.0 Hz, 1 H), 5.04 (dd, *J* = 1.6, 14.0 Hz, 1 H), 4.97 (dd, *J* = 1.6, 8.0 Hz, 1 H), 4.67 (s, 1 H), 4.59 (s, 1 H), 2.26-2.00 (m, 9 H), 1.63 (s, 3 H), 1.47-1.15 (m, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.0, 138.7, 134.9, 123.8, 114.2, 105.2, 43.5, 39.2, 35.5, 33.6, 32.5, 30.9, 28.8, 25.00, 16.2. HRMS: [M] = 204.18816 measured, 204.18780 calculated.



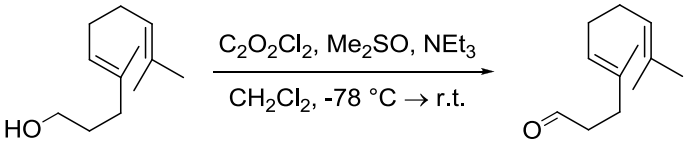
(*E*)-5-methyl-1-phenylnona-4,8-dien-1-one: A solution of *n*-butyllithium (6.6 mL, 1.6 M in hexanes) was added to a solution of diisopropylamine (1.55 mL, 11.0 mmol) in 20 mL THF at -78 °C. The reaction was stirred for one hour. The acetophenone (1.2 mL, 10.3 mmol) was then added and the solution was stirred for an additional hour. The (*E*)-7-bromo-5-methylhepta-1,5-diene (2.3 g, 12.2 mmol) was then added and the temperature of the reaction mixture was brought to room temperature. The reaction was left to stir overnight. The reaction was quenched using 0.5 M HCl (5 mL) and the product was extracted using ether (5 mL) three times. The organics were then washed with brine (50 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil (1.87 g, 8.2 mmol, 75%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 2 H), 7.57 (t, *J* = 7.1 Hz, 1 H), 7.45 (t, *J* =

7.3 Hz, 2 H), 5.84-5.73 (m, 1 H), 5.21 (t, *J* = 8.0 Hz, 1 H), 5.00 (d, *J* = 17.4 Hz, 1 H), 4.93 (d, *J* = 9.5 Hz, 1 H), 3.01 (t, *J* = 7.4 Hz, 2 H), 2.45 (dt, *J* = 7.6 Hz, 7.4 Hz, 2 H), 2.19-2.13 (m, 2 H), 2.09-2.03 (m, 2 H), 1.64 (s, 3 H).

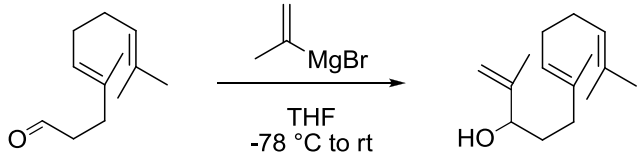


49

(*E*)-(6-methyldeca-1,5,9-trien-2-yl)benzene: (Trimethylsilyl)methylmagnesium chloride (20 mL, 1.0 M in diethyl ether) was added to a solution of (*E*)-5-methyl-1-phenylnona-4,8-dien-1-one (2 g, 8.7 mmol) in 100 mL diethyl ether. The reaction mixture was heated to reflux for 24 hours. The mixture was cooled to 0 °C and thionyl chloride (3 mL, 40 mmol) was added. The reaction was stirred for one hour at 0 °C. The reaction was quenched using saturated $NH_4Cl_{(aq)}$ (50 mL). The reaction mixture was vacuum filtered through a fritted funnel, and the aqueous layer was removed and extracted with ether (25 mL) three times. The combined organics were then dried with $MgSO_4$ and the volatiles were removed under vacuum. Silica gel flash column chromatography was performed using hexanes as the eluent (Rf = 0.6) resulting in a colorless oil (0.9 g, 3.9 mmol, 45 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.41 (dt, *J* = 7.8 Hz, 1.5 Hz, 2 H), 7.32 (tt, *J* = 7.6 Hz, 1.5 Hz, 2 H), 7.27 (dt, *J* = 7.3 Hz, 1.4 Hz, 1 H), 5.86-5.75 (m, 1 H), 5.27 (d, *J* = 1.5 Hz, 1 H), 5.17 (t, *J* = 6.4 Hz, 1 H), 5.06 (d, *J* = 1.4 Hz, 1 H), 5.01 (dd, *J* = 17.1 Hz, 1.8 Hz, 1 H), 4.93 (dd, *J* = 10.2 Hz, 2.0 Hz 1 H), 2.53 (t, *J* = 7.2 Hz, 2 H), 2.13 (q, *J* = 4.0 Hz, 2 H), 2.12 (q, *J* = 3.8 Hz, 2 H), 2.05 (q, *J* = 7.8 Hz, 2 H), 1.53 (s, 3 H). ^{13}C-NMR (151 MHz, $CDCl_3$) δ 148.3, 141.4, 138.8, 135.0, 128.1 (2C), 127.3, 126.2 (2C), 124.1, 114.4, 112.4, 39.1, 35.5, 32.4, 26.9, 16.1. HRMS: [M] = 226.17168 measured, 226.17215 calculated.

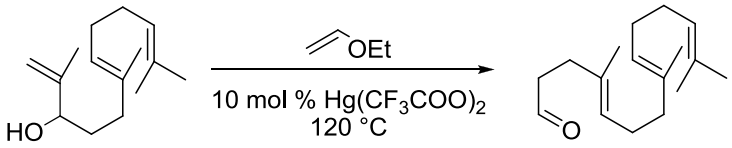


(E)-4,9-dimethyldeca-4,8-dienal: Dimethyl sulfoxide (10.7 mL, 150 mmol) was slowly added to a solution of oxalyl chloride (12.7 mL, 150 mmol) in 300 mL CH_2Cl_2 at -78 °C. A solution of 6-methylhept-5-en-1-ol[32] in 100 mL CH_2Cl_2 was added to the reaction mixture. The reaction was stirred at -78 °C for one hour. Triethylamine (35 mL, 250 mmol) was added and the reaction was warmed to room temperature. The reaction was then stirred for one hour at room temperature and then transferred to a separatory funnel. The solution was washed with 300 mL H_2O. The aqueous layer was separated and extracted with CH_2Cl_2 (100 mL) twice. The combined organics were then washed with 1 M HCl (200 mL) twice, saturated $Na_2C_2O_3$ (200 mL) twice, water (100 mL), and brine (100 mL). The organic phase was then dried with $MgSO_4$ and the volatiles were removed under vacuum resulting in a yellow oil (5.92 g, 47 mmol, 98 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1 H), 5.18 (t, *J* = 6.4 Hz, 1 H), 5.11 (t, *J* = 6.4 Hz, 1 H), 2.53 (dt, *J* = 1.6, 7.2 Hz, 2 H), 2.33 (t, *J* = 7.6 Hz, 2 H), 2.016 (s, 4 H), 1.70 (s, 3 H), 1.63 (s, 3 H), 1.61 (s, 3 H).

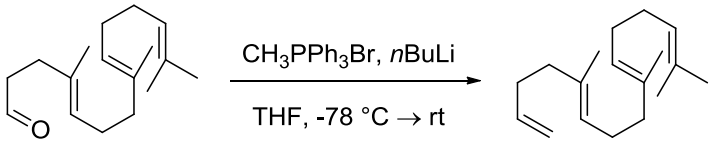


(E)-2,6,11-trimethyldodeca-1,6,10-trien-3-ol: A solution of isopropenyl magnesium bromide (4 mL, 0.5 M in THF) was added to a solution of (E)-4,9-dimethyldeca-4,8-dienal (0.20 g, 1.1 mmol) in 4 mL THF at -78 °C. The reaction mixture temperature was allwed to warm to room temperature and the reaction was stirred for 2 hours at room temperature. The

solution was quenched using saturated $NH_4Cl_{(aq)}$ (5 mL). The reaction mixture was diluted with ether (8 mL) and washed with brine (4 mL). The volatiles were removed under vacuum and silica gel flash column chromatography was performed using 10% ethyl acetate in hexanes to 20% ethyl acetate in hexanes. This resulted in a yellow oil (0.12 g, 0.54 mmol, 50%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.19-5.07 (m, 2 H), 4.95 (s, 1 H), 4.85 (s, 1 H), 4.05 (t, *J* = 6.8 Hz, 1 H), 2.14-1.97 (m, 8 H), 1.74 (s, 3 H), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.61 (s, 3 H).

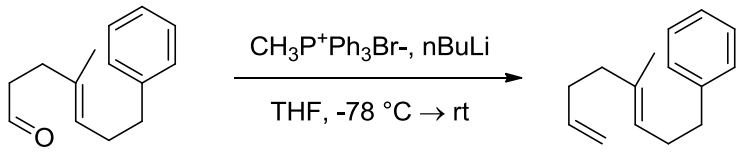


(4E,8E)-4,8,13-trimethyltetradeca-4,8,12-trienal: A solution of (E)-2,6,11-trimethyldodeca-1,6,10-trien-3-ol (0.10 g, 0.43 mmol) in 4 mL ethyl vinyl ether was added to a solution of mercury(II) trifluoroacetate (0.021 g, 0.05 mmol) in 1 mL ethyl vinyl ether. The reaction was stirred for 46 hours. The volatiles were then removed under vacuum. The crude intermediate was passed through a silica gel plug using ethyl acetate, and the remaining volatiles were removed under vacuum. The crude was dissolved in 5 mL toluene and heated to 130 °C in a pressure flask for 6 hours. Once cool, the volatiles were removed under vacuum and silica gel flash column chromatography was performed on the crude product using 10% ethyl acetate in hexanes. This resulted in a yellow oil (0.07 g, 0.28 mmol, 65 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1 H), 5.15-5.08 (m, 2 H), 4.53 (t, *J* = 7.0 Hz, 1 H), 2.50-1.82 (m, 12 H), 1.69 (s, 3 H), 1.61 (s, 6 H), 1.22 (s, 3 H).



51

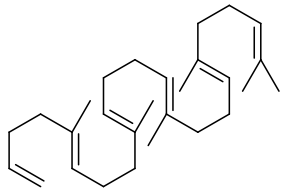
(5E,9E)-5,9,14-trimethylpentadeca-1,5,9,13-tetraene: A solution of *n*-butyllithium (3.2 mL, 5.1 mmol, 1.6 M in hexanes) was added to a solution of methyltriphenylphosphoniumbromide (1.8 g, 5.0 mmol) in 25 mL of THF at -78 °C. The reaction was stirred for one hour at -78 °C. A solution of (E)-7-(6-methoxy-3,4-dihydronaphthalen-1-yl)-4-methylhept-4-enal (1.2 g, 2.5 mmol) in 10 mL THF was added to the phosphonium ylide at -78 °C. The reaction mixture was slowly brought to room temperature and left to stir overnight. The reaction mixture was quenched using 15 mL of 0.1 M $HCl_{(aq)}$. The aqueous layer was then removed and extracted with ether. The combined organics were washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum. The resulting oil was then extracted using pentane (10 mL) three times. Silica gel flash column chromatography was performed on the crude material using hexanes (R_f = 0.5) resulting in a colorless oil (0.44 g, 1.8 mmol, 71 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.86-5.76 (m, 1 H), 5.15-5.14 (m, 3 H), 5.01 (dd, *J* = 1.6, 17.2, 1 H), 4.94 (dd, *J* = 1.6, 9.6 Hz, 1 H), 2.18-1.98 (m, 12 H), 1.70 (s, 3 H), 1.61 (s, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.8, 135.1, 134.4, 131.4, 124.6, 124.5, 124.4, 114.2, 39.7, 39.1, 32.4, 28.4, 28.3, 26.6, 25.7, 17.69, 15.98, 15.97. HRMS: [M] = 246.2348 calculated, 246.2348 measured.



55

(*E*)-(4-methylocta-3,7-dienyl)benzene, 13: A solution of *n*-butyllithium (10.5 mL, 1.6 M in hexanes) was added to a solution of methyltriphenylphosphoniumbromide (6.8 g, 19.1 mmol) in 100 mL of THF at -78 °C. The reaction was stirred for one hour at -78 °C. A solution of (*E*)-4-methyl-7-phenylhept-4-enal[61] (3.0 g, 15.1 mmol) in 20 mL THF was added to the phosphonium ylide at -78 °C. The reaction mixture was allowed to warm to room temperature and left to stir overnight. The reaction mixture was quenched using 0.1 M $HCl_{(aq)}$ (50 mL). The aqueous layer was then removed and extracted with ether (20 mL) three times. The combined organics were then washed with water (50 mL) and brine (50 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum. The resulting oil was then extracted using pentane (50 mL) three times. Silica gel flash column chromatography was performed using hexanes as the eluent (R_f = 0.5) resulting in a clear oil (2.6 g, 13 mmol, 86 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.3, 7.7 Hz, 2 H), 7.36-7.33 (m, 3 H), 5.99-5.93 (m, 1 H), 5.38 (t, *J* = 7.1 Hz, 1 H), 5.19 (dd, *J* = 1.8, 17.1 Hz, 1 H), 5.12 (dd, *J* = 1.0, 10.2 Hz, 1 H), 2.82 (t, *J* = 8.0 Hz, 2 H), 2.49 (t, *J* = 7.6 Hz, 2 H), 2.32 (dt, *J* = 6.8, 8.0 Hz, 2 H), 2.23 (dt, *J* = 7.3, 8.0 Hz, 2 H), 1.73 (s, 3 H). ^{13}C-NMR (151 MHz, $CDCl_3$) δ 142.5, 138.8, 135.3, 128.7 (2 H), 128.4 (2 H), 125.8, 124.1, 114.5, 39.2, 36.3, 32.5, 30.1, 16.1. [M] = HRMS: 200.15438 measured, 200.15645 calculated.

[61] Surendra, K.; Qiu, W.; Corey, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 9724-9726.

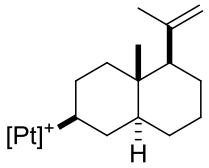


66

(5E,9E,13E,17E)-5,9,14,18,22-pentamethyltricosa-1,5,9,13,17,21-hexaene: Compound 17 was prepared following an established literature procedure.[62]

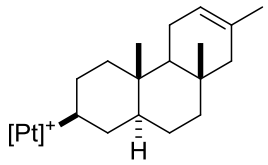
[62] Hoshino, T.; Nakano, S.; Kondo, T.; Sato, T.; Miyoshi, A. *Org. Biomol. Chem.*, **2004**, *2*, 1456-1470.

Standard Cyclization Reaction: To 30 mg of (PPP)PtI_2 (30.5 µmol) was added 15 mg of $AgBF_4$ (77.1 µmol) followed by 0.75 mL $EtNO_2$. The mixture was then stirred for 1 hour in the dark. The contents were then filtered through a 0.2 µm PTFE syringe filter, washing out the flask and syringe with 0.25 mL $EtNO_2$, into a flask containing 2 equivalents of substrate and 3 equivalents of piperidinomethyl polystyrene resin. The reaction mixture was then stirred in the dark until the reaction was complete (3-48 hours, verified by ^{31}P NMR). The reaction mixture was passed through a 0.2 µm PTFE syringe filter, rinsing with 0.25 mL $EtNO_2$. Solvent was removed under a stream of nitrogen. The complex was twice reconstituted in a minimum amount of CH_2Cl_2 and force precipitated with cold *t*BuOMe. The mixture was centrifuged and the solvent was decanted off. The crude was purified by flash column chromatography using 25% nitroethane in hexanes (R_f = 0.4) resulting in a white solid.



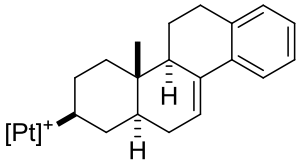
38

Compound 38: ^{31}P-NMR (162 MHz, CD_3NO_2) δ 91.0 ($J_{P\text{-}Pt}$ = 1290 Hz, 1 P), 43.04 ($J_{P\text{-}Pt}$ = 3050 Hz, 1 P), 43.01 ($J_{P\text{-}Pt}$ = 3046 Hz, 1 P). ^{1}H-NMR (400 MHz, CD_3NO_2) δ 7.94-7.56 (m, 25 H), 4.67 (s, 1 H), 4.43 (s, 1 H), 3.56-2.31 (m, 8 H), 1.56 (s, 3 H), 1.46-0.52 (m, 14 H), 0.08 (s, 3 H). ^{13}C-NMR (100 MHz, CD_3NO_2) δ 148.2, 133.6-128.9 (30 C), 110.9, 55.6, 48.2, 45.1, 37.8, 37.6, 32.9, 28.7, 27.9, 26.5, 25.9, 23.3, 11.7. $[M]^+$ = 920.3243 calculated, 920.3198 measured.



40

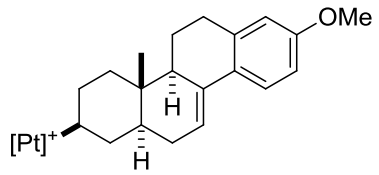
Compound 40: ^{31}P-NMR (162 MHz, CD_3NO_2) δ 89.2 ($J_{P\text{-}Pt}$ = 1280 Hz, 1 P), 41.0 ($J_{P\text{-}Pt}$ = 3060 Hz, 2 P). ^{1}H-NMR (400 MHz, CD_3NO_2) δ 7.86-7.57 (m, 25 H), 5.25 (s, 1 H), 3.40-2.12 (m, 8 H) 1.79-0.40 (m, 17 H), 1.56 (s, 3 H), 0.71 (s, 3 H), 0.04 (s, 3 H). ^{13}C-NMR (100 MHz, CD_3NO_2) δ 133.4-129.2 (32 C), 120.1 (1 C), 51.2 (1 C), 50.9 (1 C), 42.2 (1 C), 36.6 (1 C), 33.1 (2 C), 25.9 (1 C), 23.4 (2 C), 22.6 (1 C), 20.0 (2 C), 12.4 (2 C). $[M]^+$ = 960.3556 calculated, 960.3533 measured.



42

Compound 42: ^{31}P-NMR (162 MHz, CD_3NO_2) δ 91.2 ($J_{P\text{-}Pt}$ = 1030 Hz, 1 P), 43.1 ($J_{P\text{-}Pt}$ = 2430 Hz, 2 P). ^{1}H-NMR (400 MHz, CD_3NO_2) δ 7.99-7.56 (m, 25 H), 7.13-7.02 (m, 4 H), 6.27 (s, 1 H), 3.66-2.26 (m, 8 H), 1.89-0.68 (m, 14 H), 0.07 (s, 3 H). ^{13}C-NMR (100 MHz, CD_3NO_2) δ 144.7, 137.2, 136.8, 133.7-128.9 (30 C), 126.1, 125.7, 122.8, 121.5, 119.1, 49.5, 38.1, 35.0, 30.5, 28.5, 25.9, 22.3, 22.2, 17.5, 11.2, 11.2. $[M]^+$ = 980.3243 calculated, 980.3267 measured.

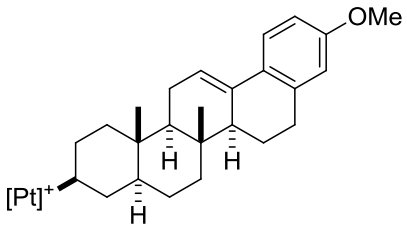
If compound 42 was left in solution for an extended period of time (>24 hours), isomerization of the double bond was observed.



44

Compound 44: ^{31}P-NMR (162 MHz, CD_3NO_2) δ 91.2 ($J_{P\text{-}Pt}$ = 1290 Hz, 1 P), 43.1 ($J_{P\text{-}Pt}$ = 3030 Hz, 2 P). ^{1}H-NMR (400 MHz, CD_3NO_2) δ 7.99-7.50 (m, 33 H), 6.10 (s, 1 H), 3.76 (s, 3 H), 3.57-2.31 (m, 8 H), 2.20-0.71 (m, 14 H), 0.06 (s, 3 H). ^{13}C-NMR (100 MHz, CD_3NO_2) δ 158.1, 138.2, 133.7-128.6 (30 C), 127.6, 124.3, 116.8, 112.7, 112.4, 110.5, 70.5, 54.4, 49.5, 45.6 (m, 1 C), 43.3 (m, 1 C), 37.7 (m, 1 C), 35.3 (m, 1 C), 34.9, 30.7, 30.4, 28.9, 22.3, 19.5, 17.5, 13.9. $[M]^+$ = 1010.3348 calculated, 1010.3314 measured.

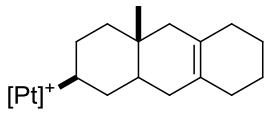
If compound **44** was left in solution for an extended period of time (>24 hours), isomerization of the double bond was observed.



46

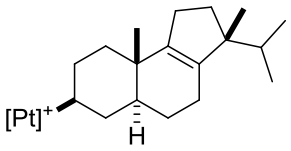
Compound 46: ^{31}P-NMR (162 MHz, CD_3NO_2) δ 91.1 ($J_{P\text{-}Pt}$ = 1290 Hz, 1 P), 43.0 ($J_{P\text{-}Pt}$ = 3040 Hz, 2 P). ^{1}H-NMR (400 MHz, CD_3NO_2) 7.95-7.54 (m, 25 H), 6.70-6.60 (m, 3 H), 6.20 (s, 1 H), 3.77 (s, 3 H), 2.82-2.29 (m, 8 H), 2.12-0.66 (m, 18 H), 0.18 (s, 3 H), 0.12 (s, 3 H). ^{13}C-NMR (100 MHz, CD_3NO_2) δ 157.9, 143.0, 138.3, 137.3, 133.5-129.0 (30 C), 124.0, 122.8, 117.3, 112.4, 70.5, 54.3 (2 C), 52.6, 43.5 (m, 1 C), 38.6, 36.9, 36.6, 35.4, 35.2 (m, 1 C), 32.1 (m, 1 C), 27.9, 24.9 (m, 1 C), 22.1, 20.5, 13.7, 12.9, 12.5, 11.2 (2 C). $[M]^+$ = 1078.3974 calculated, 1078.3974 measured.

If compound **46** was left in solution for an extended period of time (>24 hours), isomerization of the double bond was observed.



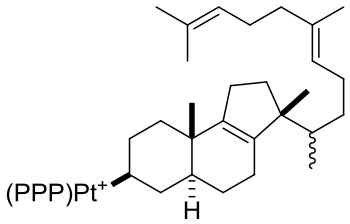
48

Compound 48: ^{31}P-NMR (162 MHz, CD_3NO_2) δ 91.3 ($J_{P\text{-}Pt}$ = 1290 Hz, 1 P), 42.9 ($J_{P\text{-}Pt}$ = 3040 Hz, 2 P). ^{1}H-NMR (400 MHz, CD_3NO_2) 7.84-7.26 (m 25 H), 3.46-2.22 (m 8 H), 1.77-0.58 (m, 20 H), 0.04 (s, 3 H). ^{13}C-NMR (100 MHz, CD_3NO_2) δ 133.6-129.2 (30 C), 126.5, 126.2, 47.6, 45.9 (m, 1 C), 45.5 (m, 1 C), 38.0, 35.7 (m, 1 C), 35.2, 32.9, 32.9, 30.4, 30.3, 29.8, 29.7, 25.1 (m, 1 C), 23.2, 23.2, 16.0 (2 C). $[M]^+$ = 932.3243 calculated, 932.3232 measured.



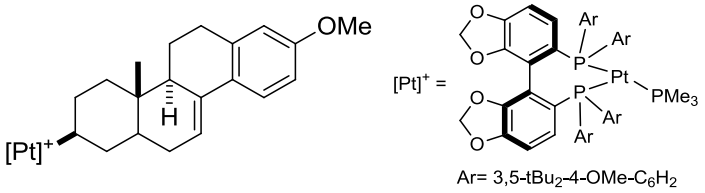
52

Compound 52: ^{31}P-NMR (162 MHz, CD_3NO_2) δ 91.0 ($J_{P\text{-}Pt}$ = 1290 Hz, 1 P), 43.14 ($J_{P\text{-}Pt}$ = 3050 Hz, 1 P), 43.11 ($J_{P\text{-}Pt}$ = 3050 Hz, 1 P). ^{1}H-NMR (400 MHz, CD_3NO_2) 7.96-7.62 (m, 25 H), 3.46-2.21 (m, 8 H), 1.82-0.58 (m, 17 H), 0.79 (s, 3 H), 0.75 (d, J = 8.8 Hz, 3 H), 0.61 (d, J = 8.9, 3 H), 0.02 (s, 3 H). ^{13}C-NMR (100 MHz, CD_3NO_2) δ 137.2, 133.9-129.2 (30 C), 127.5, 52.1, 35.4, 35.2 (m, 1 C), 33.1, 32.8 (m, 1 C), 29.7, 28.96 (m, 1 C), 28.95, 28.9, 27.3, 27.3, 26.8 (m, 1 C), 25.8, 24.2, 24.1, 21.9, 17.2, 16.7, 16.5. $[M]^+$ = 974.3712 calculated, 974.3735 measured.



67

Compound 67: Compound **67** could not be isolated as shown. NMR analysis of the worked up material (~60 %) showed multiple products.



In situ cyclization using compound 68: To 20 mg of (*R*-DTBM-SEGPHOS)PtI_2 (12.3 µmol) in 0.5 mL $EtNO_2$ was added 1.0 mg of trimethylphosphine (13.2 µmol) and the contents were stirred for 1 hour in the dark. 2 equivalents of substrate and 3 equivalents of piperidinomethyl polystyrene resin base were added followed by 6.0 mg of $AgBF_4$ (30.8 µmol) and the reaction mixture was left to stir for 14 hours in the dark. The contents of the reaction were then filtered through a 0.2 µm syringe filter, washing out the flask and syringe with 0.25 mL $EtNO_2$. ^{31}P-NMR (162 MHz, CD_3NO_2) δ 17.76 (dd, $J_{P\text{-}P}$ = 24, 409 Hz, $J_{P\text{-}Pt}$ = 1270 Hz, 1 P), 2.47 (t, $J_{P\text{-}P}$ = 22 Hz, $J_{P\text{-}Pt}$ = 1750 Hz, 1 P), -2.88 (dd, $J_{P\text{-}P}$ = 20, 409 Hz, $J_{P\text{-}Pt}$ = 1260 Hz, 1 P).

^{31}P-NMR of the crude material showed clean conversion to a platinum alkyl species. ^{1}H-NMR of the crude confirmed the existence of the platinum alkyl species by the characteristic upfield $–CH_3$ shift (0.13 ppm) and the trisubstituted alkene isomer was confirmed by the vinyl –CH shift (6.0 ppm). Attempts to isolate the compound were

unsuccessful due to its high solubility in organic solvents (as compared to the triphos ligand system) and the sensitivity (to vacuum) of the trimethylphosphine ligand on the platinum. Other solvents, such as hexamethyldisiloxane, caused an oiling out followed by precipitation with further washes. This solid was later determined to be a decomposition product. Removing the solvent under a steady stream of nitrogen or under vacuum resulted in loss of significant amounts of the trimethylphosphine and generation of new species. The compound was also susceptible to decomposition when exposed to silica gel, forming other platinum solvent adducts. Further complicating purification was a slow isomerization of the styrenic double bond at the B/C ring juncture to the tetra-substituted species (significant amounts visible within 24 h of starting the reaction).

Chapter 3 : Catalytic Platinum-Initiated Cation-Olefn Reactions with Simple Alkenes

Transitioning Catalytic Conditions to Simple Alkene Termini

Dicationic platinum complexes were shown to initiate the cation-olefin cascade cyclization of all hydrodon substrates with a terminating alkene. [63] These are considerably more difficult than the cyclization of poly-enes containing a protic terminus (OH, NH, etc.) (Figure 3.1).[64] Thus far, catalytic methodologies, especially those able to exercise absolute stereo-control have been unable to overcome the challenge of an alkene terminating group.[32] The protic terminating groups have the advantage of hydrogen-bond activation of the terminus by a base which leads to a nearly barrierless cascade when the substrate is in the correct conformation.[65] Since alkene termini don't become acidic until the cation is nearly fully formed, hydrogen-bond assistance is lost and higher energy intermediates are required which results in a decrease in cyclization rate. Enzymatic cyclizations overcome these inherent limitations by the strategic positioning of aryl-rings and bases for stabilizing cation-π interactions[9] but a fully synthetic adaptation must rely on other methods.

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[63] Sokol, J. G.; Korapala, C. S.; White, P. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 5658-5661.

[64] a) Pradal, A.; Chen, Q.; Faudot dit Bel, P.; Toullec, P. Y.; Michelet, V. *Synlett*, **2012**, *23*, 74-79. b) Cannon, J. S.; Olson, A. C.; Overman, L. E.; Solomon, N. S. *J. Org. Chem.* **2012**, *77*, 1961-1973. c) Sakakura, A.; Sakuma, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 3130-3133. d) Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888-2891. e)Liskin, D. V.; Sibbald, P. A.; Rosewall, C. F.; Michael, F. E. *J. Org. Chem.* **2010**, *75*, 6294-6296.

[65] a) Nowroozi-Isfahani, T.; Musaev, D. G.; Morokuma, K.; Gagné, M. R. *Organometallics* **2007**, *26*, 2540-2549. b) Jenson, C.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 10846-10854. c) Metivier, P.; Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1987**, *52*, 3724-3738.

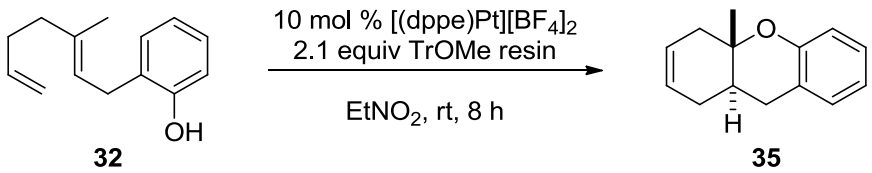


Figure 3.1: Previously reported catalytic cyclization with protic termini

Implementation and Optimization of Catalytic Conditions

It was expected that the cyclization of the alkene terminated substrates would follow the same mechanism as that proposed for their protic substrate counterparts. The bidentate dicationic platinum complex would coordinate to the monosubsitutued olefin and initiate cyclization. The cyclization would be completed when a base deprotonates the akyl product. Due to the open coordination site (the labile nitrile groups acts as a placeholder) the compound is able to undergo beta-hydride elimination, giving the desired product and a platinum-hydride. The conjugate acid of the base that deprotonated the substrate after the cyclization then acts as a proton shuttle and protonates the triphenyl methylether giving the active hydride abstractor, triphenyl carbenium (Tr^+). The Tr^+ is able to remove the hydride from the platinum complex regenerating the active platinum species.

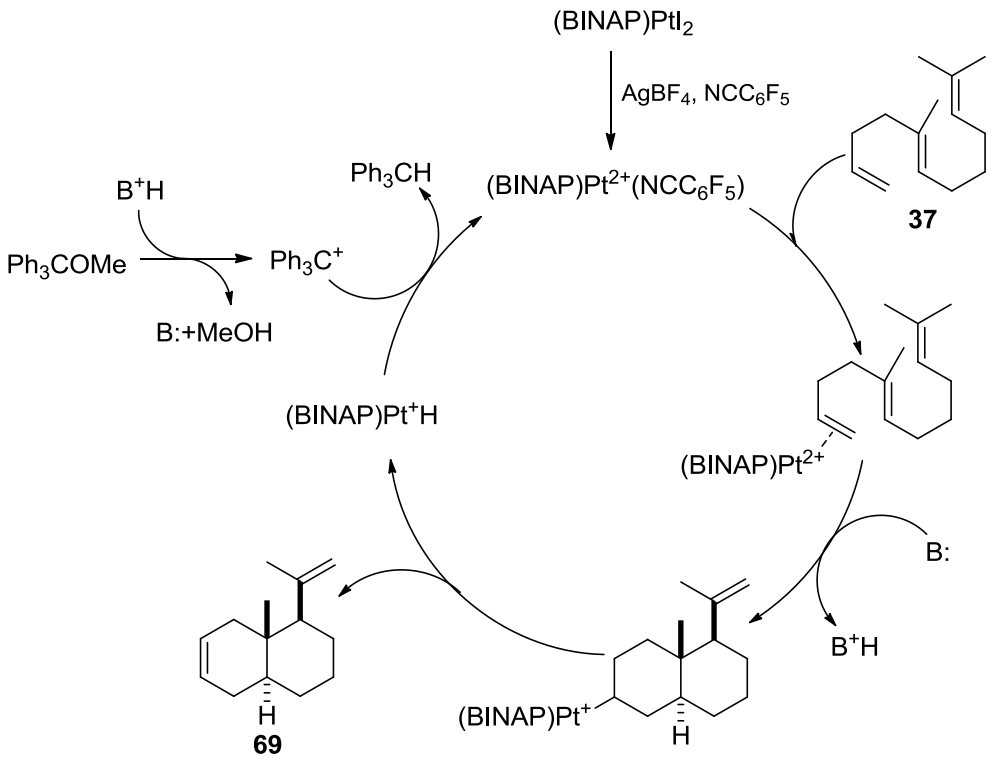


Figure 3.2: Proposed catalytic cycle for the cyclization of poly-ene substrates

Initial attempts to simply apply the conditions optimized for reactions with protic termini led to poor rates and conversions that eventually ceased prior to complete consumption of starting material. ^{31}P NMR analysis of the product showed the formation of π-allyl **70**, which is unreactive and ultimately acts as a catalyst decomposition process. A similar platinum-π-allyl complex had previous been isolated when no hydride abstractor was added to the cyclization of phenol terminated **32**. Thinking that the longer reaction times lead to catalyst deactivation, optimizations were performed.

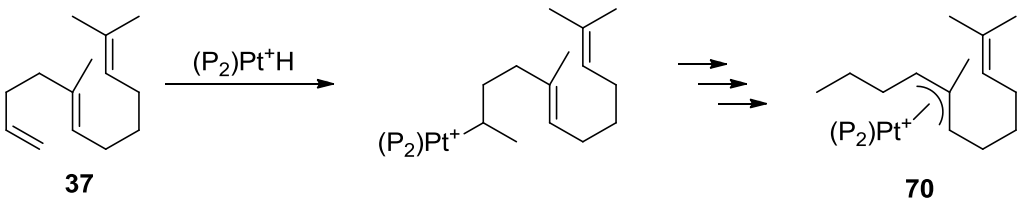


Figure 3.3: Deactivation of catalyst by formation of a π-allyl

The addition of the labile ligand pentafluorobenzonitrile significantly decreased the rate of platinum-π-allyl formation by filling vacant coordination slots on the platinum complex. Having this ligand readily available to coordinate with the platinum-hydride formed prevented coordination and insertion with free substrate and allowed for conversion of greater than 20%. Further optimization efforts sought to improve the hydride abstraction step of the proposed mechanism by the addition of an equivalent of Ph_3C^+ (Tr^+). This meant that at any point during the reaction, the concentration of hydride abstractor would be at least twice as large as the concentration of platinum-hydride and again saw a significant in jump observed product with conversions now over 50%. These conditions were utilized to search for beneficial ligand effects on a screen of common diphosphine ligands (Table 3.1). The ligand BINAP provided the highest conversion of starting material and the greatest percentage of desired product. The mass balance were minor amounts of unidentified isomeric products.

Table 3.1: Bidentate Phosphorus Ligand Screen

37 **69**

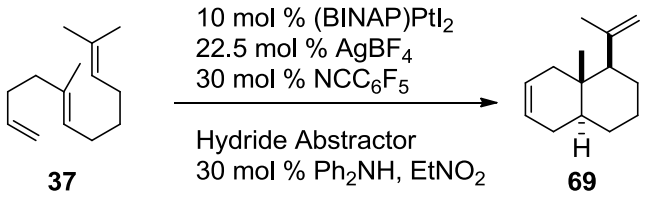
Entry	Ligand (P_2)	Consumption of **37** (%)[a]	**69** (%)[a]
1	BINAP	90	65
2	dppe	70	54
3	dppp	70	48
4	dppf	56	39

Reaction conditions: Substrate (100 µmols), Ph_2NH (30 µmols), TrOMe (160 µmols), and $TrBF_4$ (20 µmols) were added to a solution of $(P_2)PtI_2$ (10 µmols), $AgBF_4$ (25 µmols), and NCC_6F_5 (30 µmols) in $EtNO_2$ (0.5 mL) that had been filtered to remove AgI. [a] Determined by GCMS analysis.

A second round of optimization on the BINAP-based catalyst, paying particular attention to the seemingly key hydride abstraction step was undertaken (Table 3.2). In addition to TrOMe, the 4-methoxy variant, resin based versions of both and acetal-based variants were tested.[66] While dimethoxy methane (and benzaldehyde) function well with protic terminators, they led to reaction rates that were half that of TrOMe. The use of TrOMe plus an equimolar quantity (to Pt) of $TrBF_4$ ensured that the putative $P_2Pt\text{-}H^+$ intermediate reacted with at least a 2-fold excess of Tr^+. More than any other modification of the reaction conditions, extra Tr^+ was most beneficial. Increasing $TrBF_4$ up to a 5-fold excess (vs. platinum) gave the highest percentage of desired product and 100% conversion of **37** was possible. Further increases in $TrBF_4$ proved detrimental.

[66] Cochrane, N. A.; Brookhart, M. S.; Gagné, M. R. *Organometallics* **2011**, *30*, 2457-2460.

Table 3.2: Hydride Abstractor Screen



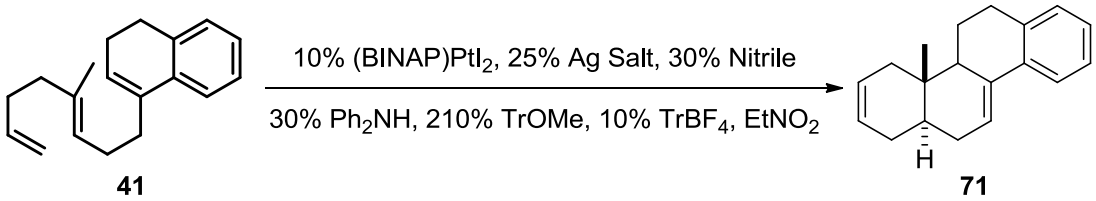
37 **69**

Entry	Hydride Abstractor	**69** (%)
1	200% TrOMe	17
2	300% TrOMe resin	14
3	200% 2(4-Meo)TrOMe	7
4	300% (4-MeO)TrOMe resin	8
5	200% TrOMe, 10% $TrBF_4$	44
6	160% TrOMe, 20% $TrBF_4$	65
7	100% TrOMe, 50 % $TrBF_4$	90
8	160% $(MeO)_2CH_2$, 10% $[Ph_2NH_2][BF_4]$	18

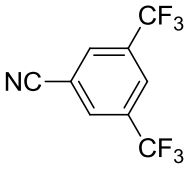
Reaction conditions: Substrate (100 µmols), Ph_2NMe (30 µmols), and hydride abstractor were added to a solution of (BINAP)PtI_2 (10 µmols), $AgBF_4$ (25 µmols), and NCC_6F_5 (30 µmols) in $EtNO_2$ (0.5 mL) that had been filtered to remove AgI. [a] Determined by GCMS analysis.

A second round of optimization were performed using a substrate that resulted in multiple products. This was to determine not just the different reagents effect on rate and converson of starting material but also on product distribution. The differences in yield observed when changing the silver salt and the nitrile suggests that both compounds have a direct relationship with the reagent which causes product isomerization, likely the Tr^+.

Table 3.3: Product Distribution Optimization



41 **71**

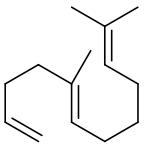
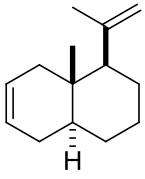
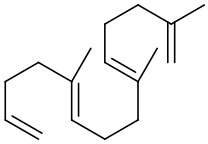
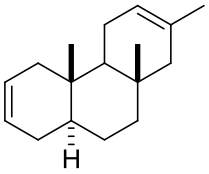
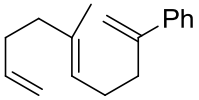
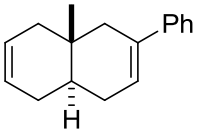
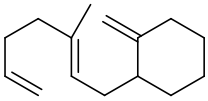
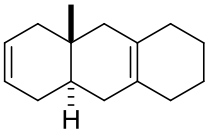
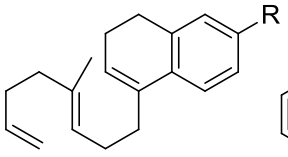
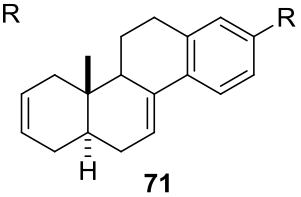
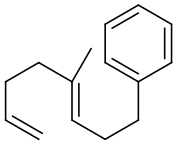
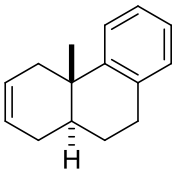
Entry	Silver Salt	Nitrile	**71** (%) of product[a]
1	$AgBF_4$	NCC_6F_5	37
2	$AgPF_6$	NCC_6F_5	33
3	$AgSbF_6$	NCC_6F_5	31
4	$AgSO_3CH_3$	NCC_6F_5	20
5	$AgBF_4$	$NCC(CH_3)_3$	36
6	$AgBF_4$		30

Reaction conditions: Substrate (100 µmols), Ph_2NMe (30 µmols), and hydride abstractor were added to a solution of (BINAP)PtI_2 (10 µmols), silver salt (25 µmols), and nitrile (30 µmols) in $EtNO_2$ (0.5 mL) that had been filtered to remove AgI. [a] Determined by GCMS analysis.

Substrate Scope and Observations

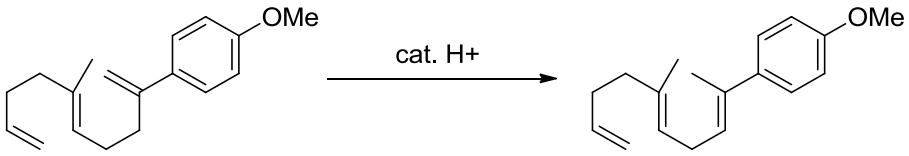
With a set of reaction conditions capable of efficiently converting **37** to **69** (90%) fully optimized, the scope of alternative poly-ene structures was investigated (Table 3.4). The tetra-ene **39** was found to efficiently generate a single diastereomer of **72** as the predominant product of the oxidative cyclization (entry 2).

Table 3.4: Substrate scope of polyolefin cyclizations

Entry	Substrate	Cyclized Product	Time[a] (h)	Conversion[b]
1	 **37**	 **69**	48	90
2	 **39**	 **72**	36	89
3	 **49**	 **73**	36	90
4	 **47**	 **74**	16	33
5	 **41** R = H	 **71**	24	50
6	**43** R = OMe	**75**	8	55
7	 **55**	 **76**	16	32

Reaction conditions: Substrate (100 µmols), Ph_2NMe (30 µmols), TrOMe (100 µmols), and $TrBF_4$ (50 µmols) were added to a solution of (BINAP)PtI_2 (10 µmols), $AgBF_4$ (25 µmols), and NCC_6F_5 (30 µmols) in $EtNO_2$ (0.5 mL) that had been filtered to remove AgI. [a]Measured at the time of complete substrate consumption. [b]Determined by GCMS analysis. Mass balance composed of all other isomers of product and starting material. Isolated yields could be obtained but difficulties in hydrocarbon separation considerably lowered the yields (5-20%). See experimental section for more information.

The nucleophilicity of the terminating alkene[67] was a good predictor of the reaction time. Poly-ene substrates with more nucleophilic terminating alkenes were thus tested, though their cyclizations met with mixed success. Some cyclized effectively (e.g. entry 3) while others displayed more complex behavior. The styrene terminated **49** proved to be an excellent substrate, providing the bicyclic diene **73** in 90% yield. In contrast, the para-methoxy substituted variant, **15**, readily isomerized to the tri-substituted (and unreactive) alkene **16** before cyclization could take place (Figure 3.4).



77 **78**

Figure 3.4: Starting material isomerization

The low yields for the dihydronaphthyl substrates **41** and **43** are due to a series of side reactions (Scheme 2). In addition to the expected reactivity, the starting materials were found to directly oxidize to the naphthyl product on treatment with Tr^+/TrOMe. Surprisingly, this potential cation-olefin substrate was found not to cyclize under standard conditions. Compounds **71** and **75** were also prone to rearrangement under the acidic conditions. This rearrangement can be accelerated by the deliberate addition of acid ($MeSO_3H$).

[67] a) Mayr, H.; Kempf, B.; Ofial, A. *Acc. Chem. Res.* **2003**, *36*, 66-77. b) Mayr, H.; Patz, M. *Angew. Chem. Int. Ed.* **1994**, *33*, 938-957.

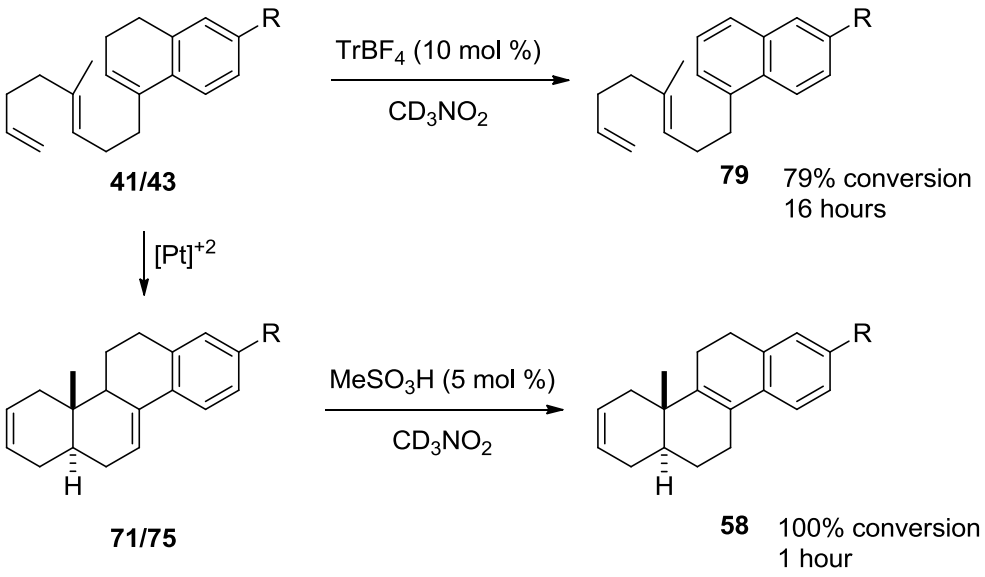


Figure 3.5: Confirmation of side reactivity of dihydro-naphthyl starting material and products

Like substrates **41** and **43**, substrate **47** was also oxidized readily by Tr^+. It is believed that the tertiary hydride at position 8, is absconded leaving behind allyl-cation **80** which can then rearrange Figure 3.6. Adding 0.2 equivalents of $TrBF_4$ to a solution of only substrate would result in complete consumption of all starting material in 24 hours to a variety of products, suggesting that the cation formed on the rearranged isomer can be quenched by abstracting a hydride from more stating material.

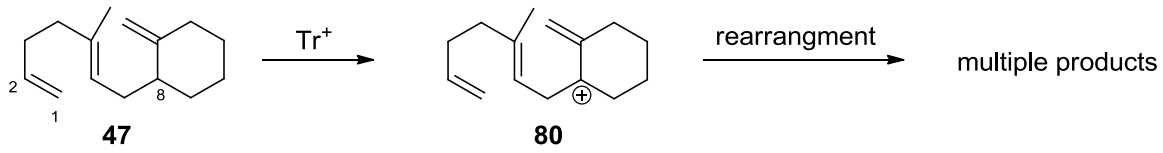


Figure 3.6: Reactivity of 47 with hydride abstractor

Aryl terminating groups have provided various amounts of success with other cyclization techniques.[26] Compound **55** differs from the other compounds in this study due to the abundance of side products. The stoichiometric cyclization of **55** with $(PPP)Pt^{+2}$ results in one product, albeit with a long reaction time and low yield due to the poor

nucleophlicity of the unsubstituted arene ring. This is not the case with the catalytic results presented here where **55** has one of the shorter reaction times but with as many as five byproducts visible by GC. This difference is likely caused by the increased electrophilicity of the platinum complex when a bidentate phosphorus ligand is used (catalytic reactions) versus when the tridentate phosphorus ligand was used (stoichiometric). The combination of the more electrophilic initiator with the less nucleophlic terminator in conjunction with the capabilities of the aryl group to perform cation-π stabilization (Figure 3.7) may result in just A ring formation, a first for this system, which has previously been reported using other initiators.[21]

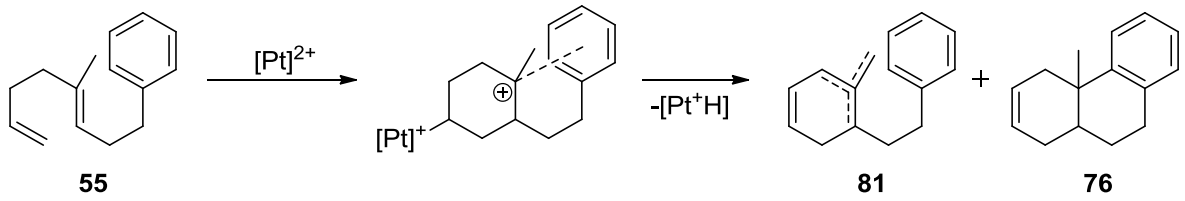


Figure 3.7: Stabilization of aryl intermediate leading to multiple products

The clean conversion of **5** to diene **6** suggests that the putative carbenium ion intermediate **A** may generate product under kinetic or thermodynamic control. DFT calculations[68] on the decalin (deplatinated) products indicated that the observed product was favored by 4.0 kcal mol^{-1} over its alternative styrene isomer (Figure 3.8). Attempts to manipulate the direction of this elimination through methyl substitutions on the carbon skeleton were unsuccessful. When the 8,8-dimethyl analog of **49** was examined (Figure 3.9), no reaction was observed, either with the standard P_2Pt^{+2} or the (triphos)Pt^{+2} initiators. An analysis of the low energy conformers of 8,8-Me_2-**49** suggested that gem-dimethyl groups

[68] DFT B3LYP/6-31G* calculations on the deplatinated analogs, MacSpartan 2008 calculations; energies were uncorrected.

deconjugate the styrene, which reduces its nucleophilicity and the stability of the benzyl cation intermediate.

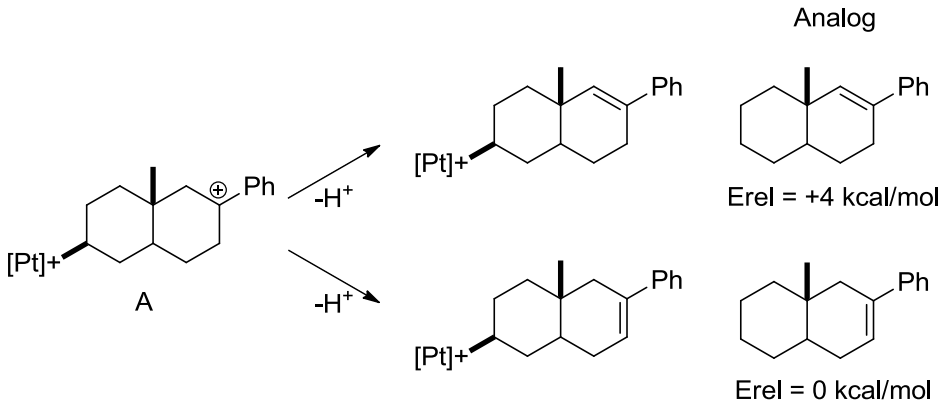


Figure 3.8: Relative energies of potential products for the cyclization of 49

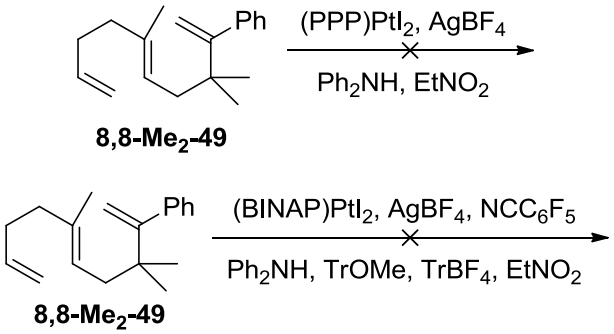


Figure 3.9: Lack of reactivity for compound 8,8-Me2-49

Attempts to utilize more nucleophilic aryl- or enol-ethers as a nucleophilic alkene terminus were also unsuccessful. When applying the standard reaction conditions to phenyl ether **82**, product **35** was observed. Reaction monitoring by GC revealed that **82** was first isomerized to **32**, and this species subsequently cyclized to the known **35**.[44] The same rearrangement was also observed for compound **83**, suggesting that the isomerization is not caused by the standard platinum coordination to the substrate. Experiments on the enol ethers **86** and **87** led to complex product mixtures, indicating that these more nucleophilic termini are not

compatible with the present catalyst system. Similar allyl enol rearrangements have been previously reported.[69]

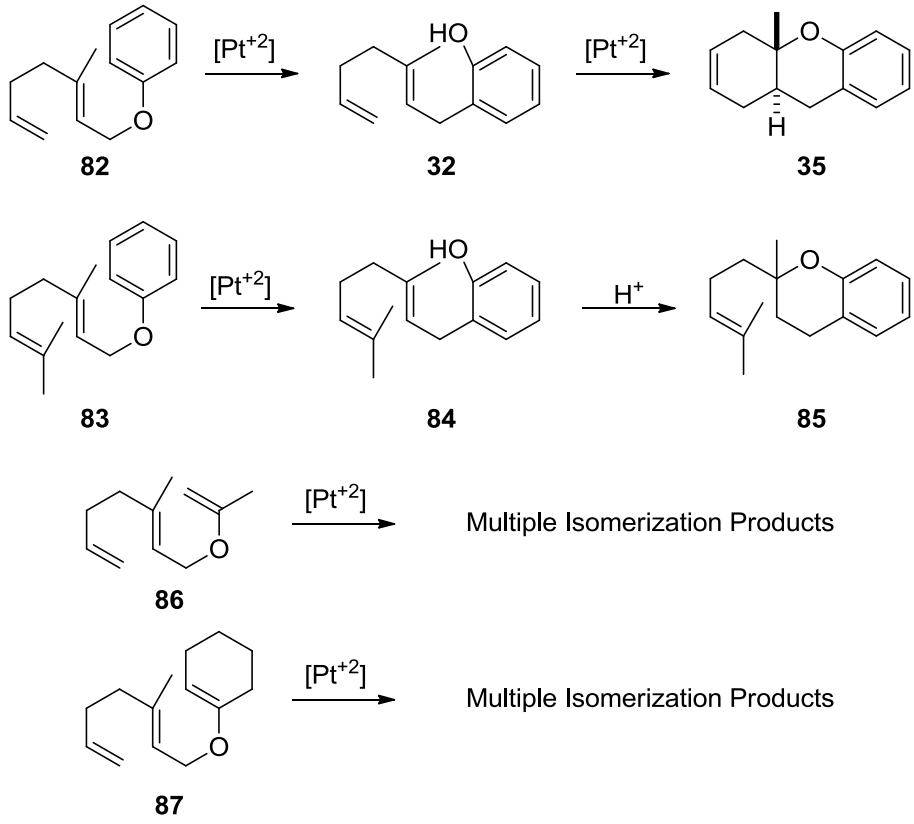


Figure 3.10: Rearrangment of aryl- and enol-ethers under standard conditions

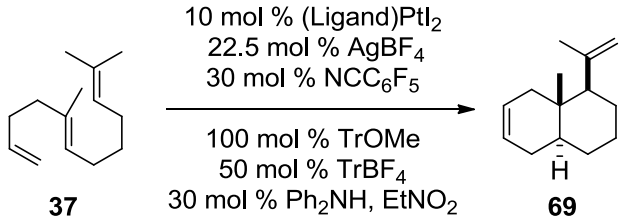
Enantioselective Investigation

The ability to catalyze the cation-olefin cyclization under the control of a P_2Pt^{+2}-catalyst suggests that enantioselective catalysts could be developed using chiral P_2 ligands. As shown in Table 3.5, the optimum conditions could be ported to catalysts carrying chiral diphosphine ligands. As before,[45] the xylyl-PHANEPHOS derived catalyst provided the optimum enantioselectivites (79% *ee*) but at the cost of conversion. The xylyl-BINAP gave a reasonable compromise between conversion and % *ee*. Experiments were also performed

[69] a) Bernard, A. M.; Cocco, M. T.; Onnis, V.; Piras, P. P. *Synthesis*, **1998**, 256-258. b) Smit, V. A.; Pogrebnoi, S. I.; Kal'yan, Y. B.; Krimer, M. Z. *Russ. Chem. Bull.* **1990**, *39*, 1760-1761.

using chiral ligands on compounds **39** and **49** but enantioselectivites could not be determined due to poor separation of the products.

Table 3.5: Cyclizations with Chiral Diphosphine Ligands



37 **69**

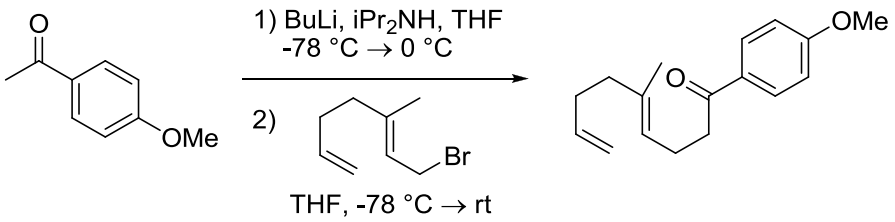
Entry	Ligand	Conversion (%)	% *ee*[a]
1	(*R*)-xylyl-PHANEPHOS	44	79
2	(*R*)-xylyl-MeO-BIPHEP	80	68
3	(*R*)-xylyl-BINAP	87	67
4	(*R*)-SEGPHOS	90	44

Reaction conditions: Substrate (100 µmols), Ph_2NH (30 µmols), TrOMe (100 µmols), and $TrBF_4$ (50 µmols) were added to a solution of $(P_2)PtI_2$ (10 µmols), $AgBF_4$ (25 µmols), and NCC_6F_5 (30 µmols) in $EtNO_2$ (0.5 mL) that had been filtered to remove AgI. [a] Determined by chiral GC analysis.

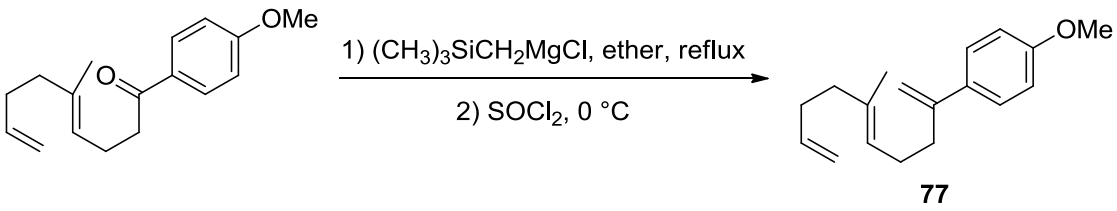
Conclusion

This represents the first electrophilic metal initiated catalytic cascade cyclization of poly-enes containing alkene terminating groups. We also learned that improving the hydride abstraction step which regenerates the active catalyst was critical for developing this methodology. While not the most comprehensive of systems, a wide range of substrates where attempted and many were able to transform into the desired product in high conversions.

Experimental Section



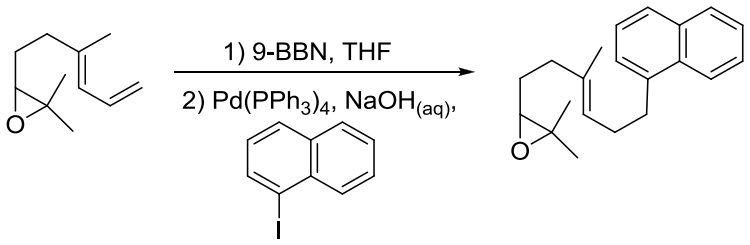
(*E*)-1-(4-methoxyphenyl)-5-methylnona-4,8-dien-1-one: A solution of *n*-butyllithium (20 mL, 1.6 M in hexanes) was added to a solution of diisopropylamine (5.2 mL, 34 mmol) in 30 mL THF at -78 °C. The reaction was stirred for one hour. The acetanisole (4.3 mL, 31 mmol) was then added and the solution was stirred for an additional hour. The (*E*)-7-bromo-5-methylhepta-1,5-diene (7.0 g, 37 mmol) was then added and the temperature of the reaction mixture was brought to room temperature. The reaction was left to stir overnight. The reaction was quenched using 0.5 M HCl (5 mL) and the product was extracted using ether (5 mL) three times. The organics were then washed with brine (50 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil (4.1 g, 16 mmol, 52%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.7 Hz, 2 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 5.84-5.74 (m, 1 H), 5.21 (t, *J* = 7.1 Hz, 1 H), 5.00 (dd, *J* = 17.0 Hz, 1.2 Hz, 1 H), 4.93 (dd, *J* = 10.1 Hz, 1.0 Hz, 1 H), 3.88 (s, 3 H), 2.95 (t, *J* = 7.6 Hz, 2 H), 2.45 (dt, *J* = 7.4 Hz, 7.3 Hz, 2 H), 2.14 (t, *J* = 7.3 Hz, 2 H), 2.07 (dt, *J* = 7.8 Hz, 3.4 Hz, 2 H), 1.64 (s, 3 H).



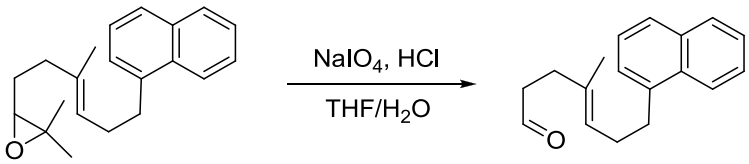
77

(*E*)-1-methoxy-4-(6-methyldeca-1,5,9-trien-2-yl)benzene, 77:

(Trimethylsilyl)methylmagnesium chloride (3.4 mL, 1.0 M in diethyl ether) was added to a solution of (*E*)-1-(4-methoxyphenyl)-5-methylnona-4,8-dien-1-one (0.40 g, 1.6 mmol) in 50 mL diethyl ether. The reaction mixture was heated to reflux for 24 hours. The mixture was cooled to 0 °C and thionyl chloride (0.44 mL, 6 mmol) was added. The reaction was stirred for an additional hour at 0 °C. The reaction was quenched using saturated $NH_4Cl_{(aq)}$ (5 mL). The reaction mixture was vacuum filtered through a fritted funnel, and the aqueous layer was removed and extracted with ether (10 mL) three times. The combined organics were then dried with Na_2SO_4 and the volatiles were removed under vacuum. Silica gel flash column chromatography was performed using hexanes as the eluent (Rf = 0.6) resulting in a colorless oil (0.24 g, 0.9 mmol, 56 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 5.88-5.80 (m, 1 H), 5.24 (d, *J* = 3.6 Hz, 1 H), 5.20 (t, *J* = 7.2 Hz, 1 H), 5.05 (dd, *J* = 17.1 Hz, 1.6 Hz 1 H), 5.01 (d, *J* = 3.0 Hz, 1 H), 4.97 (dd, *J* = 10.1 Hz, 1.0 Hz, 1 H), 3.82 (s, 3 H), 2.92 (t, *J* = 7.1 Hz, 2 H), 2.21-2.07 (m, 6 H), 1.70 (s, 3 H). ^{13}C-NMR (151 MHz, $CDCl_3$) δ 158.5, 147.6, 138.8, 134.9, 133.8, 127.9, 127.2, 126.6, 125.6, 124.2, 114.4, 113.5, 55.3, 39.1, 35.5, 32.4, 27.8, 16.0. HRMS: [M] = 256.18176 measured, 256.18272 calculated.



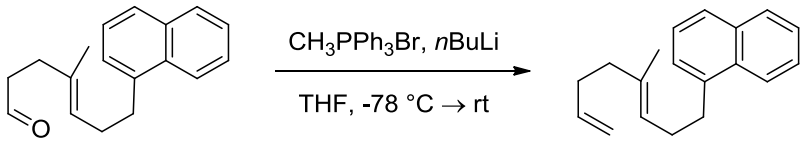
(E)-2,2-dimethyl-3-(3-methyl-6-(naphthalen-1-yl)hex-3-enyl)oxirane: A solution of 9-BBN (25mL, 0.5 M in THF) was added to a solution of (E)-2,2-dimethyl-3-(3-methylhexa-3,5-dienyl)oxirane[70] (1.87 g, 11 mmol) in 20 mL THF (at 0 °C). The reaction was slowly warmed to room temperature and then stirred overnight. A solution of 4-iodo-1,2-dihydronaphthalene (1.5 g, 6 mmol) in 20 mL THF was added followed by $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.25 g, 0.3 mmol) and sodium hydroxide (9 mL, 36 mmol, 4N in H_2O). The reaction was then stirred overnight. The aqueous layer was then separated and extracted with ether. The combined organics were washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum. Silica gel flash column chromatography was performed using 10% either in hexanes (Rf = 0.4). This resulted in a yellow oil (1.1 g, 3.7mmol, 72%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.22-7.15 (m, 4 H), 5.88 (t, *J* = 4.4 Hz, 1 H), 5.28 (t, *J* = 6.6 Hz, 1 H), 2.77-2.73 (m, 2 H), 2.49 (t, *J* = 8.0 Hz, 1 H), 2.27-2.09 (m, 8 H), 1.689-1.62 (m, 2 H), 1.60 (s, 3 H), 1.33 (s, 3 H), 1.29 (s, 3 H).



(E)-4-methyl-7-(naphthalen-1-yl)hept-4-enal: The (E)-3-(6-(3,4-dihydronaphthalen-1-yl)-3-methylhex-3-enyl)-2,2-dimethyloxirane (1.1 g, 3.8 mmol) and sodium *m*-periodate (1.1 g,

[70] K. Surendra, E. J. Corey, *J. Am. Chem. Soc.*, **2008**, *130*, 8865-8869.

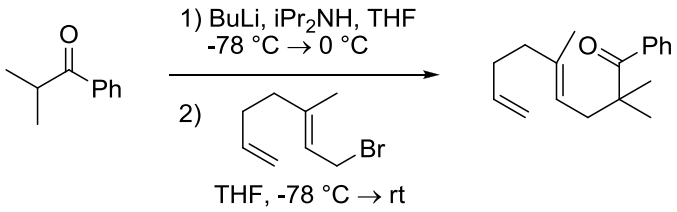
5.0 mmol) were added to a mixture of 10 mL THF and 2 mL H_2O. 5 drops of concentrated hydrochloric acid was added and the reaction was stirred for 2 hours. 20 mL of saturated $Na_2S_2O_{3\,(aq)}$ was added and the precipitate was filtered off. The aqueous layer was removed and extracted with ether three times. The combined organics were washed with saturated $NaHCO_{3(aq)}$ (20 mL) and brine (20 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil (0.74g, 2.9 mmol, 77%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 10.8 Hz, 1 H), 7.29-7.15 (m, 4 H), 5.86 (t, *J* = 4.4, 1 H), 5.25 (t, *J* = 6.4, 1 H), 2.78-2.18 (m, 12 H), 1.60 (s, 3 H).



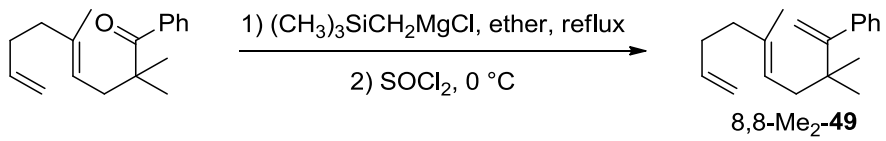
79

(E)-1-(4-methylocta-3,7-dienyl)naphthalene: A solution of *n*-butyllithium (3 mL, 1.6 M in hexanes) was added to a solution of methyltriphenylphosphoniumbromide (1.8 g, 5.0 mmol) in 20 mL of THF at -78 °C. The reaction was stirred for one hour at -78 °C. A solution of (E)-7-(3,4-dihydronaphthalen-1-yl)-4-methylhept-4-enal (0.7 g, 2.9 mmol) in 5 mL THF was added to the phosphonium ylide at -78 °C. The reaction mixture was slowly brought to room temperature and left to stir overnight. The reaction mixture was quenched using 0.1 M $HCl_{(aq)}$ (10 mL). The aqueous layer was then removed and extracted with ether. The combined organics were then washed with water (20 mL) and brine (20 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum. The resulting oil was then extracted using pentanes three times. Silica gel flash column chromatography was performed using hexanes (Rf = 0.5) resulting in a clear oil (0.49 g, 1.9 mmol, 65 %). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 4 H), 5.88 (t, *J* = 4.4 Hz, 1 H), 5.85-5.81 (m, 1 H), 5.24 (t, *J* = 7.2

Hz, 1 H), 5.04 (d, *J* = 17.2 Hz, 1 H), 4.97 (d, *J* = 10.4 Hz, 1 H), 2.75 (dt, *J* = 8.0, 11.2 Hz, 2 H), 2.48 (t, *J* = 7.6 Hz, 2 H), 2.25 (dt, *J* = 6.4, 7.2 Hz, 4 H), 2.17 (t, *J* = 7.2 Hz, 2 H), 2.09 (t, *J* = 7.4 Hz, 2 H), 1.59 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.8, 136.8, 136.2, 135.1, 134.9, 127.6, 126.5, 126.3, 124.9, 124.4, 122.6, 114.3, 39.1, 32.8, 32.4, 28.5, 27.0, 23.2, 16.1.



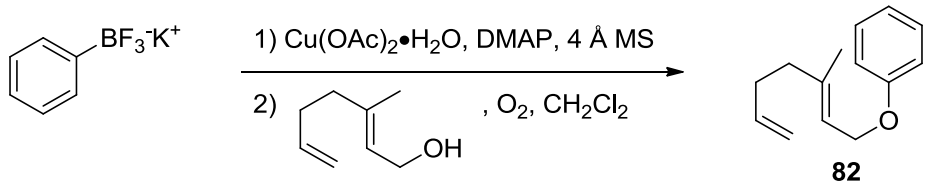
(*E*)-2,2,5-trimethyl-1-phenylnona-4,8-dien-1-one: A solution of *n*-butyllithium (3.0 mL, 1.6 M in hexanes) was added to a solution of diisopropylamine (0.7 mL, 5.0 mmol) in 15 mL THF at -78 °C. The reaction was stirred for one hour. The isobutyrophenone (0.75 mL, 5.0 mmol) was then added and the solution was stirred for an additional hour. The (*E*)-7-bromo-5-methylhepta-1,5-diene (1.0 g, 5.3 mmol) was then added and the temperature of the reaction mixture was brought to room temperature. The reaction was left to stir overnight. The reaction was quenched using 0.5 M HCl (5 mL) and the product was extracted using ether (5 mL) three times. The organics were then washed with brine (30 mL), dried with $MgSO_4$, and the volatiles were removed under vacuum resulting in a yellow oil (6.6 g, 32 mmol, 83%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.9 Hz, 2 H), 7.56 (t, *J* = 7.0 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 2 H), 5.81-5.71 (m, 1 H), 5.10 (t, *J* = 7.3 Hz, 1 H), 4.98 (d, *J* = 16.8 Hz, 1 H), 4.93 (d, *J* = 10.3 Hz, 1 H), 2.45 (d, *J* = 7.4 Hz, 2 H), 2.08-2.03 (m, 2 H), 1.88-1.82 (m, 2 H), 1.23 (s, 3 H), 0.97 (s, 3 H), 0.74 (s, 3 H).



8,8-Me_2-**49**

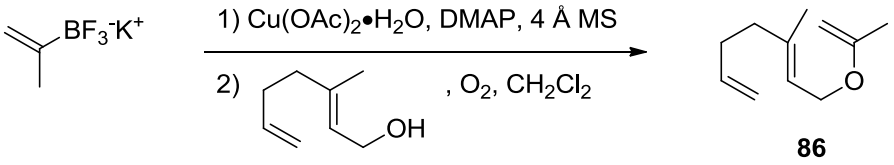
(*E*)-(3,3,6-trimethyldeca-1,5,9-trien-2-yl)benzene, 8,8-Me_2-49:

(Trimethylsilyl)methylmagnesium chloride (22 mL, 1.0 M in diethyl ether) was added to a solution of (*E*)-5-methyl-1-phenylnona-4,8-dien-1-one (2 g, 9.7 mmol) in 100 mL diethyl ether. The reaction mixture was heated to reflux for 24 hours. The mixture was cooled to 0 °C and thionyl chloride (3 mL, 40 mmol) was added. The reaction was stirred for an additional hour at 0 °C. The reaction was quenched using saturated $NH_4Cl_{(aq)}$ (50 mL). The reaction mixture was vacuum filtered through a fritted funnel, and the aqueous layer was removed and extracted with ether (25 mL) three times. The combined organics were then dried with $MgSO_4$ and the volatiles were removed under vacuum. Silica gel flash column chromatography was performed using hexanes as the eluent (Rf = 0.6) resulting in a colorless oil (1.7 g, 8.3 mmol, 86 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.43 (t, *J* = 8.0 Hz, 1 H), 7.35-7.32 (m, 2 H), 7.23 (d, *J* = 7.8 Hz, 2 H), 5.95-5.89 (m, 1 H), 5.33 (t, *J* = 7.0 Hz, 1 H), 5.13 (d, *J* = 1.2 Hz, 1 H), 5.05 (dd, *J* = 10.1 Hz, 1.0 Hz, 1 H), 5.02 (dd, *J* = 16.4 Hz, 1.0 Hz, 1 H), 4.96 (d, *J* = 1.2 Hz, 1 H), 2.30-2.22 (m, 2 H), 2.23-2.20 (m, 2 H), 2.17-2.13 (m, 2 H), 1.66 (s, 3 H), 1.19 (s, 3 H), 1.18 (s, 3 H). ^{13}C-NMR (151 MHz, $CDCl_3$) δ 158.0, 143.5, 138.9, 135.8, 129.9, 129.0, 128.2, 127.4, 126.7, 121.9, 114.5, 113.4, 110.1, 41.5, 39.4, 38.9, 32.5, 27.5, 22.1, 16.5. HRMS: [M] = 254.20267 measured, 254.2034 calculated.



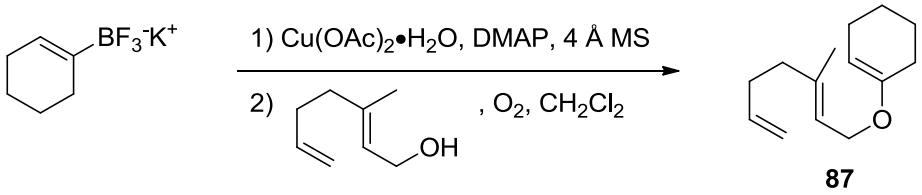
82

(*E*)-(3-methylhepta-2,6-dienyloxy)benzene, 82: A mixture of potassium phenyltriflouroborate (0.92 g, 5.0 mmol), copper(II) acetate hydrate (0.20 g, 1.0 mmol), dimethylaminopyradine (0.24 g, 2.0 mmol) and powdered 4 A molecular sieves (0.75 g) in CH_2Cl_2 (10 mL) was stirred for five minutes. The (*E*)-3-methylhepta-2,6-dien-1-ol[60] (0.31 g, 2.5 mmol) was added and the reaction mixture was sealed and placed under an oxygen atmosphere (delivered using a balloon). After 24 h, the cude mixture was filtered through a plug of celite and concentrated in vacuo. Silica gel flash column chromatography was performed using hexanes:ethyl acetate (9:1 ~ 1:1 gradient) as the eluent, resulting in a clear oil (0.49 g, 1.9 mmol, 65 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.4 Hz, 1 H), 7.10 (d, *J* = 8.4 Hz, 2 H), 7.01 (d, *J* = 8.2 Hz, 2 H), 5.94-5.84 (m, 1 H), 5.60 (t, *J* = 6.4 Hz, 1 H), 5.12 (d, *J* = 17.1 Hz, 1 H), 5.05 (d, *J* = 10.2 Hz, 1 H), 4.62 (d, *J* = 6.4 Hz, 2 H), 2.31-2.24 (m, 4 H), 1.82 (s, 3 H). ^{13}C-NMR (151 MHz, CD_3CN) δ 138.6, 137.0, 131.3, 126.5 (2C), 125.3 (2C), 124.8, 121.5, 114.0, 58.2, 38.6, 31.8, 15.2. [M] = HRMS: 202.13662 measured, 202.13577 calculated.



86

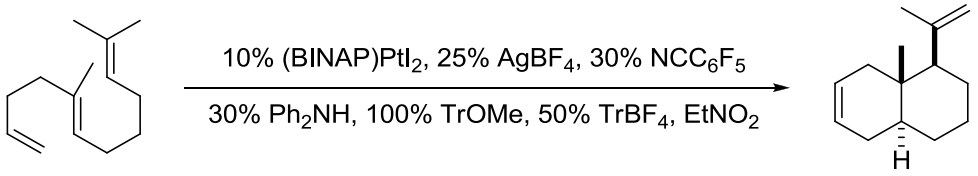
(*E*)-5-methyl-7-(prop-1-en-2-yloxy)hepta-1,5-diene, 86: A mixture of potassium isopropeneyltriflouroborate (0.74 g, 5.0 mmol), copper(II) acetate hydrate (0.19 g, 1.0 mmol), dimethylaminopyradine (0.24 g, 2.0 mmol) and powdered 4 A molecular sieves (0.75 g) in CH_2Cl_2 (10 mL) was stirred for five minutes. The (*E*)-3-methylhepta-2,6-dien-1-ol (0.31 g, 2.5 mmol) was added and the reaction mixture was sealed and placed under an oxygen atmosphere (delivered using a balloon). After 24 h, the cude mixture was filtered through a plug of celite and concentrated in vacuo. Silica gel flash column chromatography was performed using hexanes:ethyl acetate (9:1 ~ 1:1 gradient) as the eluent, resulting in a clear oil (0.49 g, 1.9 mmol, 65 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.86-5.77 (m, 1 H), 5.44 (t, *J* = 6.0 Hz, 1 H), 5.03 (dd, *J* = 1.8, 17.1 Hz, 1 H), 4.97 (dd, *J* = 2.0, 10.2 Hz, 1 H), 4.24 (d, *J* = 6.5 Hz, 2 H), 3.87 (d, *J* = 6.0 Hz, 2 H), 2.22-2.14 (m, 4 H), 1.85 (s, 3 H), 1.70 (s, 3 H). ^{13}C-NMR (151 MHz, CD_3CN) δ 138.6, 137.0, 124.7, 114.0, 112.9, 112.8, 58.2, 38.6, 31.8, 21.9, 15.2. [M] = HRMS: 166.13542 measured, 166.13577 calculated.



87

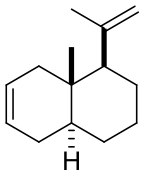
(*E*)-(3-methylhepta-2,6-dienyloxy)cyclohex-1-ene, 87: A mixture of potassium cyclohexeneyltriflouroborate (0.47 g, 2.5 mmol), copper(II) acetate hydrate (0.094 g, 0.5 mmol), dimethylaminopyradine (0.14 g, 1.1 mmol) and powdered 4 A molecular sieves (0.35 g) in CH_2Cl_2 (10 mL) was stirred for five minutes. The (*E*)-3-methylhepta-2,6-dien-1-ol

(0.16 g, 1.25 mmol) was added and the reaction mixture was sealed and placed under an oxygen atmosphere (delivered using a balloon). After 24 h, the cude mixture was filtered through a plug of celite and concentrated in vacuo. Silica gel flash column chromatography was performed using hexanes:ethyl acetate (9:1 ~ 1:1 gradient) as the eluent, resulting in a clear oil (0.49 g, 1.9 mmol, 65 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.86-5.76 (m, 1 H), 5.42 (t, *J* = 6.6 Hz, 1 H), 5.02 (dd, *J* = 1.6, 17.2 Hz, 1 H), 4.96 (dd, *J* = 1.6, 10.0 Hz, 1 H), 4.63 (t, *J* = 3.4 Hz, 1 H), 4.20 (d, *J* = 1.6 Hz, 2 H), 2.21-2.11 (m, 4 H), 2.09-2.04 (m, 4 H), 1.68 (s, 3 H), 1.59-1.52 (m, 2 H), 0.91 (m, 2 H). ^{13}C-NMR (151 MHz, $CDCl_3$) δ 154.5, 139.4, 138.3, 120.5, 114.5, 93.9, 63.2, 38.9, 31.9, 27.9, 23.6, 22.9, 22.8, 16.5. [M] = HRMS: 206.16659 measured, 206.16705 calculated.



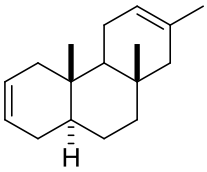
Standard Cyclization Procedure: The (BINAP)PtI_2 (10 µmol), $AgBF_4$ (22.5 µmol) and NCC_6F_5 (30 µmol) were mixed in 0.3 mL $EtNO_2$ for one hour in the dark. The mixture was filtered through a 0.2 µm PTFE syringe filter (rinsing with 0.3 mL $EtNO_2$) onto substrate (100 µmol), Ph_2NH (30 µmol), TrOMe (160 µmol) and $TrBF_4$ (20 µmol). The mixture was stirred until completion in the dark (8-48 hours, determined by GC). The mixture was passed through a silica gel plug using hexanes and the volatiles were removed under vacuum.

Product isolation is a problem associated with this chemistry due to the similar polarities of the product with starting material, alkene isomers of product and starting material, and the triphenyl methane generated as a result of the reaction. The most efficient method to isolate product was found to be the use of preparative-TLC using hexanes as the eluent. Due to minimal separation of the compounds, multiple separations were often required to obtain spectroscopically pure products. Isolated yields of these high purity products were consequently reduced to 5-20%.



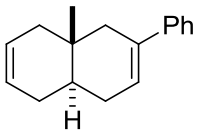
69

69: ^{1}H-NMR (600 MHz, CD_3CN) δ 5.62-5.58 (m, 2 H), 4.88 (dd, *J* = 1.0 Hz, 1.4 Hz, 1 H), 4.70 (d, *J* = 2.2 Hz, 1 H), 1.94-1.78 (m, 4 H), 1.79 (s, 3 H), 1.76-1.69 (m, 2 H), 1.48-1.24 (m, 6 H), 0.84 (s, 3 H). ^{13}C-NMR (151 MHz, CD_3CN) δ 147.7, 125.8, 125.6, 112.2, 55.9, 41.5, 40.4, 35.6, 30.0, 29.9, 28.1, 26.4, 23.6, 11.3. [M] = HRMS: 190.17271 measured, 190.17215 calculated.



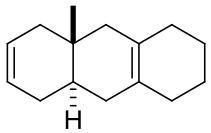
73

73: ^{1}H-NMR (600 MHz, CD_3CN) δ 5.68-5.54 (m, 2 H), 5.39 (m, 1 H), 1.92-1.65 (m, 4 H), 1.62 (s, 3 H), 1.59-1.25 (m, 9 H), 0.92 (s, 3 H), 0.81 (s, 3 H). ^{13}C-NMR (151 MHz, CD_3CN) δ 131.7, 126.1, 125.6, 120.0, 50.5, 50.3, 42.5, 41.3, 40.8, 33.0, 29.9, 29.7, 25.2, 22.9, 19.0, 12.0. [M] = HRMS: 230.20376 measured, 230.20345 calculated.



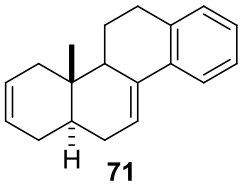
73

73: ^{1}H-NMR (600 MHz, CD_2Cl_2) δ 7.38 (t, *J* = 8.4 Hz, 2 H), 7.29 (t, *J* = 7.2 Hz, 2 H), 7.20 (d, *J* = 7.2 Hz, 1 H), 6.03 (t, *J* = 2.1 Hz, 1 H), 5.66-5.58 (m, 2 H), 2.32-1.87 (m, 7 H), 0.91 (s, 3 H). ^{13}C-NMR (151 MHz, CD_2Cl_2) δ 142.7, 135.0, 129.7, 128.1, 126.5, 125.9, 125.3, 125.0, 124.1, 123.2, 43.4, 41.3, 34.9, 31.0, 30.0, 23.1, 17.0. [M] = HRMS: 224.15715 measured, 224.15650 calculated.



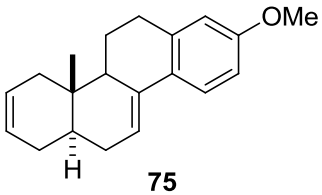
74

74: ^{1}H-NMR (600 MHz, CD_3CN) δ 5.632-5.592 (m, 2 H), 2.16-2.04 (m, 2 H), 1.90-1.85 (m, 8 H), 1.71-1.30 (m, 7 H), 0.84 (s, 3 H). ^{13}C-NMR (151 MHz, CD_3CN) δ 126.2, 126.1, 125.8, 125.4, 46.5, 40.8, 35.6, 35.3, 30.7, 30.1, 29.8, 29.5, 23.0, 23.0, 16.6. [M] = HRMS: 202.17267 measured, 202.17215 calculated.



71

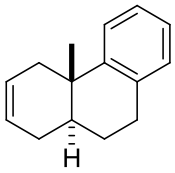
71: ^{1}H-NMR (600 MHz, CD_3CN) δ 7.71 (d, *J* = 8.6 Hz, 1 H), 7.24 (d, *J* = 7.7 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.13 (t, *J* = 7.4 Hz, 1 H), 5.75-5.64 (m, 3 H), 2.87-2.55 (m, 4 H), 2.37-2.01 (m, 4 H), 1.89-1.52 (m, 4 H), 1.05 (s, 3 H). ^{13}C-NMR (151 MHz, CD_3CN) δ 142.2, 129.1, 126.7, 126.6, 126.3, 125.9, 125.7, 125.3, 121.9, 118.7, 48.7, 38.8, 36.0, 29.8, 28.6, 26.3, 24.7, 22.8, 17.1. [M] = HRMS: 250.17276 measured, 250.17215 calculated.



75

75: ^{1}H-NMR (600 MHz, CD_3CN) δ 7.55 (d, *J* = 6.6 Hz, 1 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 6.74 (t, *J* = 3.0 Hz, 1 H), 6.73 (s, 1 H), 5.77-5.64 (m, 2 H), 3.78 (s, 3 H), 2.73-2.62 (m, 2 H), 2.36-1.98 (m, 7 H), 1.91-1.65 (m, 3 H), 1.03 (s, 3 H). ^{13}C-NMR (151 MHz, CD_3CN) δ 133.7,

130.5, 129.7, 127.8, 126.7, 125.8, 123.1, 112.9, 110.8, 106.6, 54.8, 38.8, 36.2, 30.2, 29.8, 29.0, 26.2, 24.7, 22.7, 17.1. [M] = HRMS: 280.18202 measured, 280.18272 calculated.



76

76: ^{1}H-NMR (600 MHz, CD_3CN) δ 7.34 (d, *J* = 8.0 Hz, 1 H), 7.16 (t, *J* = 7.6 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 1 H), 7.08 (t, *J* = 7.0 Hz, 1 H), 5.78-5.73 (m, 2 H), 2.90-2.48 (m, 4 H), 2.14-2.08 (m, 2 H), 1.70-1.66 (m, 3 H), 1.11 (s, 3 H). ^{13}C-NMR (151 MHz, CD_3CN) δ 135.6, 129.0, 126.5, 126.1, 125.9, 125.4, 125.2, 41.7, 39.6, 30.0, 29.5, 25.0, 21.7. [M] = HRMS: 198.1406 measured, 198.1409 calculated.

Chapter 4 : New Catalytic Cyclization Approach Using the Oxidation of Platinum Alkyl Functionalization of Platinum Alkyls

Platinum-alkyl compounds have shown the ability to undergo further functionalization.[71] Through the use of oxidizing agents, new coordination sites on the platinum complex become available and further reactivity is observed.[72] Recent advancements within the Gagné lab have demonstrated the ability to utilize numerous oxidizing agents to this desired effect.[73] These oxidation pathways have the potential to provide a more efficient way of turning over the catalytic cycle while also further functionalizing the product of platinum initiated poly-olefin cyclization.

Through the use of the F^+ source XeF_2, catalytic cyclization/fluorination reactions have been achieved (Figure 4.1).[74] It is predicted that the electrophilic F^+ is attacked by Pt, taking Pt^{II} to Pt^{IV}. Reductive elimination produces the alkyl fluoride and active platinum catalyst. Catalytic reactions were limited to protic termini as extended reaction times led to F^+ side reactions. Attempts to incorporate alkene terminated substrates with anything but pre-isolated platinum-alkyl were unsuccessful.

[71] a) Taylor, R. A.; Law, D. J.; Sunley, G. J.; White, A. J. P.; Britovsek, G. J. P. *Angew. Chem. Int. Ed.* **2009**, *48*, 5900-5903. b) Grice, K. A.; Goldberg, K. I. *Organometallics* **2009**, *28*, 953-955.
[72] Boisvert, L.; Goldberg, K. I. *Acc. Chem. Res.* **2012**, *45*, 899-910.
[73] a) Zhao, S.-B.; Becker, J. J.; Gagné, M. R. *Organometallics* **2011**, *30*, 3926-3929. b) Zhao, S.-B.; Want, R.-Y.; Nguyen, H.; Becker, J. J.; Gagné, M. R. *Chem. Commun.* **2012**, *48*, 443-445.
[74] Cochrane, N. A.; Nguyen, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2013**, *135*, 628-631.

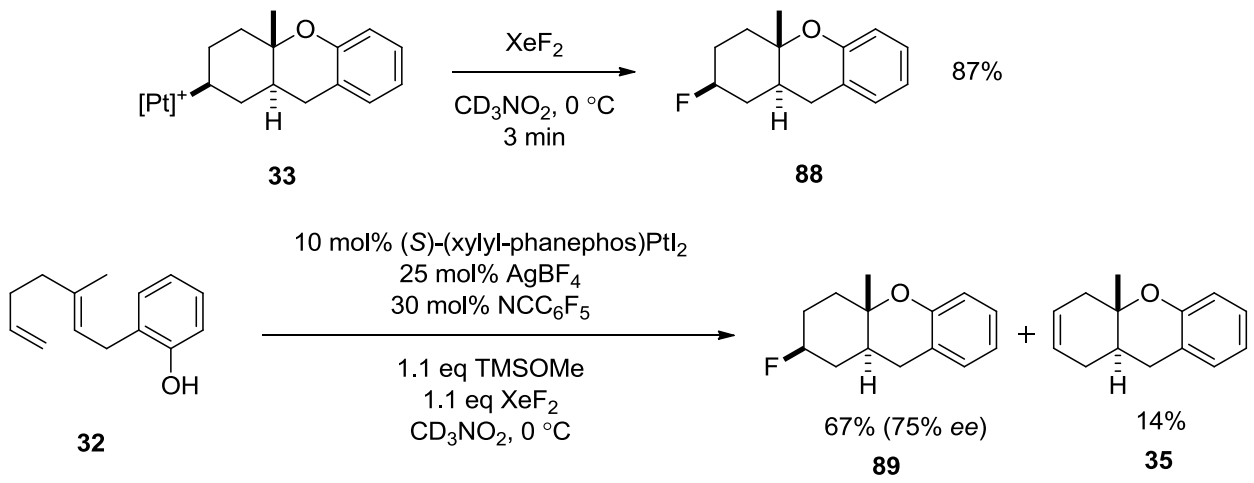


Figure 4.1: Stoichiometric and catalytic fluorination/cyclization reactions

Another recent discovery in the Gagné lab was the ability to use copper(II) based oxidants to generate a platinum(III) complex that would then undergo platinum-carbon bond hemolysis[75], regenerating an active dicationic platinum(II) species (Figure 4.2).[76] Trapping of the alkyl radical with molecular oxygen produced a mixture of ketone and alcohol. In addition to the oxygenated products, the compound that is produced by beta- hydride elimination was also observed, **35**. This product is obtained by further oxidation of the alkyl radical formed, leaving behind the unsaturated product, **35**.[77] Again, alkene terminated substrates resulted in lower conversions to oxygenated products. It was our hope that by removing any radical traps, and using an excess of milder copper oxidants (as compared to XeF_2), conditions could be optimized for the catalytic cyclization of poly-olefin substrates.

[75] a) Johansson, L.; Bryan, O. B.; Romming, C.; Tilset, M. *Organometallics* **1998**, *17*, 3957-3966. b) Chen, J. Y.; Kochi, J. K. *J. Am. Chem. Soc.* **1977**, *99*, 1450-1457.
[76] Geier, M. J.; Gagné, M. R. *Organometallics* **2013**, *32*, 380-383.
[77] Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843-855.

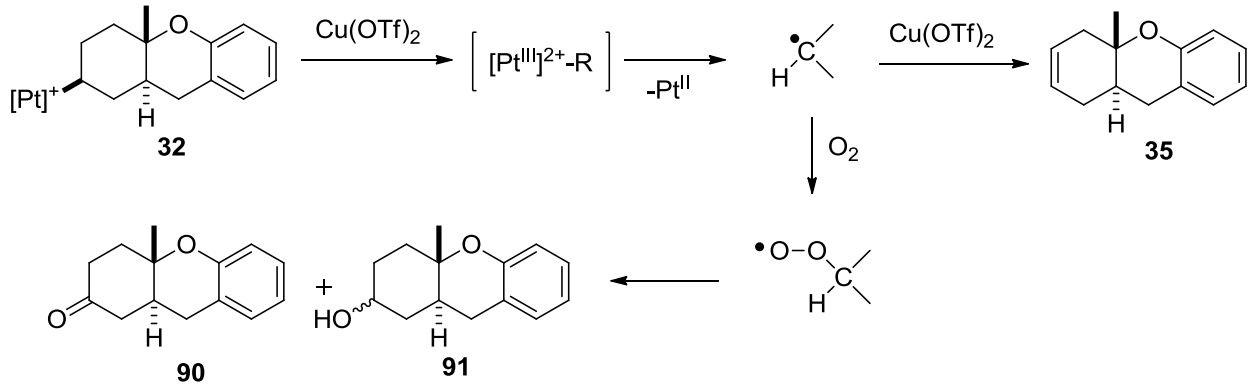


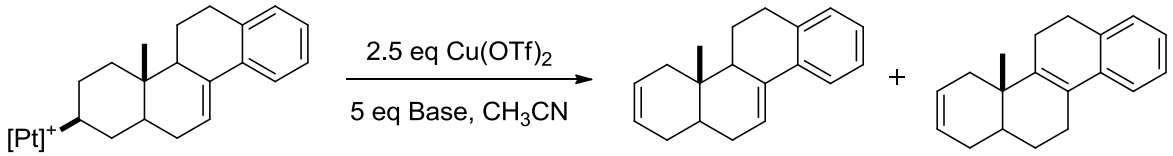
Figure 4.2: Oxidation and oxygenation of platinum alkyls

Adaptation and Optimization of the Copper Oxidation System

Initial experiments reacting platinum alkyls with $Cu(OTf)_2$ were very promising. Using an excess of the oxidant (at least 2 equivalents are needed to oxidize the Pt-alkyl and the alkyl radical) resulted in clean conversion to the dehydrogenated product. Reactions proceeded practically instantaneously in acetonitrile, but required much longer reaction times in nitromethane or methylene chloride (up to 16 hours). This was unfortunate, as running catalytic reactions in acetonitrile would be impossible due to the coordination of nitrile to platinum. The addition of an equivalent of nitrile to the reaction mixture in a different solvent returned reaction times to their previously torrid pace and left open the possibility of using small amounts of nitrile for catalytic reactions.

One side product that was of concern was the formation of HOTf after oxidation. This extremely strong acid is capable of readily isomerizing alkenes. When running stoichiometric oxidations in acetonitrile short reaction times allowed for removal of the acid prior to isomerization, except for compounds **71** and **75**. Their products had previously been shown to isomerize regularly in the presence of H^+ and that reactivity was extended here. A screen was performed to see if the addition of a base would hinder the reaction (Table 4.1).

Table 4.1: Base Screen to Reduce Isomerization of 71



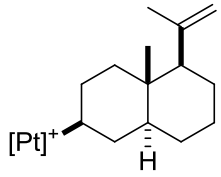
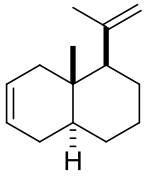
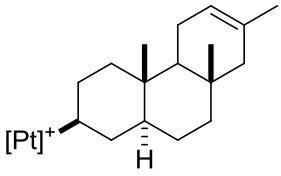
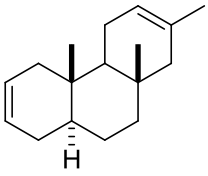
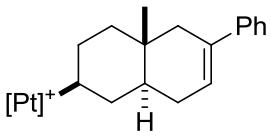
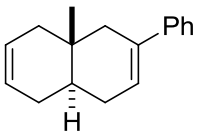
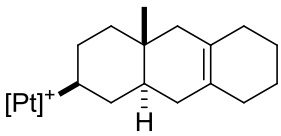
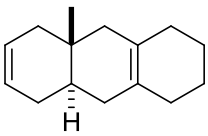
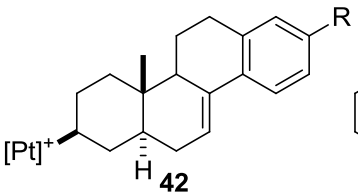
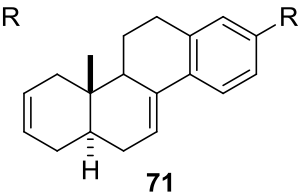
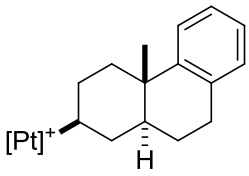
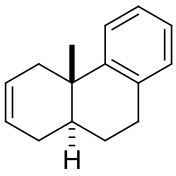
42 **71** **58**

Entry	Base	Conversion	Product Ratio (**71**:**58**)
1	Sodium Hydride	50%	6:1
2	Cesium Carbonate	100%	1.3:1
3	Potassium Carbonate	100%	1.1:1
4	Pentamethyl Piperidine	0%	NA
5	Diisopropyl Amine	0%	NA
6	Triethyl Amine	0%	NA
7	Proton Sponge	15%	5:1
8	Sodium Methoxide	100%	1:1.2
9	None	100%	1:1.2

Reaction Conditions: The base (50 µmols) and $Cu(OTf)_2$ (25 µmols) were weighed into a 1 dram vial and were then placed under vacuum and backfilled with N_2. **42** (10 µmols) in 0.5 mL of freshly distilled CH_3CN was added and the reaction was stirred for 2 minutes. [a]Determined by GCMS analysis.

The inorganic bases proved mostly ineffective at preventing isomerization with ratios that were only slightly better than when no base was used. Most amine bases were also ineffective due to their ability to ligate the copper(II) complex and prevent any oxidation from occurring. In the case of proton sponge (entry 7), the HOTf was prevented from forming but with a significant cost in conversion. Sodium hydride provided the greatest ratio of desired product to isomerized albeit still with a cost in conversion. Further optimization showed that by increasing the reaction time, conversions closer to 100% could be obtained.

Table 4.2: Oxidation of Cyclized Poly-Olefin Compounds

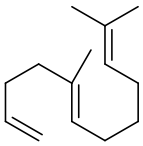
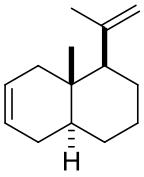
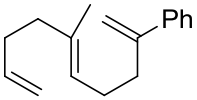
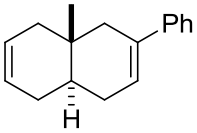
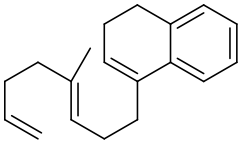
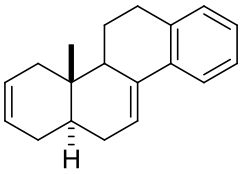
Entry	Substrate	Cyclized Product	Isolated Yield (NMR Yield)[a]
1	 **38**	 **69**	48% (88%)
2	 **40**	 **72**	56%
3	 **50**	 **73**	54% (84%)
4	 **48**	 **74**	37%
5[b]	 **42**	 **71**	42% (92%)
6[b]	**44**	**75**	37%
7	 **56**	 **76**	45%

[a]Reaction Conditions: The Platinum-alkyl (100 µmols) and $Cu(OTf)_2$ (250 µmols) were weighed into a 20 mL vial and were then placed under vacuum and backfilled with N_2. 5 mL of freshly distilled CH_3CN was added and the reaction was stirred for 5 minutes. [a]NMR yields were determined by running the reaction at 1/10 scale in an nmr tube using trimethoxybenzene as internal standard and CD_3CN as solvent. [b]For entries 5 and 6 (500 µmols of NaH was also added).

A variety of platinum-alkyl complexes were successfully oxidized (Table 4.2). While no by-products were observed by GCMS, isolated yields ranged from 37% to 56%. The small window in yield suggests that the differences in alkyl structure are insignificant in terms of how they impact the reaction. Running nmr scale reactions with trimethoxybenzene as an internal standard resulted in nmr yields ranging from 84% to 92% which match initial observations suggested that a clean product is formed. The clean products generated by this oxidation suggest that a catalytic system developed around the oxidation of platinum-alkyls should result in less byproducts than with the previously developed systems. Initial experiments on the feasibility of using this system for catalytic conversions were tested.

Using 20 mol% of the $(PPP)Pt^{2+}$ as catalyst produced some promising results (Table 4.3). Entry 1 shows that after 24 hours, essentially all the substrate had been cyclized and only a small percentage (<20%) of the product had been isomerized by HOTf. Entries 2 and 3 had less substrate consumption (despite having faster reaction times in the other methodologies that were developed) and more of their products were isomerized. This was not a surprise for entry 3 where it could be expected that over longer reaction times it may be possible to convert the entire initially observed kinetic product to the more thermodynamically stable, tetra-substituted alkene product.

Table 4.3: Preliminary Catalytic Cyclization Using Oxidatin of Platinum-Alkyls as Turnover Event

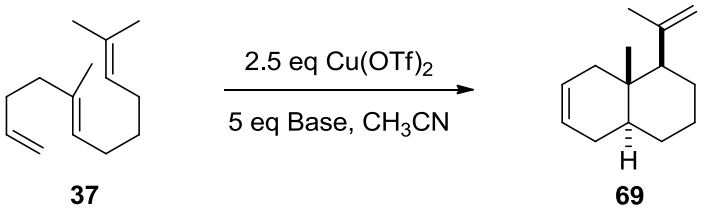
Entry	Substrate	Product	Time (h)	Consumption of Subtrate (%)[a]	Product Purity (%)[a]
1	 **37**	 **69**	4 24	65 99	76 81
2	 **49**	 **73**	4 24	73 84	67 62
3	 **41**	 **71**	4 24	56 66	53 34

Reaction conditions: Substrate (50 µmols), piperidinomethyl polystyrene resin (250 µmols), and $Cu(OTf)_2$ (125 µmols) were added to a solution of (PPP)PtI_2 (10 µmols) and $AgBF_4$ (22.5 µmols) in CH_3NO_2 (0.5 mL) that had been filtered to remove AgI. [a]Determined by GCMS analysis.

Conclusion

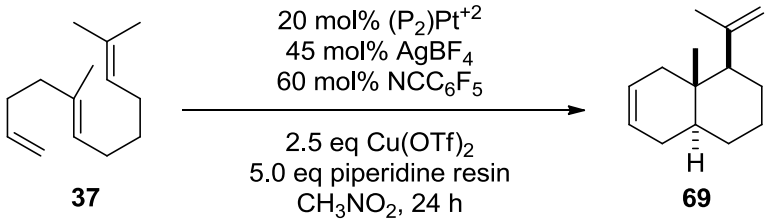
While this work is still in the preliminary stages, the use of $Cu(OTf)_2$ has already shown itself to be more promising than the electrophilic X^+ sources in the catalytic cyclization of poly-ene chains with simple alkene termini. Through further reaction optimization (base, nitrile concentration, solvent) it is very possible that an even more productive system can be produced. The development of a catalytic system for the cyclization of poly-olefin chains consisting of only simple alkenes is closer than ever.

Experimental Section



37 **69**

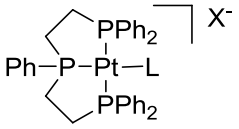
Standard Oxidation Procedure: The Platinum-alkyl (100 µmols) and $Cu(OTf)_2$ (250 µmols) were weighed into a 20 mL vial which was then placed under vacuum and backfilled with nitrogen. 5 mL of freshly distilled CH_3CN was added and the reaction was stirred for 5 minutes. 5 mL of diethyl ether was added to the solution and the mixture was passed through a silica gel plug, rinsing with diethyl ether. The volatiles were removed under vacuum and the product was isolated by preparative TLC using hexanes.



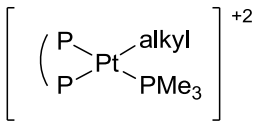
37 **69**

Standard Catalytic Cyclization Procedure: The $(BINAP)PtI_2$ (10 µmol), $AgBF_4$ (22.5 µmol) and NCC_6F_5 (30 µmol) were mixed in 0.3 mL CH_3NO_2 for one hour in the dark. The mixture was filtered through a 0.2 µm PTFE syringe filter (rinsing with 0.3 mL CH_3NO_2) onto substrate (50 µmol), piperidinomethyl polystyrene resin (250 µmol), and $Cu(OTf)_2$ (125 µmol). The mixture was stirred until completion in the dark (8-48 hours, determined by GC). The mixture was passed through a silica gel plug using hexanes and the volatiles were removed under vacuum.

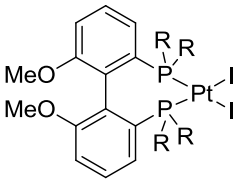
APPENDIX 1: 31P NMR Shifts

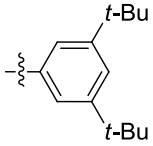
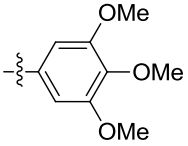
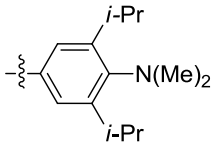
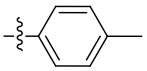
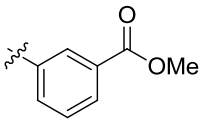
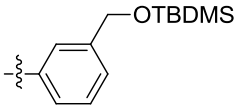
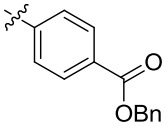
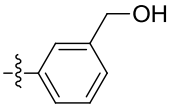
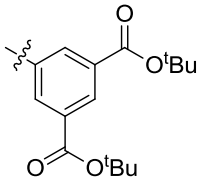
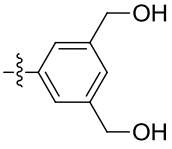
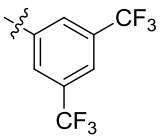


L	X^-	δ ^{31}P *trans* (ppm)	*Trans* coupling constant (Hz)	δ ^{31}P *cis* (ppm)	*Cis* coupling constant (Hz)	Solvent
NCC_6F_5	$(BF_4)_2$	86.1	3329	49.3	2352	CD_3NO_2
NCC_6F_5	$(BF_4)_2$	86	3329	49	2359	$EtNO_2$
NCC_6F_5	$(BF_4)_2$	84.7	3344	48.5	2352	CH_2Cl_2
MeOH	$(BF_4)_2$	86	2923	46.3	2419	CD_3NO_2
MeOH	$(BF_4)_2$	86	2921	46	2421	$EtNO_2$
MeOH	$(BF_4)_2$	85.2	2924	45.3	2417	CH_2Cl_2
1-Butanol	$(BF_4)_2$	85.1	2911	44.5	2422	CH_2Cl_2
$^-$OMe	$(BF_4)_2$	73.8	2665	40.9	2686	CH_2Cl_2
$^-CH_2NO_2$	$(BF_4)_2$	93.6	1940	45.7	2557	CD_3NO_2
Acetone	$(BF_4)_2$	80.4	3469	51.3	2446	Acetone-D6
Acetone	$(BF_4)_2$	79.1	3510	50.4	2436	CD_3NO_2
I	I	92.2	2886	42.4	2421	$CDCl_3$
Cl	Cl	86.3	3028	42.3	2484	CH_2Cl_2
1-Hexene	$(BF_4)_2$	106.4	2959	50.2	2265	CH_2Cl_2

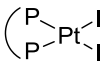


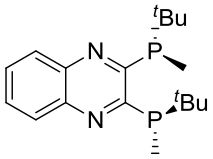
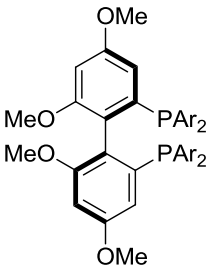
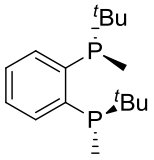
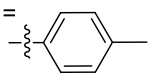
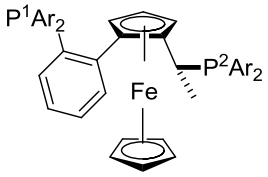
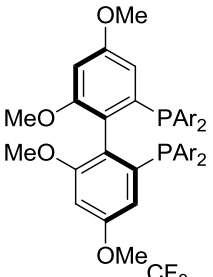
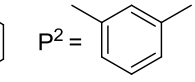
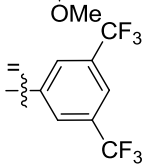
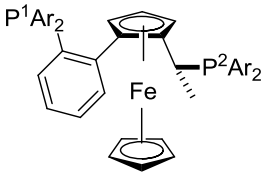
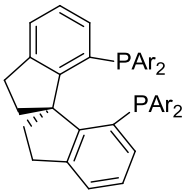
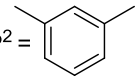
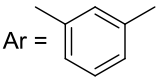
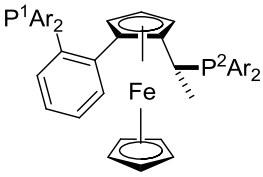
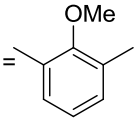
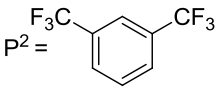
	P_2 = (*R*)-DTBM SEGPHOS		P_2 = (*R*)-xylyl-PHANEPHOS		P_2 = (*R*)-BINAP	
	δ (ppm)	J_{Pt-P} (Hz)	δ (ppm)	J_{Pt-P} (Hz)	δ (ppm)	J_{Pt-P} (Hz)
P_{cis}	17.76	1270	13.8	1450	13.9	1610
P_{trans}	2.47	1750	-0.5	1680	4.2	1860
P_{PMe3}	-2.88	1260	-15.3	2268	-15.8	2570



R	δ ^{31}P (ppm)	Coupling Constant (Hz)	Solvent	R	δ ^{31}P (ppm)	Coupling Constant (Hz)	Solvent
	21.24	3476	CD_2Cl_2		-31.5[a]	3648[a]	CD_2Cl_2
	6.94	3498	CD_2Cl_2		6.52[a]	3523[a]	CD_2Cl_2
	2.96	3497	CD_2Cl_2		2.0[a]	3480[a]	CD_2Cl_2
	2.98	3440	CD_2Cl_2		Not soluble in NMR solvents		
	2.19	3430	CD_2Cl_2		Not soluble in NMR solvents		
	2.06	3446	CD_2Cl_2		Not soluble in any NMR solvents		
	5.64	3364	CD_2Cl_2				

a) Perez-Powell, I. *Platinum Catalysed Wacker-Type Reactions* **2011**, Honours degree of MSci Chemistry Thesis.



	δ ^{31}P (ppm)	Coupling Constant (Hz)	Solvent		δ ^{31}P (ppm)	Coupling Constant (Hz)	Solvent
	32.0	3248	CD_2Cl_2		3.0	3486	CD_2Cl_2
	50.0	3366	CD_2Cl_2	Ar = 			
	22.4 2.97	3413 3515	CD_2Cl_2		5.0	3366	CD_2Cl_2
P^1 = 	P^2 =			Ar = 			
	22 2.92	3423 3498	CD_2Cl_2		12.8	3424	CD_2Cl_2
P^1, P^2 = 				Ar = 			
	20.3 1.71	3444 3364	CD_2Cl_2				
P^1 = 	P^2 = 						

APPENDIX 2: X-Ray Crystallographic Information

Single crystals were mounted in oil on the end of a MiteGen mictomount. Intensity data were collected on a Bruker-AXS SMART Apex-II diffractometer, equipped with a graphite monochromator, using either MoKα (λ = 0.71073Å) or CuKα (λ= 1.5418Å). The structures were initially solved by direct methods and completed using difference Fourier syntheses. Refinement was by least-squares techniques on F^2 using Olex2 and Shelx software. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions (C-H) = 0.96 Å and allowed to ride on the atoms to which they were bonded. Absorption corrections were made using either SADABS or TWINABS.

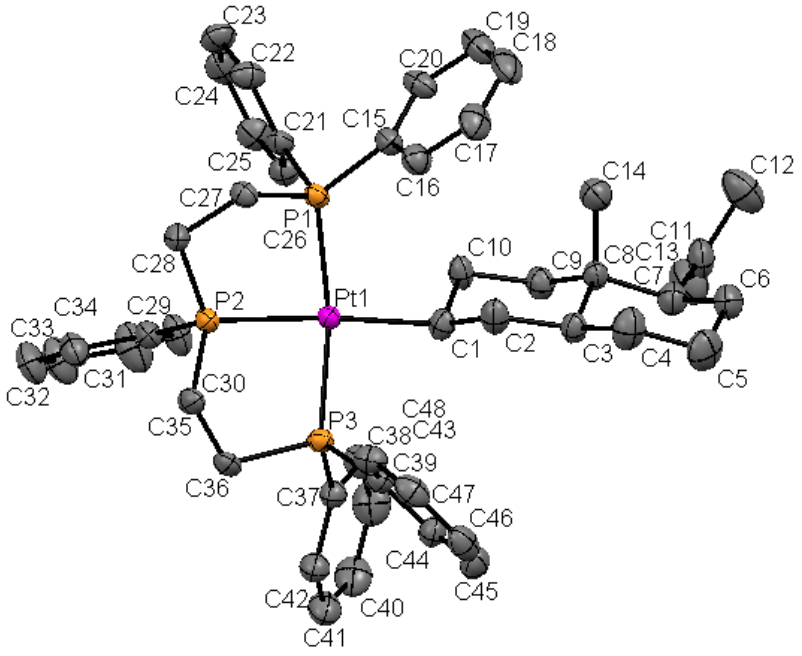


Figure A-2.4.3: ORTEP drawing of compound 38.

Ellipsoids are drawn at the 50% probability level, with hydrogen atoms, the tetrafluoroborate counter ion and a methylene chloride solvent molecule omitted for clarity.

The crystal was split resulting in two diffraction patterns displaced by approximately 5˚. TWINABS was used to correct the data and the relative occupancies refined to 67:33.

Crystal data and structure refinement for compound **38**.

CCDC Deposition Number	807498	
Empirical formula	$C_{49}H_{58}BCl_2F_4P_3P_t$	
Formula weight	1092.66	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.2776(3) Å	α = 70.170(1) °
	b = 15.9317(4) Å	β = 72.400(2) °
	c = 16.2869(6) Å	γ = 76.534(2) °
Volume	2365.87(13) $Å^3$	
Z	2	
Density (calculated)	1.534 Mg/m^3	
Absorption coefficient	3.229 mm^{-1}	
F(000)	1100	
Crystal size	0.36 x 0.21 x 0.17 mm^3	
Theta range for data collection	1.37 to 30.04°.	
Index ranges	$-13 \leq h \leq 14$, $-20 \leq k \leq 22$, $0 \leq l \leq 22$	
Reflections collected	27531	
Independent reflections	27531 [R(int) = 0.0000]	
Completeness to theta = 30.04°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5796 and 0.3872	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	27531 / 0 / 545	
Goodness-of-fit on F^2	1.071	
Final R indices [I>2sigma(I)]	R1 = 0.0449, wR2 = 0.1176	
R indices (all data)	R1 = 0.0569, wR2 = 0.1274	
Extinction coefficient	0.0062(4)	
Largest diff. peak and hole	3.227 and -1.603 $e.Å^{-3}$	

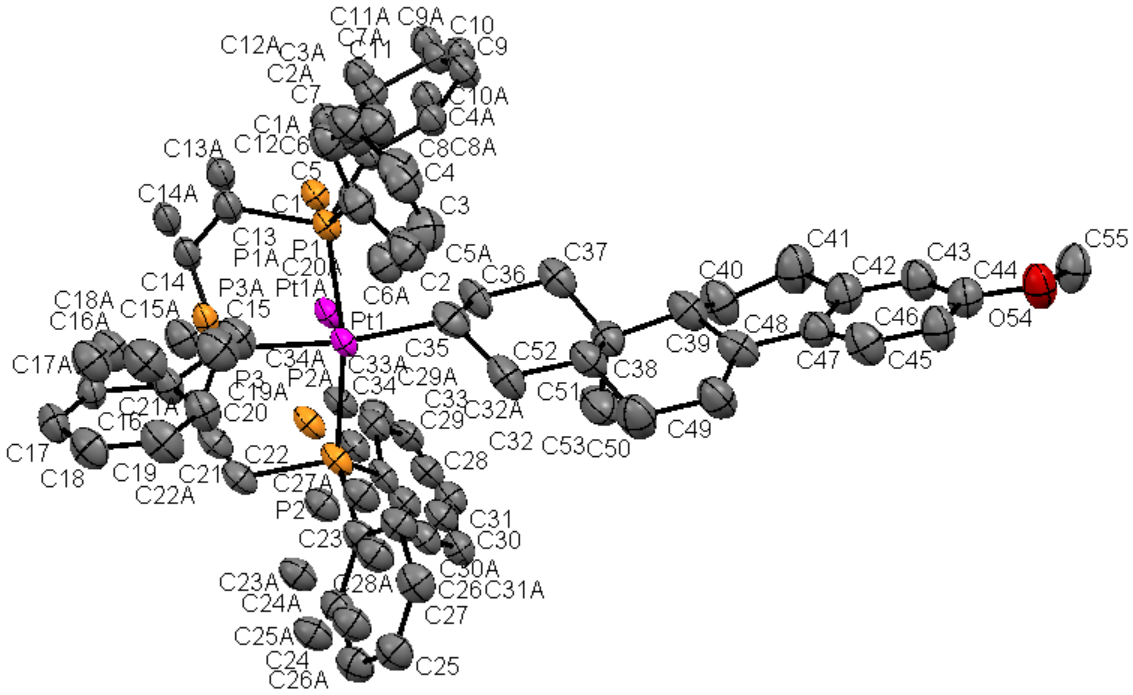


Figure A-2.4.4: ORTEP drawing of compound 44.

Ellipsoids are drawn at the 50% probability level, with hydrogen atoms, the tetrafluoroborate counter ion and a methylene chloride solvent molecule omitted for clarity.

After the initial refinement a relatively large difference peak was located close to Pt1 and lesser peaks close to the P atoms. Subsequent analysis showed a 14% disorder showing a flexing of the P—CH_2—CH_2—P chains with a consequent displacement of the phenyl rings. This was modeled using appropriate constraints and restraints.

Sample and crystal data for compound **44**.

CCDC Deposition Number	807499	
Empirical formula	$C_{56}H_{62}BCl_4F_4OP_3Pt$	
Formula weight	1267.67	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.4059(6) Å	α = 71.992(3)°
	b = 15.3570(8) Å	β = 75.077(3)°
	c = 18.3631(10) Å	γ = 84.295(3)°
Volume	2696.0(3) $Å^3$	
Z	2	
Density (calculated)	1.562 Mg/cm^3	
Absorption coefficient	7.968 mm^{-1}	
F(000)	1276	
Crystal size	0.14 x 0.15 x 0.56 mm	
Theta range for data collection	2.61 to 66.06°	
Index ranges	$-12 \le h \le 12$, $-18 \le k \le 18$, $-21 \le l \le 21$	
Reflections collected	30464	
Independent reflections	8851 [R(int) = 0.0473]	
Coverage of independent reflections	94.1%	
Absorption correction	multi-scan	
Max. and min. transmission	0.4017 and 0.0957	
Refinement method	Full-matrix least-squares on F2	
Function minimized	Σ w(Fo2 - Fc2)2	
Data / restraints / parameters	8851 / 2248 / 868	
Goodness-of-fit on F2	1.154	
Δ/σmax	0.001	
Final R indices [8200 data; I>2σ(I)]	R1 = 0.0675, wR2 = 0.1738	
R indices (all data)	R1 = 0.0719, wR2 = 0.1766	
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0737P)^2+21.7671P]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	2.728 and -1.469 $eÅ^{-3}$	
R.M.S. deviation from mean	0.153 $eÅ^{-3}$	

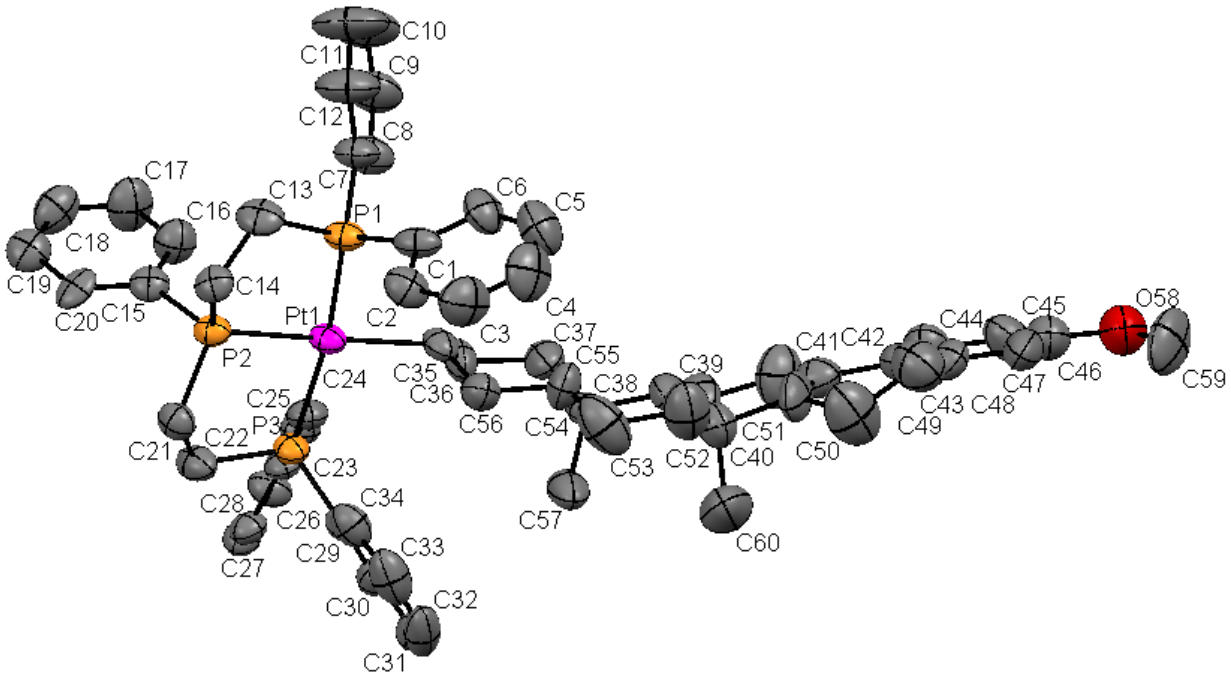


Figure A-2.4.5: ORTEP drawing of compound 46.

The crystal contained two molecules of compound 11 and two tetrafluoroborate counter ions in the unit cell. Ellipsoids are drawn at the 35% probability level, with hydrogen atoms, a second molecule of compound 11 and the BF_4^- counter ion omitted for clarity.

This structure had two molecules per asymmetric unit (Z' = 2), one was ordered and the other showed disorder in the C143—C150 region out towards the –O—CH_3 group; and a subsequent disorder of the counterions. Again this was modeled using appropriate constraints and restraints.

Crystal data and structure refinement for Compound **46**.

CCDC Deposition Number	807502	
Empirical formula	$C_{59}H_{66}BF_4OP_3P_t$	
Formula weight	1165.93	
Temperature	100 K	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 10.4476(3) Å	α = 90.00 °
	b = 58.3367(15) Å	β = 101.324(2) °
	c = 19.9200(5) Å	γ = 90.00 °
Volume	11904.5(5) $Å^3$	
Z	8	
Density (calculated)	1.301 Mg/m^3	
Absorption coefficient	5.559 mm^{-1}	
F(000)	4736	
Crystal size	0.232 x 0.226 x 0.131 mm^3	
Theta range for data collection	1.51 to 66.5°.	
Index ranges	$-12 \leq h \leq 12, 0 \leq k \leq 67, 0 \leq l \leq 23$	
Reflections collected	56357	
Independent reflections	20226 [R(int) = 0.0453]	
Completeness to theta = 66.5°	98.6	
Absorption correction	numerical	
Max. and min. transmission	0.6596, 0.4747	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	20226 / 2525 / 1388	
Goodness-of-fit on F^2	1.101	
Final R indices [I>2sigma(I)]	R_1 = 0.0730, wR_2 = 0.1584	
R indices (all data)	R_1 = 0.0852, wR_2 = 0.1632	
Largest diff. peak and hole	1.719 and -2.182 e $Å^{-3}$	

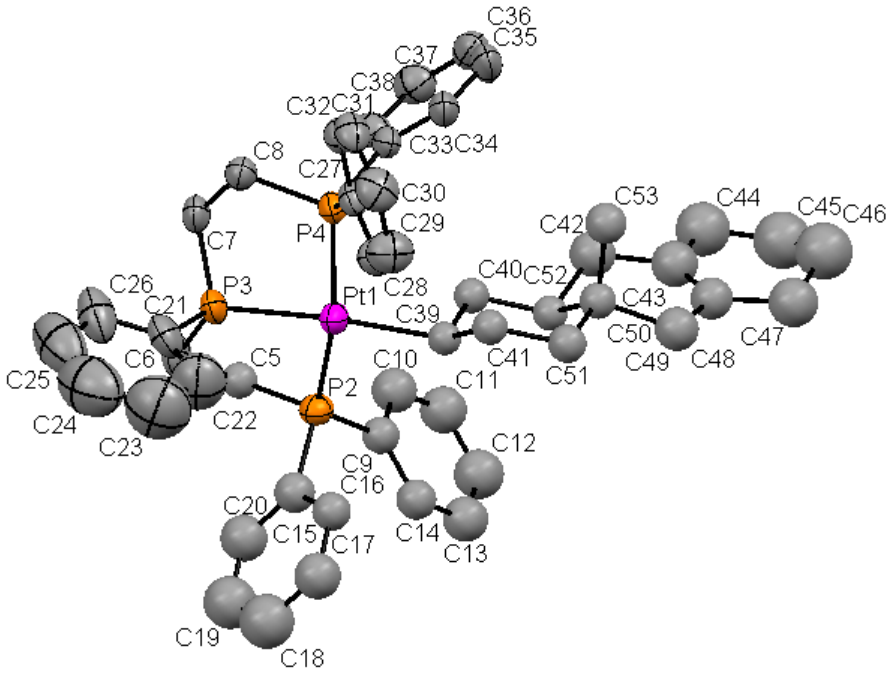


Figure A-2.4.6: ORTEP drawing of compound 48.

Ellipsoids are drawn at the 50% probability level, with hydrogen atoms and the tetrafluoroborate counter ion omitted for clarity.

This compound is a superposition of two rotomors, with opposite enantioselectivity, refined to 60:40 occupancies, but quite possibly 50:50. The ligand was modeled with restraints and constraints to have similar bond distances and geometry and the two phenyl rings attached to P2 were also treated as disordered.

Crystal data and structure refinement for Compound **48**.

CCDC Deposition Number	807500	
Empirical formula	$C_{49}H_{56}BF_4P_3P_t$	
Formula weight	1019.75	
Temperature	100 K	
Crystal system	triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.2224(3) Å	α = 75.9960(10) °
	b = 13.6050(4) Å	β = 80.9420(10) °
	c = 20.0265(5) Å	γ = 68.6910(10) °
Volume	2510.22(12) $Å^3$	
Z	2	
Density (calculated)	1.349 Mg/m^3	
Absorption coefficient	2.935 mm^{-1}	
F(000)	1028	
Crystal size	0.476 x 0.171 x 0.087 mm^3	
Theta range for data collection	1.64 to 52.88°	
Index ranges	$-12 \leq h \leq 12, -16 \leq k \leq 17, 0 \leq l \leq 25$	
Reflections collected	20112	
Independent reflections	10234 [R(int) = 0.0314]	
Completeness to theta = 52.88°	98.0	
Absorption correction	numerical	
Max. and min. transmission	0.3728, 0.8042	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10234 / 632 / 454	
Goodness-of-fit on F^2	1.057	
Final R indices [I>2sigma(I)]	R_1 = 0.0505, wR_2 = 0.1209	
R indices (all data)	R_1 = 0.0689, wR_2 = 0.1298	
Largest diff. peak and hole	1.865 and -0.722 e $Å^{-3}$	

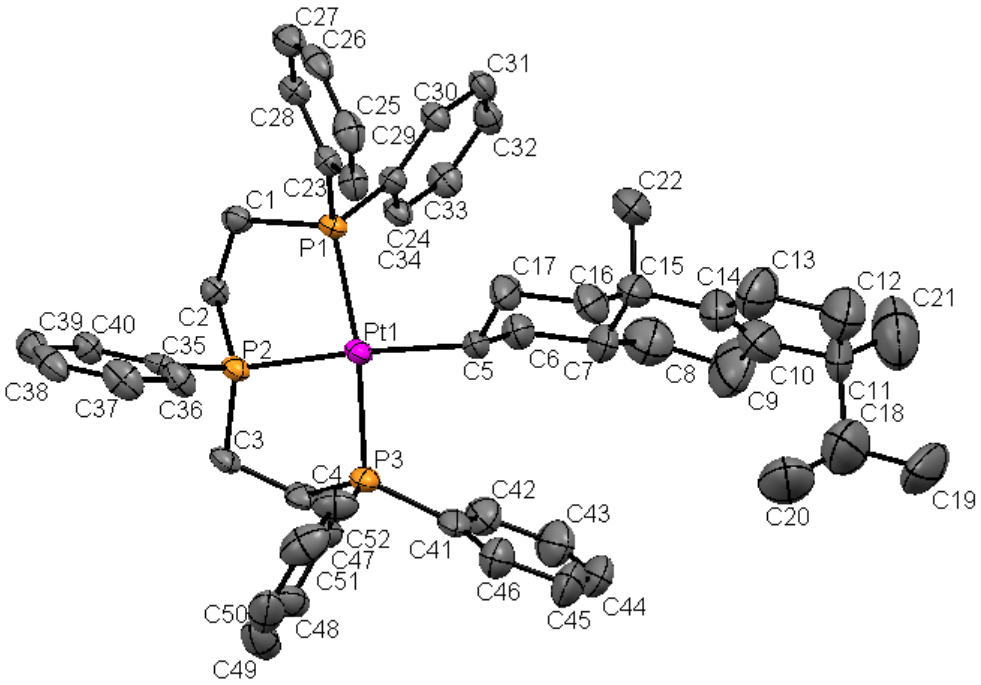


Figure A-2.4.7: ORTEP drawing of compound 52.

Ellipsoids are drawn at the 50% probability level, with hydrogen atoms, the tetrafluoroborate counter ion and a *tert*-butylmethylether solvent molecule omitted for clarity.

This molecule was ordered and well behaved.

Crystal data and structure refinement for compound **52**.

CCDC Deposition Number	807501	
Empirical formula	C57 H74 B F4 O P3 Pt	
Formula weight	1149.97	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.2481(1) Å	α= 101.713(1)°.
	b = 12.4981(2) Å	β= 90.775(1)°.
	c = 23.1998(3) Å	γ = 111.436(1)°.
Volume	2695.76(6) $Å^3$	
Z	2	
Density (calculated)	1.417 Mg/m^3	
Absorption coefficient	2.743 mm^{-1}	
F(000)	1176	
Crystal size	0.15 x 0.15 x 0.10 mm^3	
Theta range for data collection	1.80 to 25.73°.	
Index ranges	$-11 \le h \le 12$, $-15 \le k \le 15$, $-27 \le l \le 28$	
Reflections collected	51579	
Independent reflections	10186 [R(int) = 0.0455]	
Completeness to theta = 25.73°	98.9 %	
Absorption correction	SADABS	
Max. and min. transmission	0.770 and 0.682	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10186 / 39 / 612	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0423, wR2 = 0.1046	
R indices (all data)	R1 = 0.0530, wR2 = 0.1106	
Largest diff. peak and hole	1.843 and -0.974 e $Å^{-3}$	

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